Abstract:

The present invention is directed to a liquid aqueous pharmaceutical composition comprising one or more etherified cyclodextrin derivatives, at least one water-soluble polymer and at least one pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble. According to the present invention the solubility of the pharmaceutically active compound can be increased by the presence of at least one water-soluble polymer.
ETHERIFIED CYCLODEXTRIN DERIVATIVES CONTAINING LIQUID AQUEOUS 
PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION

The invention relates to the field of medicine, particularly veterinary medicine. In particular, the invention relates to a novel liquid aqueous pharmaceutical composition comprising one or more etherified cyclodextrin derivatives, at least one water-soluble polymer and at least one pharmaceutically active compound.

BACKGROUND OF THE INVENTION

Cyclodextrins are cyclic oligosaccharides containing six, seven, or eight (α-1,4)-linked D-glucopyranoside units resulting in alpha(α)-, beta(β)- and gamma(γ)-cyclodextrins. In general, cyclodextrins are pharmaceutical excipients that can solubilize various poorly soluble drugs/molecules through the formation of water-soluble drug-cyclodextrin complexes (Loftsson T et al., Journal of Pharmaceutical Sciences 2012, 101(9): 3019-3032). More specifically, cyclodextrins in aqueous solution form inclusion complexes with water-insoluble or poorly soluble drugs by taking up the lipophilic moiety of the drug molecule into the cavity of the cyclodextrin, which is hydrophobic (Brewster ME et al., Advanced Drug Delivery Reviews 2007, 59: 645-666). However, non-inclusion drug-cyclodextrin complexes can also be formed. The higher the cyclodextrin concentration increases, the higher the formation of aggregates of cyclodextrin molecules and self-assembled complexes. A further aspect with cyclodextrin containing pharmaceutical compositions is the formation of self-assembled complexes and/or formation of aggregates (Messner M et al., International Journal of Pharmaceutics 2011, 408: 235-247). Excipients that solubilize and stabilize such aggregates include small ionized molecules such as salts of organic acids and bases.

Certain etherified beta-cyclodextrin derivatives are known to improve solubility of sparingly soluble drugs, see WO 85/02767. However, in WO 85/02767 only the use of etherified beta-cyclodextrin derivatives up to a concentration of 10 % is described. A molar ratio of drug to etherified beta-cyclodextrin derivative of 1:6 to 4:1 was contemplated. The solubility of flubendazol within the above given ratio was only increased by a factor 30. However, those formulations are not suitable for the preparation of pharmaceutical compositions comprising substituted benzimidazole derivatives, such as pimobendan.

Further prior art is as follows:
US 2004/1 52664 is directed to compositions comprising cyclodextrin derivatives and prednisolone.
WO 2004/089418 deals with a fluoroquinolone comprising aqueous formulations of a pH between 4 and 7.
EP 1 920 785 discloses a liquid preparation comprising a complex of pimobendan and cyclodextrin.
Brewster ME et al. (Advanced Drug Delivery Reviews 2007, 59(7): 645-666) describe cyclodextrins as pharmaceutical solubilizers.

Bassani VL et al. (Journal of Inclusion Phenomena and Molecular Recognition in Chemistry, 1996, 25(1-3): 149-152) refer to the enhanced water solubility of albendazole by hydroxypropyl-β-cyclodextrin complexation.

The article of Piel G and co-workers (Sciences Techniques et Pratiques STP Pharma Pratiques 1999, 9(3): 257-260) is directed to the development of a parenteral and an oral formulation of albendazole with cyclodextrins.

This enables the development of a pharmaceutical composition for parenteral use, but it does not enable the development of a pharmaceutical composition for oral use. Due to the risk of severe tolerance problems and also due to concerns by pet owners that inflammation in the subcutis following injections is considered to be a risk factor in the development of sarcomas, it is highly desirable to develop an oral pharmaceutical composition.

Due to some animals’ intense sense of taste, it is particularly difficult to formulate a medication that can be administered orally and which the animal accepts resulting in an easy to use medication for animals, in particular companion animals, such as dogs, cats and horses (sufficiently good palatability).

The objective underlying the present invention is therefore to provide a pharmaceutical composition which overcomes the problems of the prior art as described above. Particularly, a pharmaceutical composition containing a sparingly water-soluble pharmaceutical active compound at palatable pH values (e.g. pH 3) shall be provided to be administered in adequate form to a subject in need thereof.

**SUMMARY OF THE INVENTION**

It is therefore provided a liquid aqueous pharmaceutical composition comprising

- one or more etherified cyclodextrin derivatives,
- at least one water-soluble polymer and
- at least one pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble,

wherein preferably the solubility of the at least one pharmaceutically active compound in water in the range of 15 to 25°C is defined as follows:

the at least one pharmaceutically active compound is poorly water-soluble if more than 100 mL of water per gram compound have to be used; it is very poorly water-soluble if more than 1,000 mL of water per gram compound have to be used; and it is water-insoluble if more than 10,000 mL water per gram compound have to be used to solubilise the compound, and preferably with the proviso that corticosteroids, in particular prednisolone and its prodrug prednisolone acetate (see US 2004/152664), and fluoroquinolones, in particular
ciprofloxacin, gatifloxacin, moxifloxacin, sitafloxacin, lomefloxacin, grepafloxacin,
gemifloxacin, norfloxacin, ofloxacin, levofloxacin, trovafloxacin and the like (see
WO 2004/089418), are independently from each other excluded as pharmaceutically active
compound which is poorly water-soluble, very poorly water-soluble or water-insoluble.

The present invention is also directed to the liquid pharmaceutical composition for use in a method for
treating a subject in need of such treatment, preferably an animal, in particular a companion animal,
even more preferred horse, dog or cat, guinea pig, hamster, cattle, goat, sheep, in particular cat or
dog, selected from among the indications: heart diseases, particularly a hypertrophic cardiomyopathy,
more particularly heart failure (HF), congestive heart failure (CHF), acute CHF, decompensated
endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic
DCM, hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), and heart failure due to
HCM, RCM, DCM and/or UCM.

It is also disclosed a process for producing the pharmaceutical composition comprising the steps
- adding at least one pharmaceutically active compound, one or more etherified cyclodextrin
derivatives, at least one water-soluble polymer and optionally one or more antioxidants to
water and mixing under stirring,
- adjusting the pH value using a pH adjustment agent.

Subject of the present invention is also a kit of parts that comprises:
a) a liquid aqueous pharmaceutical composition according to the present invention; and
b) a package leaflet including the information that the pharmaceutical composition is to be used
for the prevention and/or treatment of a heart disease, preferably heart failure and/or
hypertrophic cardiomyopathy, in a subject in need of such prevention or treatment.

It is completely unexpected that the pharmaceutical composition of the present invention can
overcome the deficiencies of prior art. The liquid aqueous pharmaceutical compositions for oral
administration comprising sparingly or not water-soluble pharmaceutically active compounds, such as
pimobendan, known from prior art are usually not suitable due to the low concentration of
pharmaceutically active compound normally achieved.

A known pharmaceutically active compound is pimobendan (4,5-dihydro-6-[2-(4-methoxyphenyl)-1 H-
benzimidazol-5-yl]-5-methyl-3(2H)-pyridazinone) disclosed in EP 0 008 391, herein incorporated by
reference in its entirety, and having the formula:

![Chemical Structure](image)
Pimobendan is a well-known compound for the treatment of congestive heart failure (CHF) originating for example from dilated cardiomyopathy (DCM) or decompensated endocardiosis (DCE) in animals, especially dogs (WO 2005/092343). Furthermore, pimobendan is also used for the treatment of hypertrophic cardiomyopathy in cats (WO 2010/060874). Pimobendan is also approved as a drug product for cardiovascular treatment of humans.

As already described in EP 0 439 030 and WO 2005/08467, pimobendan drug substance is insoluble in water: 1 g drug substance is soluble in more than 10,000 mL. At pH 7 the solubility of pimobendan is only about 0.1 mg per 100 mL.

The solubility of pimobendan in aqueous solutions depends on the pH. The solubility of pimobendan is significantly higher at pH 1 to 2.5 than at higher pH values (pH ≥ 3.0). However, the local tolerance and palatability as well as the chemical stability of such a formulation at pH 1 to 2.5 are not acceptable. The target dose of pimobendan would require a drug concentration in solution which can only be achieved at a pH of about pH 2.5 and lower in simple aqueous solutions. However, the concentration has to be significantly higher, resulting in a low volume that the animal will have to swallow, than is possible at pH > 3.0 in simple aqueous solutions. Accordingly, a pimobendan formulation comprising up to 1.5 mg/mL of pimobendan would need an increase in solubility at pH 7 by a factor of about 1000 to 1500, not achieved in prior art formulations for oral administration up to now.

On the contrary, the liquid aqueous pharmaceutical compositions according to the present invention comprising at least one pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble with the assistance of one or more etherified cyclodextrin derivatives and at least one water-soluble polymer provide an acceptable solubility of the pharmaceutically active compound such as pimobendan in aqueous solution. Thereby, an acceptable concentration of the pharmaceutically active compound is present allowing for use in an oral administration form. Due to the addition of at least one water-soluble polymer the concentration of the pharmaceutically active compound that is dissolved with the assistance of one or more etherified cyclodextrin derivatives is further increased.

Since the liquid aqueous pharmaceutical compositions according to the present invention may be formulated for oral administration the disadvantageous side effects of parenteral administration such as inflammation in the subcutis following injections may be avoided. In addition, the composition does not have to be given by a veterinarian, as is the case for parenteral administration.

Furthermore, the described formation of self-assembled complexes and/or formation of aggregates, which occurs in cyclodextrin containing pharmaceutical compositions, may be reduced or completely avoided by the presence of at least one water-soluble polymer that solubilises and stabilizes such aggregates.
Also the palatability if administered to animal patients is found to be good apparently due to a high concentration of well-palatable etherified cyclodextrin-derivatives present in the pharmaceutical composition of the present invention.

Moreover, the addition of some excipients such as at least one antioxidant have been found to be advantageous in order to further increase the concentration of the pharmaceutically active compound to be used and/or to further stabilize the liquid pharmaceutical composition and to have a preserving (antimicrobial) effect.

### DETAILED DESCRIPTION OF THE INVENTION

Before the embodiments of the present invention are described in further details it shall be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. All given ranges and values may vary by 1 to 5% unless indicated otherwise or known otherwise by the person skilled in the art, therefore, the term "about" was usually omitted from the description and claims.

Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the substances, excipients, carriers, and methodologies as reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

The present invention is based on the surprising unexpected observation that in cyclodextrin containing pharmaceutical compositions the unwanted self-assembled complexes and/or aggregates may be minimized or completely prevented by the presence of at least one water-soluble polymer that solubilise and stabilize such aggregates. Furthermore, a higher solubility of the at least one pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble was surprisingly observed.

According to the present invention a liquid aqueous pharmaceutical composition is provided. The term "aqueous" is to be understood in the meaning that the pharmaceutical composition contains water as a solvent, whereby also one or more other solvents may optionally be present. According to one preferred embodiment water is the only solvent of such pharmaceutically composition.
The liquid aqueous pharmaceutical composition comprises at least one pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble. According to the European Pharmacopoeia the solubility of a compound in water in the range of 15 to 25°C is defined as follows:

<table>
<thead>
<tr>
<th>Solvent in mL per gram compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very readily soluble</td>
</tr>
<tr>
<td>Readily soluble</td>
</tr>
<tr>
<td>Soluble</td>
</tr>
<tr>
<td>Hardly soluble</td>
</tr>
<tr>
<td>Poorly soluble</td>
</tr>
<tr>
<td>Very poorly soluble</td>
</tr>
<tr>
<td>Water-insoluble</td>
</tr>
</tbody>
</table>

Thus, according to the present invention the at least one pharmaceutically active compound is poorly water-soluble, very poorly water-soluble or water-insoluble. Preferably, the at least one pharmaceutically active compound is poorly water-soluble if more than 100 mL of water per gram compound have to be used; it is very poorly water-soluble if more than 1,000 mL of water per gram compound have to be used; and it is water-insoluble if more than 10,000 mL water per gram compound must be used to solubilise the compound.

The at least one pharmaceutically active compound is preferably a benzimidazole derivative. The benzimidazole derivative is preferably a substituted benzimidazole. The term "substituted benzimidazole" as used herein means, but is not limited to thiabendazol, fuberidazol, oxibendazol, parbendazol, cambendazol, mebendazol, fenbendazol, flubendazol, albendazol, oxfendazol, nocodazol, astemisol and pimobendan, pharmaceutically acceptable salts, derivatives, metabolites or prodrugs thereof. Most preferably, the term benzimidazole derivative as used herein means pimobendan, or any pharmaceutically acceptable salts thereof.

In another aspect the at least one pharmaceutically active compound is preferably an oxicam derivative. The oxicam derivative is preferably a substituted oxicam. The term "substituted oxicam" as used herein means, but is not limited to ampiroxicam, droxicam, lornoxicam, piroxicam, tenoxicam and meloxicam, pharmaceutically acceptable salts, derivatives, metabolites or prodrugs thereof. Most preferably, the term oxicam derivative as used herein means meloxicam, or any pharmaceutically acceptable salts thereof.

In another aspect the at least one pharmaceutically active compound is preferably an imidazolinone derivative. The imidazolinone derivative is preferably a substituted imidazolinone. The term "substituted imidazolinone" as used herein means, but is not limited to 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin), pharmaceutically acceptable salts, derivatives, metabolites or prodrugs thereof. Most preferably, the term imidazolinone derivative as used herein means 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin), or any pharmaceutically acceptable salts thereof.
In another aspect the at least one pharmaceutically active compound is preferably a glucopyranosyl-
substituted benzene derivative. The glucopyranosyl-substituted benzene derivative is preferably a substitutef glucopyranosyl-substituted benzene derivative. The term "substituted glucopyranosyl-
substituted benzene derivative" as used herein means, but is not limited to 1-cyano-2-(4-cyclopropyl-
benzyl)-4-(beta-D-glucopyranos-1-yl)-benzene, pharmaceutically acceptable salts, derivatives, metabolites or prodrugs thereof. Most preferably, the term glucopyranosyl-substituted benzene derivative as used herein means 1-cyano-2-(4-cyclopropyl-benzyl)-4-(beta-D-glucopyranos-1-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-(beta-D-
glucopyranos-1-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline.

The liquid aqueous pharmaceutical composition according to the present invention contains the at least one pharmaceutically active compound as disclosed herein, particularly in form of a substituted benzimidazole, more particularly pimobendan, preferably in the range of from 0.01 g/100 mL to 1 g/100 mL, more preferably from 0.05 g/100 mL to 0.5 g/100 mL, most preferably from 0.1 g/100 mL to 0.25 g/100 mL.

Due to the low aqueous solubility of the pharmaceutically active compound as disclosed herein, preferably a substituted benzimidazole such as pimobendan, at pH values that are acceptable for an oral pharmaceutical composition, one or more solubilizing excipients need to be added to the formulation.

In the present invention such solubilizing excipients are one or more etherified cyclodextrin derivatives.

The liquid aqueous pharmaceutical composition according to the present invention contains the one or more etherified cyclodextrin derivatives preferably in the range of from 5 g/100 mL to 40 g/100 mL more preferably from 10 g/100 mL to 35 g/100 mL, most preferably from 20 g/100 mL to 35 g/100 mL per one etherified cyclodextrin derivative.

The term "etherified cyclodextrin derivative" as used herein includes but is not limited to alpha-, beta- or gamma-cyclodextrin ethers. Preferably the one or more etherified cyclodextrin derivatives as used herein means etherified beta-cyclodextrins, more preferably of the chemical formula I.
in which the residues R are independently from each other hydroxyalkyl groups and part of the residues R may optionally independently from each other be alkyl groups. A partially etherified beta-cyclodextrin of formula I is preferably used, in which the residues R are independently from each other hydroxyethyl, hydroxypropyl or dihydroxypropyl groups. Optionally, part of the residues R may for instance be methyl or ethyl groups.

The use of partially methylated beta-cyclodextrins with 7 to 14 methyl groups in the beta-cyclodextrin molecule as they are known from DE 31 182 18 does not fall under the present invention.

Partial ethers of beta-cyclodextrin comprising only alkyl groups, such as methyl, ethyl and the like, may be particularly suitable in accordance with the invention if they have a low degree of substitution, preferably as defined below of 0.05 to 0.2.

Even more preferably, the one or more etherified cyclodextrin derivatives as used herein are hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, dihydroxypropyl-beta-cyclodextrin, sulphobutyl-ether-p-cyclodextrin.

Most preferably, the one or more etherified cyclodextrin derivatives as used herein are hydroxypropyl-beta-cyclodextrin (HPpCD), referred to as hydroxypropylbetadex in the European Pharmacopoeia. Hydroxypropyl-beta-cyclodextrin (HPpCD) of pharmaceutical grade is marketed for example under the Trademark Cavasol® W7 HP Pharma and can be ordered from Wacker, Germany.

Beta-cyclodextrin is a compound with ring structure consisting of 7 anhydro glucose units; it is also referred to as cycloheptaamylose. Each of the 7 glucose rings contains in 2-, 3-, and 6-position three hydroxy groups which may be etherified. In the partially etherified one or more β-cyclodextrin derivatives used according to the invention only part of these hydroxy groups is etherified with hydroxyalkyl groups and optionally further with alkyl groups. When etherifying with hydroxyalkyl groups which can be carried out by reaction with the corresponding alkylene oxides, the degree of substitution is stated as molar substitution (MS), viz. in mole alkylene oxide per anhydroglucose unit (compare U.S. Patent 3,459,731, column 4). In the hydroxyalkyl ethers of beta-cyclodextrin used in accordance with the invention the molar substitution is preferably between 0.05 and 10, more
preferably between 0.2 and 2. Particularly preferred is a molar substitution of about 0.40 to about 1.50. The etherification with alkyl groups may be stated directly as degree of substitution (DS) per glucose unit which as stated above is 3 for complete substitution. Partially etherified beta-cyclodextrins are used within the invention which preferably comprise besides hydroxyalkyl groups also alkyl groups, especially methyl or ethyl groups, up to a degree of substitution of 0.05 to 2.0, more preferably 0.2 to 1.5. Most preferably the degree of substitution with alkyl groups is between about 0.5 and about 1.2.

As solubilizing excipient hydroxypropyl-beta-cyclodextrin (HP-β-CD) showed very advantageous effects and resulted in the largest increase in solubility of a pharmaceutically active compound to be used such as pimobendan or a pharmaceutically acceptable salt thereof.

Thus, according to one aspect, the present invention relates to a liquid aqueous pharmaceutical composition comprising one or more etherified cyclodextrin derivatives, at least one water-soluble polymer and at least one pharmaceutically active compound, particularly in form of a substituted benzimidazole, more particularly pimobendan, wherein the one or more etherified cyclodextrin derivative is selected from the group consisting of: alpha-, beta-, and/or gamma-cyclodextrin ether.

According to a further aspect, the present invention relates to a liquid aqueous pharmaceutical composition as described above, comprising one or more etherified cyclodextrin derivatives, at least one water-soluble polymer and at least one pharmaceutically active compound as disclosed herein, particularly in form of a substituted benzimidazole, more particularly pimobendan, wherein the one or more etherified cyclodextrin derivative is etherified beta-cyclodextrin. Preferably, that etherified beta-cyclodextrin is hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, or dihydroxypropyl-beta-cyclodextrin. Even more preferably, that etherified beta-cyclodextrin is hydroxypropyl-beta-cyclodextrin (HPpCD), referred to as hydroxypropylbetadex in the European Pharmacopoeia.

According to the invention it has been found that the concentration of the pharmaceutically active compound as disclosed herein that is dissolved with the assistance of one or more etherified cyclodextrin derivatives is further increased by the addition of at least one water-soluble polymer.

Furthermore, the undesired formation of self-assembled complexes and/or formation of aggregates may be further reduced or completely avoided by the presence of at least one water-soluble polymer such as cellulose derivatives which solubilize and stabilize such aggregates.

According to the invention the at least one water-soluble polymer has preferably a molar mass of 5,000 to 500,000 g/mol, more preferably 10,000 to 300,000 g/mol, even more preferably 15,000 to 200,000 g/mol, even more preferred 20,000 to 200,000 g/mol. Examples for said water soluble polymer are hydroxypropyl methylcellulose (hypromellose, HPMC), hydroxypropyl cellulose, carboxymethylcellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, ethylcellulose, methylcellulose, polyvinylpyrrolidone, polyvinylacetate as well as combinations or copolymers thereof, preferably hydroxypropyl methylcellulose (hypromellose).
The liquid aqueous pharmaceutical composition according to the present invention contains the at least one water-soluble polymer preferably in the range of from 0.01 g/100 mL to 0.75 g/100 mL more preferably from 0.02 g/100 mL to 0.50 g/100 mL, most preferably from 0.05 g/100 mL to 0.30 g/100 mL.

The liquid aqueous pharmaceutical composition according to the present invention may contain one or more excipients. The one or more excipients can be selected from the group consisting of an antioxidant, buffer, preservatives, pH adjustment agent, colorants or taste-masking/modifying ingredients including flavours.

Preferably at least one water-soluble antioxidant may be added as excipient. More preferably, at least one water-soluble polymer and at least one water-soluble antioxidant are coexistent in the liquid aqueous pharmaceutical composition according to the present invention.

In a preferred embodiment, the liquid aqueous pharmaceutical composition of the present invention further comprises at least one water-soluble antioxidant, so that the liquid aqueous pharmaceutical composition comprises at least one water-soluble polymer and at least one water-soluble antioxidant.

According to the invention it is preferred that the liquid aqueous pharmacologically composition comprises at least one water-soluble antioxidant in order to stabilize the pharmaceutical composition and to have a preserving (antimicrobial) effect. Only a small number of antioxidants are known which are water-soluble and come into question. Water-soluble antioxidants that can be used comprise ascorbic acid or salts thereof, particularly sodium ascorbate; citric acid (anhydrous and/or monohydrate) or salts thereof, particularly sodium citrate; erythorbic acid; fumaric acid; malic acid; monothioglycerol; phosphoric acid; sodium metabisulphite; potassium metabisulphite; propionic acid; sodium bisulfite; sodium sulfate; resveratrol, butylhydroxyanisol, gallate derivatives, particularly propylgallate, or combinations thereof, preferably ascorbic acid or salts thereof, citric acid (anhydrous and/or monohydrate) or salts thereof, sodium metabisulfite, or potassium metabisulfite. Particularly preferred is ascorbic acid or salts thereof.

A system comprising one or more cyclodextrin derivatives, at least one water-soluble polymer and at least one water-soluble antioxidant has been shown to be particularly efficient to solubilise and stabilise the above described liquid aqueous pharmaceutical compositions without having a negative effect on the concentration of the pharmaceutically active compound in the pharmaceutical compositions. Accordingly, in a preferred embodiment, the liquid aqueous pharmaceutically composition of the invention comprises one or more cyclodextrin derivatives, at least one water-soluble polymer, at least one water-soluble antioxidant and at least one pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble, preferably with the proviso that corticosteroids, in particular prednisolone and its prodrug prednisolone acetate (see US 2004/1 52664), and fluoroquinolones, in particular ciprofloxacin, gatifloxacin, moxifloxacin,
sitafloxacin, lomefloxacin, grepafloxacin, gemifloxacin, norfloxacin, ofloxacin, levofloxacin, trovafloxacin and the like (see WO 2004/089418), are independently from each other excluded as pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble.

Furthermore, the presence of at least one water-soluble antioxidant has a positive influence on the pharmaceutical composition of the present invention:

The water-soluble antioxidant, preferably ascorbic acid or salts thereof, was found to chemically stabilize the formulation. Furthermore, small amounts of antioxidant, for example ascorbic acid, surprisingly provided a qualitatively small solubilising effect for the pharmaceutically active compound, such as pimobendan, this compound dissolved more quickly when antioxidant, such as ascorbic acid, was present in the solution.

In addition, if excipients are used which are susceptible to oxidation an antioxidant may prevent such an oxidation so that at least one antioxidant should preferably be added.

The positive effects of the at least one antioxidant are observed independently of the concentration of the at least one antioxidant used. Therefore, already small amounts of antioxidant may have a benefit for the pharmaceutical composition according to the present invention.

In a further aspect the liquid aqueous pharmaceutical composition according to the present invention comprises at least one water-soluble antioxidant preferably in the range 0.2 g/1 00 mL to 2.0 g/1 00 mL, in particular from 0.3 g/1 00 mL to 1.0 g/1 00 mL.

According to the invention the pH of the pharmaceutical composition for oral use has preferably a pH value of 2 to 10, more preferably 3 to 10, more preferably 3 to 8, more preferably 3.1 to 8, more preferably 3 to 7, even more preferably 3.2 to 7, even more preferably 2.5 to 5, most preferably 3 to 5. Particularly preferred is pH 3.3 to 6, particularly 3.4 to 5, especially 3.4 to 4. By using the lowest preferred but still acceptable pH value range, it is possible to further increase the solubility of the pharmaceutically active compound, such as pimobendan, compared to that at higher pH values. Besides the better solubility of the pharmaceutically active compound compared to higher pH values, the lower pH value range has the further advantage of improved preservative efficacy. Particularly, it was found that it is advantageous to use liquid aqueous pharmaceutically composition having a pH range of 3 to 4.5, preferably 3.5, since aqueous solutions with a pH value in the acidic range have an improved antimicrobial activity even without a preservative.

Thus, according to a further aspect, the present invention relates to a liquid aqueous pharmaceutical composition as described above, comprising at least one pharmaceutically active compound in the form of at least one substituted benzimidazole or a pharmaceutically acceptable salt thereof or a substituted oxicam or a pharmaceutically acceptable salt thereof or a substituted imidazolinone or a
pharmaceutically acceptable salt thereof or a substituted glucopyranosyl-substituted benzene derivative or a pharmaceutically acceptable form and/or salt thereof, one or more etherified cyclodextrin derivatives in the form of etherified beta-cyclodextrin, at least one water-soluble polymer and optionally at least one water-soluble antioxidant.

Therefore, the present invention preferably relates to a liquid aqueous pharmaceutical composition as described above, comprising

a) at least one pharmaceutically active compound in the form of a substituted benzimidazole or a pharmaceutically acceptable salt thereof, preferably thiabendazol, fuberidazol, oxibendazol, parbendazol, cambendazol, mebendazol, fenbendazol, flubendazol, albendazol, oxfendazol, nocardazol, astemisol or pimobendan, or pharmaceutical acceptable salts thereof, more preferably pimobendan or a pharmaceutically acceptable salt thereof;

b) one or more etherified cyclodextrin derivatives in the form of etherified beta-cyclodextrin, preferably hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, dihydroxypropyl-beta-cyclodextrin, more preferably hydroxypropyl-beta-cyclodextrin (HPpCD);

c) at least one water-soluble polymer with a molar mass of 5,000 to 500,000 g/mol, preferably 10,000 to 300,000 g/mol, even more preferred 15,000 to 200,000 g/mol, even more preferred 20,000 to 200,000 g/mol, preferably hydroxypropyl methylcellulose, hydroxypropyl cellulose, or methylcellulose, more preferably hydroxypropyl methylcellulose (hypromellose); and

d) optionally, but according to a preferred embodiment, at least one water-soluble antioxidant, preferably ascorbic acid or a salt thereof; citric acid (anhydrous and/or monohydrate) or a salt thereof; sodium metabisulfite, potassium metabisulfite or resveratrol.

Therefore, the present invention preferably relates to a liquid aqueous pharmaceutical composition as described above, comprising

a) at least one pharmaceutically active compound in the form of a substituted oxicam or a pharmaceutically acceptable salt thereof, preferably ampiroxicam, droxica, lornoxicam, piroxicam, tenoxicam and meloxicam, or pharmaceutical acceptable salts thereof, more preferably meloxicam or a pharmaceutically acceptable salt thereof;

b) one or more etherified cyclodextrin derivatives in the form of etherified beta-cyclodextrin, preferably hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, dihydroxypropyl-beta-cyclodextrin, more preferably hydroxypropyl-beta-cyclodextrin (HPpCD);

c) at least one water-soluble polymer with a molar mass of 5,000 to 500,000 g/mol, preferably 10,000 to 300,000 g/mol, even more preferred 15,000 to 200,000 g/mol, even more preferred 20,000 to 200,000 g/mol, preferably hydroxypropyl methylcellulose, hydroxypropyl cellulose, or methylcellulose, more preferably hydroxypropyl methylcellulose (hypromellose); and

d) optionally, but according to a preferred embodiment, at least one water-soluble antioxidant, preferably ascorbic acid or a salt thereof; citric acid (anhydrous and/or monohydrate) or a salt thereof; sodium metabisulfite, potassium metabisulfite or resveratrol.
Therefore, the present invention preferably relates to a liquid aqueous pharmaceutical composition as described above, comprising
a) at least one pharmaceutically active compound in the form of a substituted imidazolinone or a pharmaceutically acceptable salt thereof, preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin) or a pharmaceutically acceptable salt thereof;
b) one or more etherified cyclodextrin derivatives in the form of etherified beta-cyclodextrin, preferably hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, dihydroxypropyl-beta-cyclodextrin, more preferably hydroxypropyl-beta-cyclodextrin (HPpCD);
c) at least one water-soluble polymer with a molar mass of 5,000 to 500,000 g/mol, preferably 10,000 to 300,000 g/mol, even more preferred 15,000 to 200,000 g/mol, even more preferred 20,000 to 200,000 g/mol, preferably hydroxypropyl methylcellulose, hydroxypropyl cellulose, or methylcellulose, more preferably hydroxypropyl methylcellulose (hydroxypropyl cellulose); and
d) optionally, but according to a preferred embodiment, at least one water-soluble antioxidant, preferably ascorbic acid or a salt thereof; citric acid (anhydrous and/or monohydrate) or a salt thereof; sodium metabisulfite, potassium metabisulfite or resveratrol.

Therefore, the present invention preferably relates to a liquid aqueous pharmaceutical composition as described above, comprising
a) at least one pharmaceutically active compound in the form of a substituted glucopyranosyl-substituted benzene derivative or a pharmaceutically acceptable salt thereof, preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-((β-D-glucopyranosyl-1-yl)-benzene, or any pharmaceutical acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-((β-D-glucopyranosyl-1-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline;
b) one or more etherified cyclodextrin derivatives in the form of etherified beta-cyclodextrin, preferably hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, dihydroxypropyl-beta-cyclodextrin, more preferably hydroxypropyl-beta-cyclodextrin (HPpCD);
c) at least one water-soluble polymer with a molar mass of 5,000 to 500,000 g/mol, preferably 10,000 to 300,000 g/mol, even more preferred 15,000 to 200,000 g/mol, even more preferred 20,000 to 200,000 g/mol, preferably hydroxypropyl methylcellulose, hydroxypropyl cellulose, or methylcellulose, more preferably hydroxypropyl methylcellulose (hydroxypropyl cellulose); and
d) optionally, but according to a preferred embodiment, at least one water-soluble antioxidant, preferably ascorbic acid or a salt thereof; citric acid (anhydrous and/or monohydrate) or a salt thereof; sodium metabisulfite, potassium metabisulfite or resveratrol.

The liquid aqueous pharmaceutical composition according to the present invention preferably comprises:
a) 0.01 g/100 mL to 1 g/100 mL substituted benzimidazole or a pharmaceutically acceptable salt thereof, preferably pimobendan or a pharmaceutically acceptable salt thereof, or a substituted oxim or a pharmaceutically acceptable salt thereof, preferably meloxicam or a
pharmaceutically acceptable salt thereof, or a substituted imidazolinone or a pharmaceutically acceptable salt thereof, preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoïn) or a pharmaceutically acceptable salt thereof, or a substituted glucopyranosyl-substituted benzene derivative or a pharmaceutically acceptable form and/or salt thereof, preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-[(β-D-glucopyranos-1-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-[(β-D-glucopyranos-1-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline;

b) 5 g/100 mL to 40 g/100 mL of one or more etherified cyclodextrin-derivatives, preferably hydroxypropyl-beta-cyclodextrin;

c) 0.01 g/100 mL to 0.75 g/100 mL of at least one water-soluble polymer, preferably hydroxypropyl methylcellulose (hypromellose)

d) optionally, but according to a preferred embodiment, 0.2 g/100 mL to 2.0 g/100 mL of at least one water-soluble antioxidant, preferably ascorbic acid or a salt thereof.

According to another aspect the liquid aqueous pharmaceutical composition according to the present invention preferably comprises:

a) 0.1 g/100 mL to 0.25 g/100 mL pimobendan or a pharmaceutically acceptable salt thereof or meloxicam or a pharmaceutically acceptable salt thereof or 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoïn) or a pharmaceutically acceptable salt thereof or 1-cyano-2-(4-cyclopropyl-benzyl)-4-[(β-D-glucopyranos-1-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-[(β-D-glucopyranos-1-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline;

b) 20 g/100 mL to 35 g/100 mL of a hydroxypropyl-beta-cyclodextrin;

c) 0.05 g/100 mL to 0.30 g/100 mL of hydroxypropyl methylcellulose (hypromellose);

d) 0.3 g/100 mL to 1.0 g/100 mL of an antioxidant, preferably ascorbic acid or a salt thereof;

wherein optionally the pH of the composition is between 2 to 10, preferably 3 to 10, more preferably 3 to 8, more preferably 3 to 7, more preferably 2.5 to 5, even more preferably 3 to 5, even more preferably 3.4 to 5 and most preferably 3.4 to 4.

With regard to the palatability if administered to animal patients the liquid aqueous pharmaceutically composition is well accepted.

The liquid aqueous pharmaceutical composition provides an acceptable solubility of the pharmaceutically active compound as disclosed herein, such as pimobendan in aqueous solution, according to which a minimum concentration of the pharmaceutically active compound is present allowing for use in an oral administration form. For example, the minimum concentration of
pimobendan is preferably 1.5 mg/mL = 0.15% (m/V). Furthermore, there is only a negligible crystal growth of the pharmaceutically active compound, if any, during the storage period.

The person skilled in the art knows the effective dosage of pharmaceutically active compounds as disclosed herein, such as benzimidazole derivatives, in particular pimobendan, and is readily able to adjust this dosage which is to be administered to the patient such as an animal patient, in need thereof. In order to have a general guidance in this connection a general therapeutic effective target dose, in particular for the treatment of HCM in cats, is about 0.1 mg to 0.5 mg pimobendan twice daily per kg bodyweight of the animal, preferably about 0.3 mg pimobendan twice daily per kg bodyweight of the animal.

The liquid aqueous pharmaceutical composition according to the present invention is intended for oral and/or parenteral administration, particularly oral solutions may be provided.

According to a preferred embodiment of the present invention the liquid aqueous pharmaceutical composition comprises the pharmaceutically active compound in form of a substituted benzimidazole, preferably pimobendan, or a substituted oxicam, preferably meloxicam, or a substituted imidazolinone, preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin) or a substituted glucopyranosyl-substituted benzene derivative, preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline, in a therapeutically effective amount of up to 5 mg/mL, preferably of 1.5 to 4 mg/mL, even more preferably of 1.5 to 3 mg/mL.

According to a further aspect, the present invention also relates to a method of treatment and/or prevention of diseases, wherein cardiotonic, hypotensive, anti-inflammatory and anti-thrombotic substances have a therapeutic benefit, preferably directed to a subject suffering from heart diseases, particularly a hypertrophic cardiomyopathy, comprising the step of administering to such subject in need of such treatment a therapeutically effective amount of any of the liquid aqueous pharmaceutical compositions as described herein.

Preferably, the liquid aqueous pharmaceutical composition of the present invention is administered in a therapeutically effective amount from about 0.075 mg to about 0.5 mg in form of a substituted benzimidazole derivative, preferably pimobendan, or a substituted oxicam, preferably meloxicam, or a substituted imidazolinone preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin) or a substituted glucopyranosyl-substituted benzene derivative, preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzene and one or more amino acids,
acids, preferably wherein the one or more amino acids is proline, more preferably L-proline, per kg bodyweight of the animal, more preferably from about 0.2 mg to about 0.4 mg of the pharmaceutically active compound in form of a substituted benzimidazole derivative, preferably pimobendan, or a substituted oxicam, preferably meloxicam, or a substituted imidazolinone preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1 H-imidazol-2-one (imepitoïn) or a substituted glucopyranosyl-substituted benzene derivative, preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-[(β-D-glucopyranos-1-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-[(β-D-glucopyranos-1-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline, per kg bodyweight of the animal, even more preferably about 0.3 mg of the pharmaceutically active compound in form of a substituted benzimidazole derivative, preferably pimobendan, or a substituted oxicam, preferably meloxicam, or a substituted imidazolinone preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1 H-imidazol-2-one (imepitoïn) or a substituted glucopyranosyl-substituted benzene derivative, preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-[(β-D-glucopyranos-1-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-[(β-D-glucopyranos-1-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline, per kg bodyweight of the animal. Preferably, two doses are to be administered per day (twice daily administration).

The subject/patient in need of any such treatment mentioned above is a mammal, preferably a companion animal. The term "animal" as used herein includes but is not limited to companion animals such as dogs, cats, guinea pigs, hamsters, horses, cattle, goats, sheep or the like. Preferably, the subject in need of such treatment is a dog, horse or cat, most preferably a cat or dog.

The liquid aqueous pharmaceutical composition according to the present invention is for use in a method for treating a patient in need of such treatment, preferably selected from among the indications: heart failure (HF), congestive heart failure (CHF), acute CHF, decompensated endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic DCM, hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), and heart failure due to HCM, RCM, DCM and/or UCM.

More preferably, the liquid aqueous pharmaceutical composition according to the present invention is for use in a method for treating a subject in need of such treatment, preferably an animal, in particular a companion animal, even more preferred horse, dog or cat, guinea pig, hamster, cattle, goat, sheep, in particular cat or dog, selected from among the indications: heart diseases, particularly a hypertrophic cardiomyopathy, more particularly heart failure (HF), congestive heart failure (CHF), acute CHF, decompensated endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic DCM, hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), and heart failure due to HCM, RCM, DCM and/or UCM.
The present invention is also directed to the use of a liquid aqueous pharmaceutical composition as above defined for preparing a pharmaceutical composition for the treatment or prevention of diseases in a subject in need of such treatment, preferably selected from among the above indications.

In a preferred embodiment, the liquid aqueous pharmaceutical composition as defined above for use in the above mentioned methods is for oral and/or parenteral administration, preferably oral administration.

Also subject of the present invention is a kit of parts that comprises:

a) a liquid aqueous pharmaceutical composition as described above; and

b) a package leaflet including the information that the pharmaceutical composition is to be used for the prevention and/or treatment of a heart disease, preferably heart failure and/or hypertrophic cardiomyopathy, in a subject in need of such prevention or treatment.

According to a further aspect, the present invention also relates to a manufacturing process for the production of any of the liquid aqueous pharmaceutical compositions as described herein. A preferable process for producing the pharmaceutical composition comprises the steps of:

- adding at least one pharmaceutically active compound, one or more etherified cyclodextrin derivatives, at least one water-soluble polymer and optionally one or more antioxidants to water and mixing under stirring,
- adjusting the pH value using a pH adjustment agent.

In this regard it should be taken into account that the process of manufacturing may be arbitrarily selected from manufacturing processes of liquid pharmaceutical compositions known from prior art.

In the following a representative process is described which should not be construed to limit the present invention.

At first, the one or more etherified cyclodextrin derivatives and the at least one water-soluble polymer are added to the most part of the water under stirring thereby obtaining a first liquid mixture. Then, an ultrasonic treatment of such first liquid mixture, preferably under stirring, may be optionally performed. The obtained first liquid mixture is incubated at room temperature, preferably without stirring, for one or more minutes, preferably 10 minutes, and the desired pH value using a pH adjustment agent is adjusted. Afterwards, the at least one pharmaceutically active compound and optionally one or more antioxidants as well as further excipients, if so desired, are added to the first liquid mixture during stirring thereby obtaining a second liquid mixture. Then, an ultrasonic treatment of the second liquid mixture, preferably under stirring, is optionally performed. The obtained second liquid mixture is incubated at room temperature, preferably without stirring, for one or more minutes, preferably 10 minutes, and the desired pH value is adjusted using a pH adjustment agent. Subsequently the remaining water is added to the obtained second liquid mixture under stirring and the pH value is
determined and adjusted, if necessary, using a pH adjustment agent to the desired pH value thereby obtaining the liquid aqueous pharmaceutical composition of the present invention.

The at least one pharmaceutically active compound, one or more etherified cyclodextrin derivatives, at least one water-soluble polymer and one or more antioxidants are those as already described in detail supra. The pH adjustment agent is preferably hydrochloric acid and/or sodium hydroxide.

The amounts used depend from the at least one pharmaceutically active compound used as well as the intended treatment, administration route and the patient to be treated. The person skilled in the art is readily able to select and adjust the required amounts by his general knowledge.

The invention described will now be illustrated by figures. However, it is expressly pointed out that the figures are intended solely as an illustration and should not be regarded as restricting the invention.

BRIEF DESCRIPTION OF THE FIGURES

Further advantages, features, characteristics and aspects of the present invention arise from the figures which show as follows:

Figure 1 is a schematic diagram wherein the solubility of pimobendan is shown as a function of concentration of hydroxypropyl-beta-cyclodextrin and presence of hydroxypropyl methylcellulose (HPMC).

Figure 1 is a schematic diagram wherein the solubility of pimobendan is shown as a function of concentration of hydroxypropyl-beta-cyclodextrin and presence of hydroxypropyl methylcellulose (HPMC). Therefore, in Figure 1 the effect of HPMC on the solubility of pimobendan was illustrated, and also the effect of concentration of hydroxypropyl-beta-cyclodextrin on the pimobendan solubility. A concentration of HPMC of 0.1% (m/V) was used. The pH value was set to 4.5 using hydrochloric acid in all solutions.

In Figure 1 it can be seen that the results confirm that HPMC significantly increases the solubility of pimobendan.

The invention described will now be illustrated by Examples. However, it is expressly pointed out that the Examples and description are intended solely as an illustration and should not be regarded as restricting the invention. In the following the invention shall be illustrated in form of exemplary pharmaceutical compositions. However, the present invention is not limited to the described compositions, but other components, amounts and additives are possible.
EXAMPLES

Example 1
Manufacturing process

In the following Table 1 exemplary pharmaceutical compositions according to the present invention are given in detail:

Table 1: Exemplary pharmaceutical compositions according to the present invention

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Content [g/100 mL]</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimobendan</td>
<td>0.15 – 0.25</td>
<td>Pharmacologically active compound</td>
</tr>
<tr>
<td>Hydroxypropyl-β-cyclodextrin</td>
<td>15 – 35</td>
<td>Etherified cyclodextrin</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>0.05 – 2.5</td>
<td>Water-soluble polymer</td>
</tr>
<tr>
<td>Ascorbic acid and/or</td>
<td>0.05 – 1.0</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>• sodium ascorbate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sodium metabisulfite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• citric acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sodium citrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochloric acid 0.1 M</td>
<td>ad pH 3.1 – 4.0</td>
<td>pH adjustment</td>
</tr>
<tr>
<td>Water</td>
<td>ad 100 mL</td>
<td>Solvent</td>
</tr>
</tbody>
</table>

The production procedure of an exemplary pharmaceutical composition according to the present invention for a single small scale batch (100 mL) with a target pH value of 3.5 in form of a general instruction is as follows:

Weigh hydroxypropyl methylcellulose (HPMC) and hydroxypropyl-β-cyclodextrin into a 100 mL glass bottle and mix.
Add about 90% of the required amount of purified water. Add a stir bar for a magnetic stirrer.
Sonicate for 60 minutes in an ultrasonic bath set to 60°C. Stir occasionally using the magnetic stirrer.
Let incubate at room temperature without stirring for 10 minutes. Adjust pH to 3.80 ± 0.15
Let stand overnight.
Weigh ascorbic acid and pimobendan into a small weighing vessel. Transfer to the glass bottle and mix using the magnetic stirrer.
Sonicate for 60 minutes in an ultrasonic bath set to 50°C. Stir occasionally using the magnetic stirrer.
Let incubate at room temperature without stirring for 10 minutes. Adjust pH to 3.60 ± 0.05
Let stand overnight.
Determine pH and, if necessary, adjust to 3.50 ± 0.05.
Alternatively, the production procedure of an exemplary pharmaceutical composition according to the present invention for a single small scale batch (100 mL) with a target pH value of 3.5 in form of a general instruction is as follows:

Weigh hydroxypropyl methylcellulose (HPMC) and water into a 100 mL beaker and mix until a homogenous solution is obtained. Weigh the hydroxypropyl-β-cyclodextrin into a 100 mL glass bottle. The HPMC solution is then added to the 100 mL glass bottle. The mixture is stirred until a homogenous solution is obtained. Let incubate at room temperature without stirring for about 10 minutes. Weigh the pimobendan into the mixture and mix until homogenized. Weigh the sorbic acid into the mixture and mix until homogenized. Weigh the antioxidant (for example ascorbic acid) into the mixture and mix until a homogenous solution is obtained. Let incubate at room temperature without stirring for about 10 minutes. Adjust pH to 3.5 ± 0.1.
A liquid aqueous pharmaceutical composition comprising
one or more etherified cyclodextrin derivatives;
at least one water-soluble polymer; and
at least one pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble,
wherein preferably the solubility of the at least one pharmaceutically active compound in water in the range of 15 to 25°C is defined as follows:
the at least one pharmaceutically active compound is poorly water-soluble if more than 100 mL of water per gram compound have to be used; it is very poorly water-soluble if more than 1,000 mL of water per gram compound have to be used; and it is water-insoluble if more than 10,000 mL water per gram compound have to be used to solubilise the compound, and preferably with the proviso that corticosteroids, in particular prednisolone and its prodrug prednisolone acetate, and fluoroquinolones, in particular ciprofloxacin, gatifloxacin, moxifloxacin, sitafloxacin, lomefloxacin, grepafloxacin, gemifloxacin, norfloxacin, ofloxacin, levofloxacin and trovafloxacin, are independently from each other excluded as pharmaceutically active compound which is poorly water-soluble, very poorly water-soluble or water-insoluble.

2. The liquid aqueous pharmaceutical composition according to claim 1, wherein the pharmaceutical composition further comprises at least one water-soluble antioxidant.

3. The liquid aqueous pharmaceutical composition according to claim 1 or 2, wherein the one or more etherified cyclodextrin derivatives are selected from the group consisting of: alpha-, beta-, and gamma-cyclodextrin ethers, preferably etherified beta-cyclodextrin having the chemical formula I

![Chemical structure](image)

(I)
in which the residues R are independently from each other hydroxyalkyi groups and part of the residues R may optionally independently from each other be alkyl groups, more preferably hydroxyethyl-beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, dihydroxypropyl-beta-cyclodextrin, and most preferably hydroxypropyl-beta-cyclodextrin.
4. The liquid aqueous pharmaceutical composition according to any of claims 1 to 3, wherein the water-soluble polymer has a molar mass of 5,000 to 500,000 g/mol, preferably 10,000 to 300,000 g/mol, even more preferred 15,000 to 200,000 g/mol, even more preferred 20,000 to 200,000 g/mol.

5. The liquid aqueous pharmaceutical composition according to any of claims 1 to 4, wherein the at least one water-soluble polymer is selected from hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, carboxymethylcellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, ethylcellulose, methylcellulose, polyvinylpyrrolidone, polyvinylacetate as well as combinations or copolymers thereof, preferably hydroxypropyl methylcellulose (hypromellose).

6. The liquid aqueous pharmaceutical composition according to any of claims 2 to 5, wherein the at least one water-soluble antioxidant is selected from the group consisting of ascorbic acid or pharmaceutically acceptable salts thereof, particularly sodium ascorbate; citric acid (anhydrous and/or monohydrate) or pharmaceutically acceptable salts thereof, particularly sodium citrate; erythorbic acid; fumaric acid; malic acid; monothioglycerol; phosphoric acid; sodium metabisulfite; potassium metabisulfite; propionic acid; sodium bisulfite; sodium sulfite; resveratrol; butylhydroxyanisol; gallate derivatives, particularly propylgallate, or combinations thereof, preferably ascorbic acid or pharmaceutically acceptable salts thereof, citric acid (anhydrous and/or monohydrate) or pharmaceutically acceptable salts thereof, sodium metabisulfite, or potassium metabisulfite.

7. The liquid aqueous pharmaceutical composition according to any of claims 1 to 6, wherein the at least one pharmaceutically active compound is selected from

(i) benzimidazole derivatives, preferably substituted benzimidazole derivatives, more preferably thiacarbazol, fuberidazol, oxibendazol, parbendazol, cambendazol, mebendazol, fenbendazol, flubendazol, albendazol, oxfendazol, nociodal, astemisol and pimobendan, pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof, most preferably pimobendan and pharmaceutically acceptable salts thereof; or

(ii) oximic derivatives, preferably substituted oximic derivatives, more preferably ampiroxicam, droxicam, lornoxicam, piroxicam, tenoxicam and meloxicam, pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof, most preferably meloxicam and pharmaceutically acceptable salts thereof; or

(iii) imidazolinone derivatives, preferably substituted imidazolinone derivatives, more preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin), pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof, most preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin) and pharmaceutically acceptable salts thereof; or
(iv) glucopyranosyl-substituted benzene derivatives, preferably substituted glucopyranosyl-substituted benzene derivatives, more preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-yl)-benzene, pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof, most preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline.

8. The liquid aqueous pharmaceutical composition according to any of claims 1 to 7, wherein the composition contains the at least one pharmaceutically active compound, preferably benzimidazole derivatives, more preferably substituted benzimidazole derivatives, even more preferably thibendazol, fuberidazol, oxibendazol, parbendazol, cambendazol, mebendazol, fenbendazol, flubendazol, albendazol, oxfendazol, nodocazol, astemisol and pimobendan, pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof, most preferably pimobendan and pharmaceutically acceptable salts thereof, or preferably oxicam derivatives, preferably substituted oxicam derivatives, more preferably ampiroxicam, droxicam, lornoxicam, piroxicam, tenoxicam and meloxicam, pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof, most preferably meloxicam and pharmaceutically acceptable salts thereof; or preferably imidazolinone derivatives, preferably substituted imidazolinone derivatives, more preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin), pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof, most preferably 1-(4-chlorophenyl)-4-(4-morpholinyl)-2,5-dihydro-1H-imidazol-2-one (imepitoin) and pharmaceutically acceptable salts thereof; or preferably glucopyranosyl-substituted benzene derivatives, preferably substituted glucopyranosyl-substituted benzene derivatives, more preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-yl)-benzene, pharmaceutically acceptable salts, derivatives, metabolites or pro-drugs thereof, most preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-yl)-benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-yl)-benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline, in the range of from 0.01 g/100 mL to 1 g/100 mL, more preferably from 0.05 g/100 mL to 0.5 g/100 mL, most preferably from 0.1 g/100 mL to 0.25 g/100 mL.

9. The liquid aqueous pharmaceutical composition according to any of claims 1 to 8, wherein the composition contains the at least one water-soluble polymer in the range of from 0.01 g/100 mL to 0.75 g/100 mL more preferably from 0.02 g/100 mL to 0.50 g/100 mL, most preferably from 0.05 g/100 mL to 0.30 g/100 mL.

10. The liquid aqueous pharmaceutical composition according to any of claims 2 to 9, comprising
a) at least one pharmaceutically active compound in the form of a substituted benzimidazole or a pharmaceutically acceptable salt thereof, preferably thiamazole, fuberidazol, oxibendazol, parbendazol, cambendazol, mebendazol, fenbendazol, flubendazol, albendazol, oxendazol, nocardazol, astemizol or pimobendan, or pharmaceutically acceptable salts thereof, more preferably pimobendan or a pharmaceutically acceptable salt thereof; or in the form of a substituted oximic or a pharmaceutically acceptable salt thereof, preferably amproxicam, dromicam, lornoxicam, piroxicam, tenoxicam and meloxicam, or pharmaceutical acceptable salts thereof, more preferably meloxicam or a pharmaceutically acceptable salt thereof; or in the form of a substituted imidazoline or a pharmaceutically acceptable salt thereof, preferably 1-(4-chlorophenyl)-4-(4-morpholiny1)-2,5-dihydro-1H-imidazol-2-one (imepitol) or a pharmaceutically acceptable salt thereof; or in the form of a substituted glucopyranosyl-substituted benzene derivative or a pharmaceutically acceptable salt thereof, preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)benzene, or pharmaceutical acceptable salts thereof, more preferably 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline;

b) one or more etherified cyclodextrin derivatives in the form of etherified beta-cyclodextrin, preferably hydroxyethyl-beta-cyclodextrin, hydroxypyrrol-beta-cyclodextrin, dihydroxypyrrol-beta-cyclodextrin, more preferably hydroxypropyl-beta-cyclodextrin (HPpCD);

c) at least one water-soluble polymer with a molar mass of 5,000 to 500,000 g/mol, preferably 10,000 to 300,000 g/mol, even more preferably 15,000 to 200,000 g/mol, preferably hydroxypropyl methylcellulose, hydroxypropyl cellulose, or methylcellulose, more preferably hydroxypropyl methylcellulose (hypromellose); and

d) optionally at least one water-soluble antioxidant, preferably ascorbic acid or a pharmaceutically acceptable salt thereof; citric acid (anhydrous and/or monohydrate) or a pharmaceutically acceptable salt thereof; sodium metabisulfite, potassium metabisulfite or resveratrol.

11. The liquid aqueous pharmaceutical composition according to any of claims 2 to 10, wherein the composition comprises:

a) 0.1 g/1 00 mL to 0.25 g/1 00 mL pimobendan or a pharmaceutically acceptable salt thereof; or meloxicam or a pharmaceutically acceptable salt thereof; or 1-(4-chlorophenyl)-4-(4-morpholiny1)-2,5-dihydro-1H-imidazol-2-one (imepitol) or a pharmaceutically acceptable salt thereof; or 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)benzene, or any pharmaceutically acceptable form and/or salt thereof, wherein the pharmaceutically acceptable form preferably is a crystalline complex between 1-cyano-2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)benzene and one or more amino acids, preferably wherein the one or more amino acids is proline, more preferably L-proline;
b) 20 g/100 mL to 35 g/100 mL of a hydroxypropyl-beta-cyclodextrin;
c) 0.05 g/100 mL to 0.30 g/100 mL of hydroxypropyl methylcellulose (hypromellose);
d) 0.3 g/100 mL to 1.0 g/100 mL of an antioxidant, preferably ascorbic acid or a pharmaceutically acceptable salt thereof.

12. The liquid pharmaceutical composition according to any of claims 1 to 11, wherein the pH of the composition is between 2 to 10, preferably 3 to 10, more preferably 3 to 8, more preferably 3 to 7, more preferably 2.5 to 5, even more preferably 3 to 5, even more preferably 3.4 to 5 and most preferably 3.4 to 4.

13. The liquid aqueous pharmaceutical composition according to any of claims 1 to 12, wherein the composition is for oral and/or parenteral administration, preferably oral administration.

14. The liquid aqueous pharmaceutical composition according to any of claims 1 to 13 for use in a method for treating a subject in need of such treatment, preferably an animal, in particular a companion animal, even more preferred horse, dog or cat, guinea pig, hamster, cattle, goat, sheep, in particular cat or dog, selected from among the indications: heart diseases, particularly a hypertrophic cardiomyopathy, more particularly heart failure (HF), congestive heart failure (CHF), acute CHF, decompensated endocardiosis (DCE), dilated cardiomyopathy (DCM), asymptomatic (occult) CHF, asymptomatic DCM, hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), and heart failure due to HCM, RCM, DCM and/or UCM.

15. A process for producing the pharmaceutical composition according to any of the claims 1 to 13, comprising the steps
- adding at least one pharmaceutically active compound, one or more etherified cyclodextrin derivatives, at least one water-soluble polymer and optionally one or more antioxidants to water and mixing under stirring,
- adjusting the pH value using a pH adjustment agent.

16. A kit of parts that comprises:
   a) a liquid aqueous pharmaceutical composition according to any of claims 1 to 13; and
   b) a package leaflet including the information that the pharmaceutical composition is to be used for the prevention and/or treatment of a heart disease, preferably heart failure and/or hypertrophic cardiomyopathy, in a subject in need of such prevention or treatment.
INTERNATIONAL SEARCH REPORT

PCT/EP2014/065203

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K9/08 A61K47/40

ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>claims 1-22 examples</td>
<td>1-16</td>
</tr>
<tr>
<td>X</td>
<td>WO 2004/089418 AL (DSM IP ASSETS BV [NL]; BABU MANOJ MAZHUVAUCHERI [US]; TAPAN NI RANJAN) 21 October 2004 (2004-10-21)</td>
<td>1, 2, 4-6, 9, 12-16</td>
</tr>
<tr>
<td>Y</td>
<td>examples cl aims</td>
<td>1-16</td>
</tr>
<tr>
<td>Y</td>
<td>EP 1 920 785 AL (BOEHRINGER INGELHEIM VETMED [DE]) 14 May 2008 (2008-05-14)</td>
<td>1-16</td>
</tr>
</tbody>
</table>

[ ] Further documents are listed in the continuation of Box C.  [ ] See patent family annex.

* Special categories of cited documents:
   *A* document defining the general state of the art which is not considered to be of particular relevance
   *E* earlier application or patent but published on or after the international filing date
   *L* document which may throw doubts on priority claim(s) on which is cited to establish the publication date of another citation or other special reason (as specified)
   *O* document referring to an oral disclosure, use, exhibition or other means
   *P* document published prior to the international filing date but later than the priority date claimed
   *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
   *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
   *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
   *A* document member of the same patent family

Date of the actual completion of the international search: 7 August 2014

Date of mailing of the international search report: 14/08/2014

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

Authorized officer:
Schul e, Stefani e
### DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>BASSANI V L ET AL: &quot;ENHANCED WATER-SOLUBILITY OF ALBENDAZOLE BY HYDROXYPROPYL-ß-CYCLODEXTRIN COMPLEXATION&quot;, JOURNAL OF INCLUSION PHENOMENA AND MOLECULAR RECOGNITION IN CHEMISTRY, KLUWER, DORDRECHT, NL, vol. 25, no. 1-3, 1 March 1996 (1996-03-01), pages 149-152, XP008076331, ISSN: 0923-0750, DOI: 10.1007/BF01041557, the whole document</td>
<td>1-16</td>
</tr>
<tr>
<td>Y</td>
<td>PIEL ET AL: &quot;DEVELOPMENT OF A PARENTERAL AND AN ORAL FORMULATION OF ALBENDAZOLE WITH CYCLODEXTRINS&quot;, SCIENCES TECHNIQUES ET PRATIQUES STP PHARMA PRATIQUES, PARIS, FR, vol. 9, no. 3, 1 January 1999 (1999-01-01), pages 257-260, XP008076739, ISSN: 1157-1497, the whole document</td>
<td>1-16</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>US 2004152664 A1</td>
<td>05-08-2004</td>
<td>US 2004152664 A1</td>
</tr>
<tr>
<td>WO 2005072745 A2</td>
<td>11-08-2005</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2006523687 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA05011115 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2005085446 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2004089418 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2007316712 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR PI0718541 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2668733 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL 2007003201 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 101534864 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2089060 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2010508372 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20090084925 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 577067 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 200829571 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2008207629 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200902085 A1</td>
</tr>
</tbody>
</table>