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(54) Title: MODIFIED RELEASE PHARMACEUTICAL FORMULATIONS COMPRISING DEFERIPRONE

(57) Abstract: The invention is directed to pharmaceutical compositions for oral administration in form of coated tablets that exhibit delayed release properties when administered as either whole or half tablets. In particular, the invention is directed to delayed release tablets comprising deferiprone, said tablets being suitable for twice daily oral administration. The invention is also directed to methods of making and using the same.

MODIFIED RELEASE PHARMACEUTICAL FORMULATIONS COMPRISING DEFERIPRONE

FIELD OF INVENTION

The invention relates to pharmaceutical formulations comprising the iron chelator deferiprone.

In particular the invention is directed to a modified release formulation suitable for twice-a-day oral administration for the treatment of iron overload which occurs in patients suffering for example, from thalassemia, sickle cell disease, hemochromatosis, and myelodysplasia.

BACKGROUND OF THE INVENTION

Deferiprone, also known as 3-hydroxy- 1,2-dimethylpyridin-4-one, is a bidentate ligand which binds to iron in a 3:1 molar ratio.

It is used in the treatment of generalized iron overload, particularly in conditions where frequent blood transfusions lead to iron overload including, e.g., thalassemia and Sickle Cell Disease (SCD).

The introduction of deferiprone in the current therapy has represented an important advancement as it Liver Iron Concentration (LIC) and cardiac iron overload.

In particular, *Maggio A* et al. Blood Cells Mol Dis. 2002, 28(2):196–198) and *Galanello R* et al. Haematologica. 2006, 91(9):1241–1243 suggested that deferiprone monotherapy seems to be superior to deferoxamine monotherapy in improving myocardial siderosis and cardiac function.

With regards to safety, the most frequent adverse events are gastrointestinal disorders due to gastrointestinal irritation. Such discomfort could cause patients to refrain from taking the medication, leading to a worsening of their condition. Other observed adverse events are musculoskeletal disorders (arthralgia), Alanine Aminotransferase (ALT) increase, agranulocytosis and neutropenia.

Agranulocytosis seems to be an idiosyncratic response and it is more frequent in the first year of treatment. The incidence of neutropenia and agranulocytosis is stable and seems to be not related with dose (Hider RC et al N Engl J Med. 2018;379:2140–2150).

Deferiprone is endowed with a long half-life of 2-3 hour) but with an unpleasant bitter taste.

Said drug is sold as Immediate Release (IR) 500 mg and 1000 mg tablets, as well as a 100 mg/ml liquid formulation, generally, under the trade name Ferriprox®.

In view of its pharmacological and ADME profile, and in order to improve the compliances of the patients, recently, deferiprone has also been launched commercially as 1000 mg Delayed Release (DR) tablets for oral administration.

Said tablets are suitable for a twice daily administration being bioequivalent in the steady state to the same daily dose of an immediate release tablet administered three times daily.

The commercial tablets are also debossed with a score line, to make it easy for the patient to break the tablets into two approximately equal parts for dosing flexibility.

The composition of the DR tablets has been disclosed in WO 2019/082128, and it comprises: (a) a core comprising the active pharmaceutical ingredient and an enteric polymer with pH-dependent solubility, and (b) an enteric coating.

In fact, the oral pharmaceutical dosage forms containing deferiprone, due to its potential for irritation and damage to the gastric mucosa and the relatively high solubility in an acid environment, shall be provided with an enteric coating (e.g. polymeric films with solubility at pH> 5) in order to avoid, or at least reduce, the release of the active principle during the permanence of the unit in the stomach, avoiding reaching plasma concentrations responsible for possible systemic adverse reactions.

To sustain the release, in the case of the marketed deferiprone product, as enteric polymer in the tablet core, hydroxypropyl methylcellulose acetate succinate (HPMC-AS) is used.

However, HPMC-AS has a pH-dependent solubility.

This could lead to a release influenced by the external environment that the unit has to face during the transit along the regions in which the release of the active principle takes place, that are characterized by physiological fluids having different pH's, and hence less predictable being at the mercy of random microenvironmental variation of the pH.

Therefore, it would be advantageous to provide a tablet suitable for twice a day oral administration, with improved properties in terms of reproducibility of the expected release profiles.

Some documents of the prior art disclose deferiprone formulations comprising *inter alia* hydroxypropylmethyl cellulose polymer as excipient (Aguilar-De-Levya A et al Pharm Dev Tech 2014, 19,728-734; Kaul D et al J Drug Dev Ind Pharm 1992, 18, 1023-1035; US 2006/122273; CN 106983746). However, they are silent about the problem of improving the reproducibility of the release profile.

The technical solution is provided by the present invention.

SUMMARY OF THE INVENTION

The invention provides a pharmaceutical formulation in form of modified release enteric coated tablets suitable for twice-a-day oral administration, wherein the core of the tablet comprises: a) deferiprone in an amount comprised between 85.0 to 95.0%, b) a hydroxyproylmethylcellulose polymer having a viscosity of 100 cP alone or in mixture thereof

with a hydroxyproylmethylcellulose polymer having a viscosity of 4000 cP as a modifying release agent in an amount comprised between 4.0 and 10.0%, c) a lubricant and/or glidant in an amount from 0.2 to 2.0%, and d) other suitable pharmaceutically acceptable excipients in an amount comprised between from 0 to 5%, all the amounts calculated by weight on the total weight of the formulation.

Other suitable pharmaceutically acceptable excipients may belong to the classes of pH adjusting agents, and bulking agents.

Therefore, in a second aspect the invention provides a process for the preparation of a coated deferiprone tablet as described above, which process comprises the following steps:

(i) mixing deferiprone with the modifying release agent and the other pharmaceutically acceptable excipients, if present, to form a mixture;

(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator followed by drying and screening to produce a granulate;

(iii) mixing the granulate obtained in step (ii) with the lubricant and/or glidant excipient to form a mixture;

(iv) compressing the mixture obtained in step (iii) to form a tablet; and

(v) coating the tablet.

In an alternative aspect, the process comprises the steps of:

(i) mixing deferiprone with the modifying release agent and the other pharmaceutically acceptable excipients, if present, to form a mixture;

(ii) adding the lubricant and/or glidant excipient and further mixing;

(iii) directly compressing the mixture obtained in step (ii) to form a tablet; and

(iv) coating the tablet.

In a third aspect, the invention is directed to the claimed pharmaceutical composition for use for the treatment of diseases which cause an overload of iron, or for the prevention and/or treatment of diseases which are caused by an overload of iron.

In a fourth aspect, the invention is directed to the claimed pharmaceutical composition in the manufacture of a medicament for the treatment of diseases which cause an overload of iron, or for the prevention and/or treatment of diseases which are caused by an overload of iron.

In a fifth aspect, the invention refers to a method for the treatment of diseases which cause an overload of iron, or for the prevention and/or treatment of diseases which are caused by an overload of iron thereof in a patient in a need thereof, said method comprising orally administering the claimed pharmaceutical composition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 - Dissolution tests of HPMC formulations carried out in 900 ml of pH 6.8 medium, basket (apparatus 1) having rotational speed of 100 rpm. The line with a triangular indicator is referred to as the commercial product.

Figure 2- Dissolution tests of HPMC formulations carried out in 900 ml of pH 4.5 medium, paddle (apparatus 2) having rotational speed of 50 rpm. The line with a triangular indicator is referred to as the commercial product.

Figure 3 -Dissolution tests of HPMC formulations carried out in 900 ml of pH 1.2 medium (120 min) and then pH 6.8 medium, basket (apparatus 1) having rotational speed of 100 rpm. The line with a triangular indicator is referred to as the commercial product

Figure 4 - Dissolution tests of HPMC formulations carried out in 900 ml of pH 1.2 medium (120 min) and then pH 6.8 medium, basket (apparatus 1) having rotational speed of 100 rpm. The line with a triangular indicator is referred to as the commercial product

Figure 5- Dissolution tests of HPMC formulations carried out in 900 ml of pH 1.2 medium (120 min) and then pH 6.8 medium, basket (apparatus 1) having rotational speed of 100 rpm. The line with a triangular indicator is referred to as the commercial product

Figure 6 - Dissolution tests of the half-coated tablets in 900 ml of pH 1.2 medium (120 min) and then pH 6.8 medium, basket (apparatus 1) having rotational speed of 100 rpm. The line with a triangular indicator is referred to as the commercial product

DEFINITIONS

As used herein, the indefinite articles "a" or "an" should be understood to refer to "one or more" of any recited or enumerated component. For example, "a tablet" refers to one or more tablets.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

When the term "about" is used in conjunction with a numerical value or range, it modifies that value or range by extending the boundaries above and below the numerical values set forth. The term "about" is used herein to modify a numerical value above and below the stated value by a variance of 10 percent, up or down (higher or lower), i.e., ± 10%, unless a different variance is indicated (e.g., ± 30%, ± 20%, ± 5%, ± 1%, etc.).

Wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of and/or "consisting essentially of are also provided. To the extent that the term "includes" or "including" is used in the specification or the claims, it is

intended to be inclusive in a manner similar to the term "comprising" as that term is interpreted when employed as a transitional word in a claim.

As used herein, the term "active ingredient" or "active pharmaceutical ingredient" (API) or “drug” are used as synonymous and mean any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals.

The terms "iron overload" or "overload of iron" are used interchangeably herein and refer to medical conditions where the body contains or stores too much (or "excess") iron. An example is transfusional iron overload, where the excess iron is introduced by one or more blood transfusions.

In the present context, the term "hydrophilic" describes that something 'likes water', i.e. a hydrophilic molecule or portion of a molecule is one that typically is electrically polarized and capable of forming hydrogen bonds with water molecules, enabling it dissolve more readily in water than in oil or other "non-polar" solvents.

Conversely, the term "hydrophobic" denotes a compound tending to be electrically neutral and non-polar, and thus preferring other neutral and nonpolar solvents or molecular environments.

For “pH dependent solubility” it is meant a substance having different solubilities at different pHs. These pH-dependent solubility differences lead to pH-dependent dissolution profiles.

The expression “insoluble or poorly water soluble” refers to a substance having a solubility in water as defined in the European Pharmacopoeia Ed. 4th, 2003, page 2891.

"Core" or "tablet core" as used herein comprises an active ingredient, e.g., deferiprone, and one or more excipients compressed into an uncoated tablet. The core can be coated with various coatings, including an enteric coating.

In the present context, the terms "controlled release", “prolonged release”, "modified release" and “delayed release” are intended to be equivalent terms covering any type of release of deferiprone from a composition of the invention that is appropriate to obtain a specific therapeutic or prophylactic response after administration to a subject". The terms refer to protecting an active ingredient, e.g., deferiprone, from rapid release at acidic pH, e.g., in the stomach, while enabling the active ingredient to be released at a higher rate at a higher pH, e.g., in the intestines. In some aspects, DR will be understood to mean that, when tested in USP apparatus 2 at 75 rpm, the extent of dissolution will be around 20 ± 5% at 1 hour in 0.1N HC1, and the rate of dissolution will be substantially higher (e.g., over 30%, e.g. over 40%, in 1 hour) in phosphate buffer with pH 6.8 than the rate of dissolution in 0. 1N HC1.

"Disintegrant" as used herein refers to an excipient that is insoluble in water, but swells when wetted to cause a tablet to disintegrate.

"Dissolution" as used herein refers to the process by which a solute forms a solution in a solvent.

"Enteric coat" or "enteric coating" as used herein refers to a coating comprising an enteric polymer. An enteric coating can serve to prevent or delay a tablet's dissolution or disintegration in a gastric environment.

For “burst effect” it is meant the initial rapid release before the release rate reaches a stable profile, occurring immediately upon at the change of pH in the release medium.

"Enteric coated tablet" means a tablet having a core comprising an active ingredient, which is coated with an enteric coating.

"Enteric polymer" as used herein is understood to mean a polymer that is relatively insoluble at the acidic pH of the fasted stomach (e.g., about pH 1 to about pH 4), but soluble at higher pH (e.g., about pH 4.5 to about pH 8), which corresponds to the pH in the small intestine or thereafter, particularly in the duodenum or ileum.

The terms “fillers”, “diluents” and “bulking agents” are used as synonymous.

With the term “bioequivalence" it is meant the absence of a significant difference between the bioavailability, i.e., the extent of absorption and peak concentration, between two pharmaceutical drug products (e.g., a test product and a reference product) over the course of a period of time, at the same dose and under the same conditions,

The determination of whether or not a test product is bioequivalent to a reference product is determined by performing a study, referred to as a bioequivalence or comparative bioavailability study, in a group of subjects, usually about 18-36 subjects or more, under controlled conditions.

The study can be done in a "crossover" design, which means that the study is done in 2 or more phases, usually at least a week apart, depending in part on the half-life of the drug. In the first phase, half the subjects are randomly assigned to ingest the test product first and the other half ingest the reference product first. In the second phase, each subject ingests the alternate product.

In each phase, blood samples are drawn from each subject, on a predetermined schedule after ingestion of the test product. The blood samples are then analyzed to determine serum concentrations of the drug (test product, e.g., deferiprone) at each time point. For example, drugs are bioequivalent if they enter circulation at the same rate when given in similar doses under similar conditions. Parameters often used in bioequivalence studies are t_{max}, C_{max}, C_{min}, $AUC_{0\text{-}infinity}$, $AUC_{0\text{-}t}$.

In the present context "t_{max}" denotes the time to reach the maximal plasma concentration (C_{max}) after administration; $AUC_{0\text{-}infinity}$ denotes the area under the plasma concentration versus time curve from time 0 to infinity; $AUC_{0\text{-}t}$ denotes the area under the plasma concentration versus time curve from time 0 to time t; W50 denotes the time where the plasma concentration is 50% or

more of C_{max}; W75 denotes the time where the plasma concentration is 75% or more of C_{max}; and MRT denotes mean residence time for tacrolimus.

"Fasted state" as used herein refers to abstinence from food for a defined period of time after a meal (typically, at least several hours, e.g., 4 or 6 hours, after a meal).

"Fed state" as used herein refers to administration with a meal or soon after a meal (e.g., within about 1 hour).

The term "chemical stable" refers to stability of the active agent in the formulation, wherein changes in the drug assay values and/or impurities content are equal to or lesser than 5%, preferably lesser than 3%, during storage at 25^{0}C and 60% relative humidity (RH), or 40^{o}C and 75% RH, for at least 1 month.

The term "vitro–in vivo correlation (IVIVC) refers an in vitro dissolution test that is predictive of the in vivo performance of the drug product.

"Gastric distress" as used herein refers to discomfort of the gastrointestinal (GI) tract, e.g., one or more of pain, cramping, bloating, nausea, indigestion, heartburn, and gas.

"Half tablet" as used herein means either of the two parts of a tablet obtained by splitting the tablet into two parts of equal or approximately equal weight. In some embodiments, a half tablet is from about 40% to about 60% by weight of the whole tablet from which the half was derived. In some aspects, the approximately equal weight of each half tablet is about 45-55% of the total weight of the whole tablet.

"Percent" or "%" as used herein refers to weight percentage (w/w) unless otherwise specified.

"Scored tablet" as used herein refers to a tablet that is debossed with one or more lines, also known as a "score line", to facilitate splitting the tablet, e.g., to enable administration of a half tablet. In some aspects, the tablet can be scored with two, three, four, or more score lines.

"Tablet" as used herein refers a solid oral pharmaceutical dosage form. In some embodiments, the tablet is a compressed tablet.

"Whole tablet" means a complete tablet, i.e., not broken or split into parts.

In the present context, viscosity is expressed in centipoise (1 cP = 0.01 P) which is more commonly used than the poise itself. The analogous unit in the International System of Units is the pascal-second (Pa·s). 1 cP corresponds to 1 mPa·s.

Terms such as "treating" or "treatment" or "to treat" or "ameliorating" or "alleviating" or "to alleviate" can refer to both 1) therapeutic measures that cure, slow down, lessen symptoms of, reverse, and/or halt progression of a diagnosed pathologic condition or disorder and 2) prophylactic or preventative measures that prevent, reduce the incidence of, reduce the risk of, and/or slow the development of a targeted pathologic condition or disorder. Thus, those in need of

treatment include those who already have the disorder; those prone to developing the disorder; and those in whom the disorder is to be prevented. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those who already have the condition or disorder as well as those prone to developing the condition or disorder or those in which the condition or disorder is to be prevented or incidence reduced.

By "subject" or "individual" or "patient," is meant any human subject, for whom diagnosis, prognosis, treatment, or therapy is desired.

By "therapeutically effective dose or amount" or "effective amount" is intended an amount of active pharmaceutical ingredient, e.g., deferiprone, that when administered brings about a positive therapeutic response with respect to treatment of or reducing the risk of a disease in a subject to be treated.

It will be understood that the deferiprone DR tablets used as the "reference" or "reference product" herein are Ferriprox® tablets (1000 mg) as approved by FDA and sold in the United States.

DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns pharmaceutical formulations for the prevention and/or treatment of diseases which are caused by an excess of iron, especially compositions providing modified release of the active ingredient.

The active ingredient in the inventive formulations is deferiprone. However, within the scope of the present invention is deferiprone in any physical form (crystals, amorphous powder, any possible polymorphs, any possible solvate. Included are also pharmaceutically acceptable salts and/or solvates thereof. Preferably, deferiprone is used as a base in its anhydrous form.

According to a first embodiment, the invention is directed to a pharmaceutical formulation in form of modified release enteric coated tablets suitable for twice-a-day oral administration, wherein the core of the tablet comprises; a) deferiprone in an amount comprised between 85.0 to 95.0%, b) a hydroxyproylmethylcellulose polymer having a viscosity of 100 cP alone or in mixture thereof with a hydroxyproylmethylcellulose polymer having a viscosity of 4000 cP as a modifying release agent in an amount comprised between 4.0 and 10.0%, c) a lubricant and/or glidant in an amount from 0.2 to 2.0% and d) other suitable pharmaceutically acceptable excipients in an

amount comprised between from 0 to 5%, all the amounts calculated by weight on the total weight of the formulation.

It has been found that, within the limits of the statistical significance, an in vitro release similar to commercial deferiprone DR tablets could be obtained with hydrophilic polymers as modifying release agent.

In particular, the tablet-core of the pharmaceutical dosage form object of the present invention has the advantage of having a composition based on excipients with non-pH-dependent solubility, and hence they are not directly interfering with the release of deferiprone at the different pH values of the gastrointestinal tract.

This substantiates an undeniable improvement in terms of reproducibility of the expected release profiles.

A further surprising advantage linked to the use of these polymers will become evident from the following description.

Advantageously hydroxyproylmethylcellulose polymer (HPMC) Methocel® K100LV which is a thickener with low substitution, yielding a viscosity of about 100 cP at a 2% addition in water at 20°C.

Said polymer could be used in combination with hydroxyproylmethylcellulose polymer (HPMC) Methocel®K4M which is a medium molecular weight hydroxypropyl methylcellulose (HPMC) thickener. It will yield a viscosity of about 4,000 cP at a 2% addition in water at 20°C.

They are both commercially available from DuPont (Delaware, USA) or from Colorcon Inc (California, USA).

Advantageously, is modifying release agent in present in an amount comprised between 4.0 and 10.0%, preferably between 7 and 8% by weight.

In a preferred embodiment, Methocel® K100LV could be used alone in an amount of 7.5%, while in another preferred embodiment, a mixture of Methocel® K100LV and Methocel® K4M in an amount of 5% by weight could be utilised, preferably wherein the two polymers are in the amount of 2% and 3.0% by weight, respectively (ratio 40:60 w/w).

Deferiprone may cause gastric irritation if released in the fasted stomach, and some degradation by acidic hydrolysis.

Therefore, the tablets of the invention will be provided by an enteric coating, which serves both to delay dissolution of deferiprone and to avoid dissolution in the stomach, in particular in fasted patient, and a diluent such as water, ethanol, propylene glycol or mixture thereof.

Due to the coating, the tablets as per the invention are formulated to have a neglectable dissolution in the fasted stomach but will more rapidly dissolve in the intestines.

Suitable enteric polymers for the enteric coating include, e.g., hydroxyxypropyl methylcellulose acetate succinate (also referred to as hypromellose acetate succinate or HPMCAS), HPMC phthalate (also referred to as hypromellose phthalate), polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, methacrylic acid copolymers (e.g., methacrylic acid copolymer Type C Dispersion 30%), derivatives thereof, and any combination thereof.

In some embodiments, the preferred enteric polymers in the enteric coating are HPMC acetate succinate and methacrylic acid copolymers, e.g., methacrylic acid copolymer type C, in aqueous dispersion.

In some embodiments, the enteric polymer in the coating is about 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2%, 2.5%, 3%, 3.5%, or 4%, by weight of the tablet, or a range between any two of the preceding values, e.g., 0.5-1%, 0.5-2%, 0.5-3%, 0.5-4%, 0.6-1%, 0.6-2%, 0.6-3%, 0.6-4%, 0.7-1%, 0.7-2%, 0.7-3%, 0.7-4%, 1-1.5%, 1.1-1.7%, 1-2%, 1.5-2%, 1-3%, 1-3.5%, or 1-4%, by weight of the tablet. In other embodiments, the enteric polymer in the coating is about 2.0% or about 3.0% by weight of the tablet.

It has been found that, for the tablets of the present invention, a thicker coating (2-3% by weight) would be preferable to obtain a release profile similar to the reference product, whose coating is about 1-4-1.5% weight.

In some embodiments, the enteric coating comprises, in addition to the enteric polymer, other excipients, including for example, a plasticizer, a lubricant or anti-tack agent such as talc, an opacifier, a colorant, a diluent, or any combination thereof.

Advantageously, the enteric coating plasticizer is diethyl phthalate, citrate esters such as triethyl citrate, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutyl sebecate, castor oil, or any combination thereof.

In other embodiments, the enteric coating may further comprise a diluent e.g., lactose, sucrose, fructose, mannitol, and the like, or combinations thereof. In some embodiments, the enteric coating comprises talc as the lubricant or anti-tack agent.

In a preferred embodiment the enteric coating comprises a methacrylic acid copolymer dispersion, preferably an ethacrylic acid - ethyl acrylate copolymer (1:1) dispersion in water and propylene glycol. The ethacrylic acid - ethyl acrylate copolymer (1:1) is known as Eudragit® L30-D55 and is commercially available from Evonik Operations GmbH, Essen Germany.

In an alternative preferred embodiment, the enteric coating comprises methacrylic acid-methacrylate copolymer (1:1) in an alcoholic solution, preferably in concentration of 5-15% w/w, more preferably 10% w/w, with triethyl citrate as plasticizer, preferably in a concentration in relation to the polymer of 2-5% w/w, more preferably of 3% w/w.

Methacrylic acid- methacrylate copolymer (1:1) is known as Eudragit® L100 (dissolution pH around 6.8) and is commercially available, for example from Sigma-Aldrich (Missouri, USA).

The coating shall be performed according to methods known to the skilled person, typically for a time comprised 15 and 20 minutes.

In some embodiments, the core may comprise one or more pharmaceutically acceptable excipients such as bulking agents and/or basic excipient.

Advantageously, the buking agent that when present is utilizes to increase tablet hardness, could be selected from the group consisting of calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, alpha-lactose monohydrate.

Advantageously the basic excipient could be selected from the group consisting of metal oxides, metal hydroxides, basic salts of weak acids, and a combination thereof. Metal oxides include, but are not limited to, magnesium oxide, aluminum oxide, and zinc oxide. Metal hydroxides include, but are not limited to, sodium hydroxide, potassium hydroxide, magnesium hydroxide, and calcium hydroxide. Basic salts of weak acids include, but are not limited to, sodium or potassium salts of carbonate, bicarbonate, acetate, and citrate. In certain embodiments, the basic excipient is magnesium oxide, meglumine or a combination thereof. In some embodiments, the basic excipient is magnesium oxide.

The tablets shall also comprise a lubricant to prevent sticking to the tooling during compression into tablets), and/or a glidant to improve flow in the tableting process), or combinations thereof.

Advantageously, the lubricant is selected from the group consisting of, but not limited to, magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, or combination thereof.

Preferably the lubricant is magnesium stearate.

Advantageously, the glidant is selected from the group consisting of, but not limited to, colloidal silicon dioxide, starch and talc, preferably colloidal silicon dioxide or any combination thereof.

In a preferred embodiment, the core of tablet comprises a mixture of magnesium stearate and colloidal silicon dioxide.

As an exemplary embodiment, the core of said coated formulations comprises:

a) deferiprone in an amount of 91% by weight;

b) Methocel® K100LV in an amount of 7.5% by weight; and

c) a mixture of a lubricant and glidant in an amount of 1.5% by weight.

In another exemplary embodiment, the core of the coated formulation comprises:

a) deferiprone in an amount of 93% by weight:
b) Methocel® K100LV in an amount of 2.0% by weight;
c) Methocel®K4M in an amount of 3.0 by weight;
d) a mixture of a lubricant and glidant in an amount of 2.0% by weight.

Advantageously, the pharmaceutical tablets of the invention are debossed with a score line, to make it easy for the patient to break the tablets into two approximately equal parts to enable administration of half tablets, allowing a dosing flexibility.

Needless-to-say, when the tablet is broken, its surface at the interface is no longer protected by the enteric coating, and some dissolution in the stomach acid could be observed.

On the other hand, as long as said dissolution is around 20% % at acidic pH, or even better below this value, this is considered acceptable.

As a further advantage, as reported in Figure 6, although the release is a little bit higher at low pH than the commercial tablets was observed, the half tablets of the invention, when a change of the pH occurs, do not show any undesired burst effect, and exhibit a smoother release of the active ingredient in the first phase of the dissolution.

In fact, it is well known that transient higher concentrations and hence plasma levels of deferiprone, could be associated with transient increase of liver enzymes and other side effects (Cohen ER et al Br J Haematology, 2000, 108, 305-312).

Advantageously, a tablet of the present disclosure embraces the attributes of an enteric coated tablet without its deficiencies, so that tablets can be halved, to enable fine tuning of the dosing to administer whole tablets, half tablets or any combination thereof. Half tablets of the disclosure substantially resist dissolution in acidic media (0.1 N HC1), representing the fasted stomach contents, as do whole tablets; and, at a higher pH, representing the contents of the small intestine, also exhibit a rate of dissolution similar to whole tablets, but without the undesired burst effect of the reference product on the market.

The release profile of the tablets of the invention has been determined in different dissolution media varying the pH according to the conditions reported in Examples 2 and 3.

Since it has been reported in WO 2019/082128for Ferriprox® tablets, that deferiprone modified release formulations exhibit a good IVIV correlation -, it is contemplated that the in vitro release profile will reflect the in vivo behaviour.

The tablets according to the invention give rise to a dissolution profile at pH 6.8 similar to that of Ferriprox® tablets as approved by FDA and sold in the United States, so it is contemplated

that they will show the same bioavailability at the steady state, making it suitable for a twice a day oral administration.

It is contemplated that said formulation would turn out to be bioequivalent in the steady state, to the immediate release Ferriprox® tablets for three times a day administration, the mean ratio of AUC (over 24 hours) and the mean ratio of C_{max} for the tablets of the invention relative to the immediate release (IR) tablets would be within 80% to 125%.

In other words, in the steady state, the modified release tablets of the present invention when administered twice-a-day would be able to achieve the same maximum peak concentrations (C_{max}) as IR tablets of Ferriprox®, when the IR tablets were given three times a day, and the total amount absorbed (AUC) was the same for both products over a 24-hour period.

The invention also provides a process for the preparation of a coated deferiprone tablet as described above, which process comprises:

i) mixing deferiprone with the modifying release agent and the pharmaceutically acceptable excipients, if present, to form a mixture;

ii) wet-granulating the mixture obtained in step (i) in a high shear granulator followed by drying and screening to produce a granulate;

iii) mixing the granulate obtained in step (ii) with the lubricant and/or glidant excipient to form a mixture;

iv) compressing the mixture obtained in step (iii) to form a tablet;

v) and coating the tablet.

In an alternative embodiment, the process comprises the following steps:

i) mixing deferiprone with the modifying release agent and the pharmaceutically acceptable excipients, if present, to form a mixture;

ii) adding the lubricant and/or glidant excipient and further mixing;

iii) directly compressing the mixture obtained in step (ii) to form a tablet; and

iv) coating the tablet.

Apparatus and conditions for direct compression and/or compression upon granulation are known to the skilled person in the art.

The tablets could be prepared in any suitable weight, but preferably the weight of each single unit would be in the range of 800 to 1500 mg, preferably of 1000 mg to 1200 mg.

For avoidance of doubts, reference is made to the extensive literature on the subject for these and other pharmaceutically acceptable excipients and procedures mentioned herein, see in particular Handbook of Pharmaceutical Excipients, Third Edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and

Lexikon der Hilfsstoffe fi.ir Pharmazie, Kosmetik and angrenzende Gebiete edited by H.P. Fiedler, 4th Edition, Editor Cantar, Aulendorf and earlier editions.

.The present invention provides dosing regimens useful for the therapeutic use of the pharmaceutical formulations described herein.

Typically, the oral daily dose of deferiprone could range from 75 mg/kg to 100 mg/kg.

In some embodiments, the deferiprone composition of the present invention is administered to a subject in need thereof twice daily.

The unit dose of deferiprone the tablets shall be comprised between 500 and 1200 mg, preferably between 600 and 1000 mg, depending on the frequency of administration.

The claimed formulations are useful for the treatment of diseases which cause an overload of iron, or for the prevention and/or treatment of diseases which are caused by an overload of iron

In some embodiments, the subject in need thereof suffers from iron overload due to transfusional iron overload, or due diseases such as thalassemia, myelodysplasia, sickle cell disease or hemochromatosis.

In some embodiments, the subject in need thereof suffers from a neurodegenerative disease (e.g., Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, Friedreich's Ataxia, Pantothenate Kinase Associated Neurodegeneration (PKAN), or neurodegeneration with brain iron accumulation (NBIA).

In some embodiments, the subject in need thereof suffers from iron overload that is transfusional iron overload. In certain aspects, the subject suffers from transfusional iron overload and whose prior chelation therapy is inadequate.

In certain aspects, the subject suffers from transfusion iron overload and has a cardiac MRI T2* of 20 ms or less (e.g., 10 ms).

The invention is illustrated in detail by the following examples.

EXAMPLES

Example 1 – Preparation of the tablets

Tablets were prepared by direct compression using a rotary tablet press (Officine Meccaniche Ronchi, AM8S) equipped with oblong punches having dimensions of 22 mm X 10 mm. Compression force was set at 25 kN in order to have tablets with a crushing strength of about 70 N.

The hydrophilic matrices consisted of mixtures containing 1000 mg of active and different percentages of hypromellose polymer (HPMC) in two viscosity grades (Methocel® K100LV, Methocel® K4M, Colorcon, USA).

Table 1. Formulations of oblong tablets formulated with hydrophilic swellable excipient

MATRIX NAME	API (mg)	Methocel® K100LV (mg)	Methocel® K4M (mg)
M K100LV 5%	1000	50	/
M K4M 5%	1000	/	50
M K100LV 7.5%	1000	75	/
M K100LV 10%	1000	100	/
M K4M 10%	1000	/	100
M K100LV 2% and K4M 3%	1000	20	30
M K100LV 3% and K4M 3%	1000	30	30
M K1000LV 5% and K4M 2.5%	1000	50	25
M K100LV 5% and K4M 3.25%	1000	50	32,5
M K100LV 5% and K4M 4%	1000	50	40

Example 2 - Dissolution test

The spectrum of maximum absorption of the active was acquired in the various fluids in which the release tests will be conducted by means of a spectrophotometer.

Compositions of dissolution media are reported below.

pH 1.2: for 1 L, 3.73 g KCl, 7.07 ml HCl 1 N (deionized water up to volume);

pH 4.5: for 1 L, 6.80 g of KH_2P0_4 (deionized water up to volume);

pH 6.8: for 1 L, 6.80 g KH_2P0_4, 0.90 g of NaOH {deionized water up to volume).

Calibration curves were built for each of the release media both at the wavelength of 276 nm at which a peak of absorbance was recorded, and at 243nm, in which reduced absorption was observed, in order not to exceed the instrument maximum absorbance value.

The release test of the commercial product was analyzed at the wavelength of 276 nm both in pH 4.5 phosphate, and with the pH change mode (HCI 0.1 N for the first 120 minutes and phosphate buffer pH 6.8 for the remainder of the test). At high values of absorbance (over 30% of the release) sampling, dilutions and manual readings was performed.

Release tests were carried out in a dissolution test paddle apparatus (USP type 2) with a rotation speed of 50 rpm and basket apparatus (USP type 1) with a rotation speed of 100 rpm. The tests were always conducted in 900 mL of dissolution medium at 37 °C.

For the experimental formulations, the active ingredient was quantified by spectrophotometry at a wavelength of 243 nm.

The results for the uncoated tablets at pH 6.8 and 4.5 are reported in Figures 1 and 2.

It can be appreciated that, the tablets comprising Methocel® K100LV 7,5% or a mixture of Methocel® K100LV 2% and K4M 3% exhibit the release profile more similar to the reference product.

Example 3 - Gastroresistant coating

Starting from the results of the non-coated tablets, those formulated with

- Methocel® K100LV 7.5%
- Methocel® K100LV 2% and K4M 3%

were selected to be coated with a gastroresistant film.

Tablets were then coated with a different acrylic polymer having a dissolution pH around 6 and formulated in aqueous dispersion:

- Eudragit® L30-D55 aqueous dispersion 60% w/w (containing 25% solids)
- Deionized water 38% w/w
- Propylene glycol 2% w/w

Process parameters were the followings:

- Nozzle: 0.8 mm
- Atomization pressure: 0,8 bar
- Control pressure: 2 bar
- Pattern pressure: 0,5 bar
- Peristaltic pump: 2 rpm
- Air temperature: 57 °C

Coating process lasted for 20 minutes and samples were collected every 5 minutes in order to test different coating amounts by dissolution test. The analysis has been carried out in the same conditions of the previous ones.

The results are reported in Figures 3 and 4.

K100LV 7.5% tablets had more difficulties in getting coated in the first minutes. For this formulation, in fact, the coating process lasted 5 minutes more than for the K100LV 2% K4M 3% tablets; both reached a 2% weight at the end.

As an alternative method of coating, Eudragit® L100 (dissolution pH around 6.8) in an alcoholic solution (10% w/w) with triethyl citrate (3% w/w in relation with the polymer) was applied.

The coating process has been conducted in a small coating pan (opening diameter 10cm) and with the following process parameters:

- Nozzle: 0.8 mm
- Atomization pressure: 0,5 bar
- Control pressure: 0,6 bar
- Pattern pressure: 2 bar
- Peristaltic pump: 2 rpm

- Air temperature: 50 °C

The process has been stopped when the tablets reached a weight gain (wg) of 3%.

Dissolution tests have been conducted at 37 ° in Apparatus 1 (basket) with a rotational speed of 100 rpm in the following dissolution media:

- pH 1.2 (for 1 L, 3.73 g KCl, 7.07 mL HCl 1N and deionized water up to volume) for the first 120 minutes
- pH 6.8 (for 1 L, 6.80 g KH_2PO_4, 0.90 g of NaOH and deionized water up to volume) for the rest of the dissolution time.

The results are reported in Figure 5.

It can be appreciated, that a release very similar to the reference product was obtained for the K100LV 7.5% tablets.

The release profile of the half tablets according to the invention, coated with Eudragit® L30-D55 was also investigated versus half tablets of the reference product.

Dissolution tests have been conducted at 37 ° in Apparatus 1 (basket) with a rotational speed of 100 rpm in the following dissolution media:

- pH 1.2 (for 1 L, 3.73 g KCl, 7.07 mL HCl 1N and deionized water up to volume) for the first 120 minutes
- pH 6.8 (for 1 L, 6.80 g KH_2PO_4, 0.90 g of NaOH and deionized water up to volume) for the rest of the dissolution time.

The results are reported in Figure 6.

As it can be observed from the Figure, although the release of the active ingredient is a little bit higher at low pH than the commercial tablets, the half tablets of the invention, when a change of the pH occurs, do not show any undesired burst effect, with a smoother release of the active ingredient in the first phase of the dissolution.

CLAIMS

1 A pharmaceutical formulation in form of modified release enteric coated tablets suitable for twice-a-day oral administration, wherein the core of the tablet comprises: a) deferiprone in an amount comprised between 85.0 to 95.0%, b) a hydroxyproylmethylcellulose polymer having a viscosity of 100 cP alone or in mixture thereof with a hydroxyproylmethylcellulose polymer having a viscosity of 4000 cP as a modifying release agent in an amount comprised between 4.0 and 10.0%, c) a lubricant and/or glidant in an amount from 0.2 to 2.0% and d) other suitable pharmaceutically acceptable excipients in an amount comprised between from 0 to 5%, all the amounts calculated by weight on the total weight of the formulation.

2 The pharmaceutical formulation according to claim 1, wherein the modifying release agent consists of a hydroxyproylmethylcellulose polymer having a viscosity of 100 cP in an amount of 7.5% by weight.

3 The pharmaceutical formulation according to claim 1, wherein the modifying release agent consists of a mixture of hydroxyproylmethylcellulose polymer having a viscosity of 100 cP alone or in mixture thereof with a hydroxyproylmethylcellulose polymer having a viscosity of 4000 cP in an amount of 5% by weight.

4 The pharmaceutical formulation according to claim 3, wherein the ratio between the two polymers is 40:60 w/w.

5 The pharmaceutical formulation according to any one of the preceding claims, wherein the lubricant is selected is selected from the group consisting of magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, talc, and a combination thereof.

6 The pharmaceutical formulation according to claim 5, wherein the lubricant is magnesium stearate.

7 The pharmaceutical composition according to any one of the preceding claims, wherein the glidant is selected from the group consisting of colloidal silicon dioxide, starch and talc and combination thereof.

8 The pharmaceutical composition according to claim 7, wherein the glidant is colloidal silicon dioxide.

9 The pharmaceutical formulation according to any one of the preceding claims, wherein the other suitable pharmaceutically acceptable excipients are selected from the classes of pH adjusting agents, and bulking agents.

10 The pharmaceutical formulation according to any one of the preceding claims, wherein the enteric coating comprises an enteric polymer, a diluent, and optionally a plasticizer.

11 The pharmaceutical formulation according to claim 10, wherein the enteric coating comprises an ethacrylic acid - ethyl acrylate copolymer (1:1) dispersion in water and propylene glycol.

12 The pharmaceutical formulation according to claim 10, wherein the enteric coating comprises methacrylic acid- methacrylate copolymer (1:1) in an alcoholic solution with triethyl citrate.

13 The pharmaceutical formulation according to any one of the preceding claims, wherein the core of the tablet comprises from 500 to 1500 mg of deferiprone.

14 The pharmaceutical formulation according to claim 13, wherein the core of the tablet comprises 1000 mg of deferiprone.

15 The pharmaceutical formulation according to any one of the preceding claims, which is suitable for twice-day administration.

16 A process for the preparation of the pharmaceutical formulation according to any one of claims 1 to 15, said process comprising the following steps:

(i) mixing deferiprone with the modifying release agent and the other pharmaceutically acceptable excipients, if present, to form a mixture;
(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator followed by drying and screening to produce a granulate;
(iii) mixing the granulate obtained in step (ii) with the lubricant and/or glidant excipient to form a mixture; compressing the mixture obtained in step (iii) to form a tablet; and
(iv) coating the tablet.

17 A process for the preparation of the pharmaceutical formulation according to any one of claims 1 to 15, said process comprising the following steps:

(i) mixing deferiprone with the modifying release agent and the other pharmaceutically acceptable excipients, if present, to form a mixture;

(ii) adding the lubricant and/or glidant excipient and further mixing;

(iii) directly compressing the mixture obtained in step (ii) to form a tablet; and

(iv) coating the tablet.

18 The pharmaceutical composition according to any one of claims 1 to 15, for use for the treatment of diseases which cause an overload of iron, or for the prevention and/or treatment of diseases which are caused by an overload of iron.

19 The pharmaceutical composition for use according to claim 18, wherein the disease is thalassemia or sickle cell anemia.

20 The pharmaceutical composition for us according to claim 18, wherein said iron overload is transfusional iron overload.

Figure 1

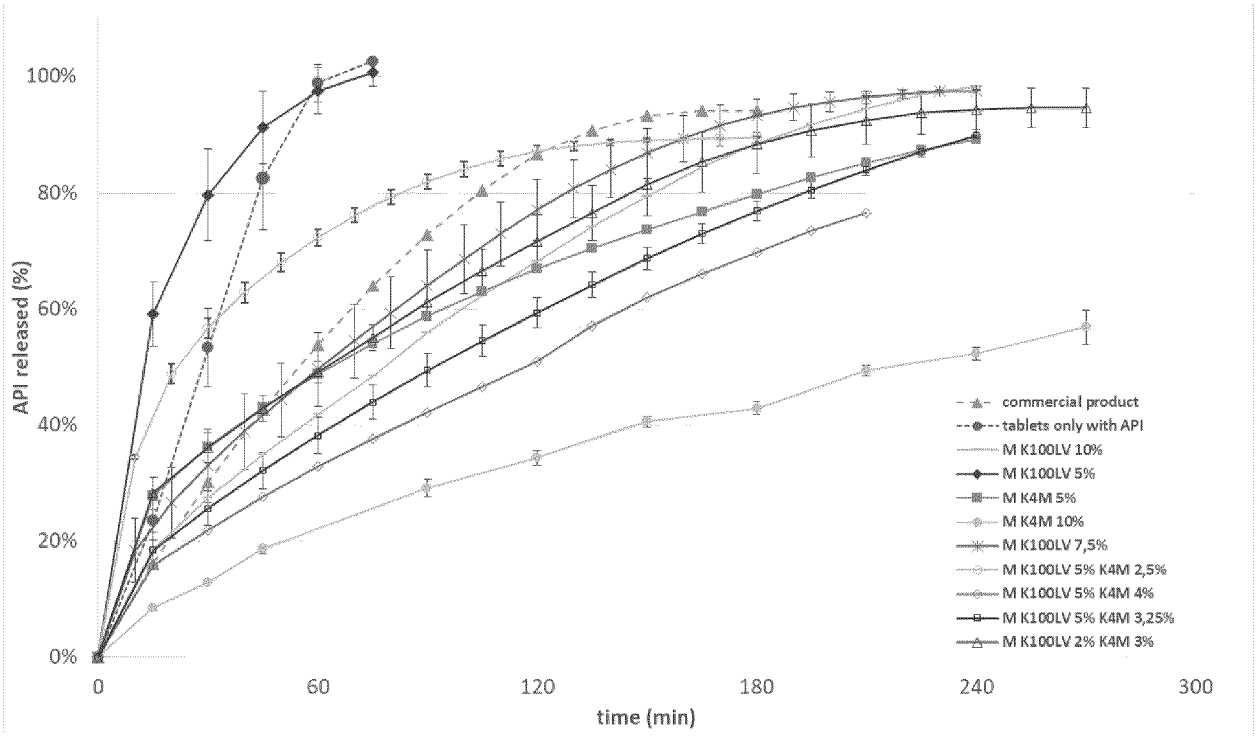


Figure 2

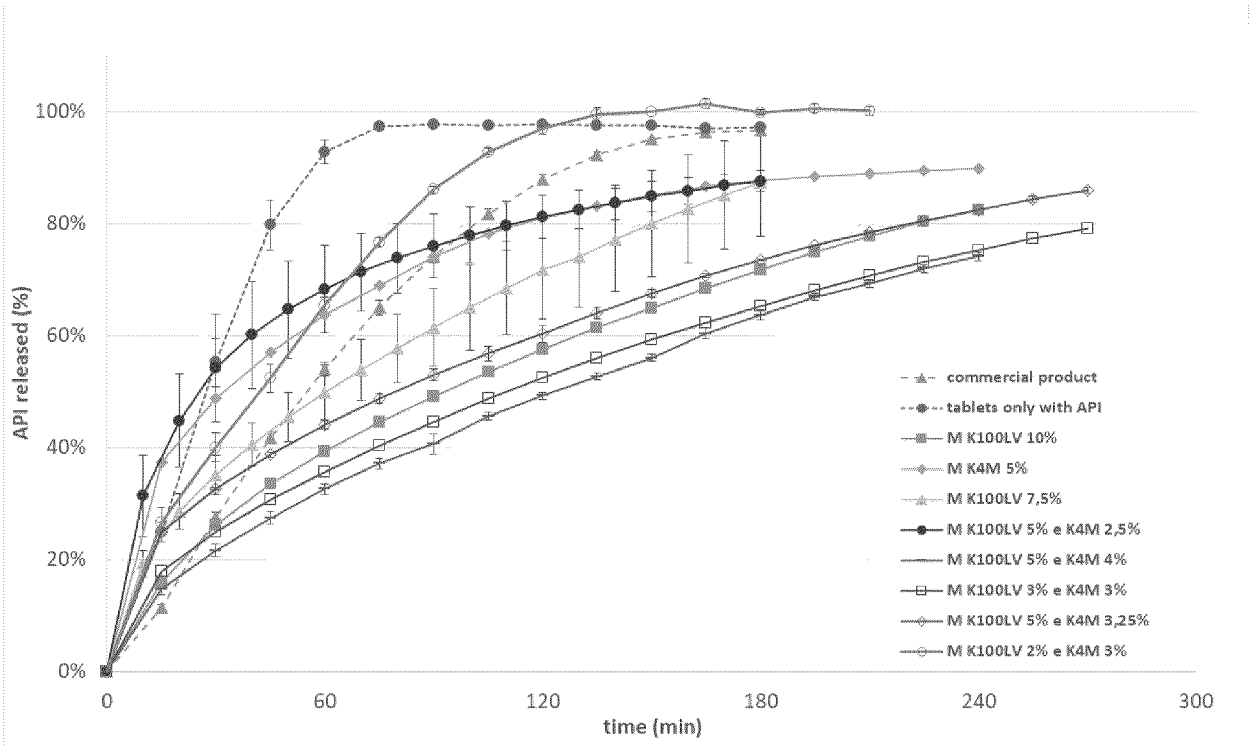


Figure 3

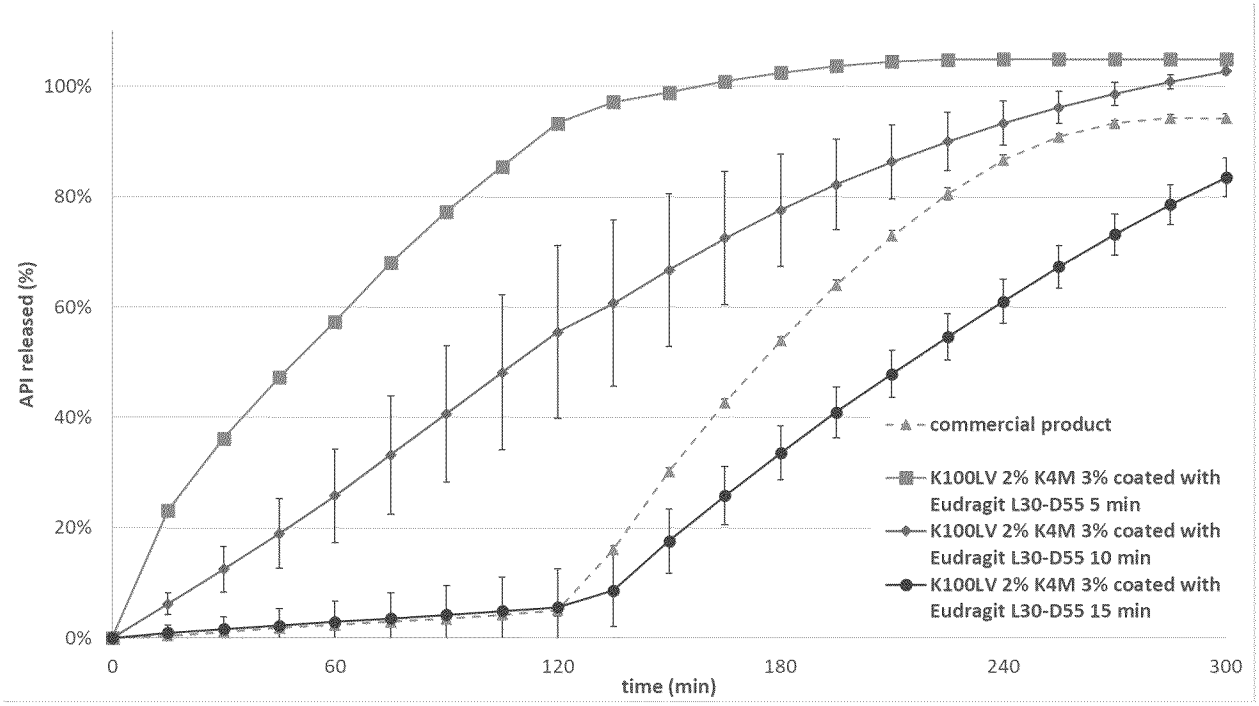


Figure 4

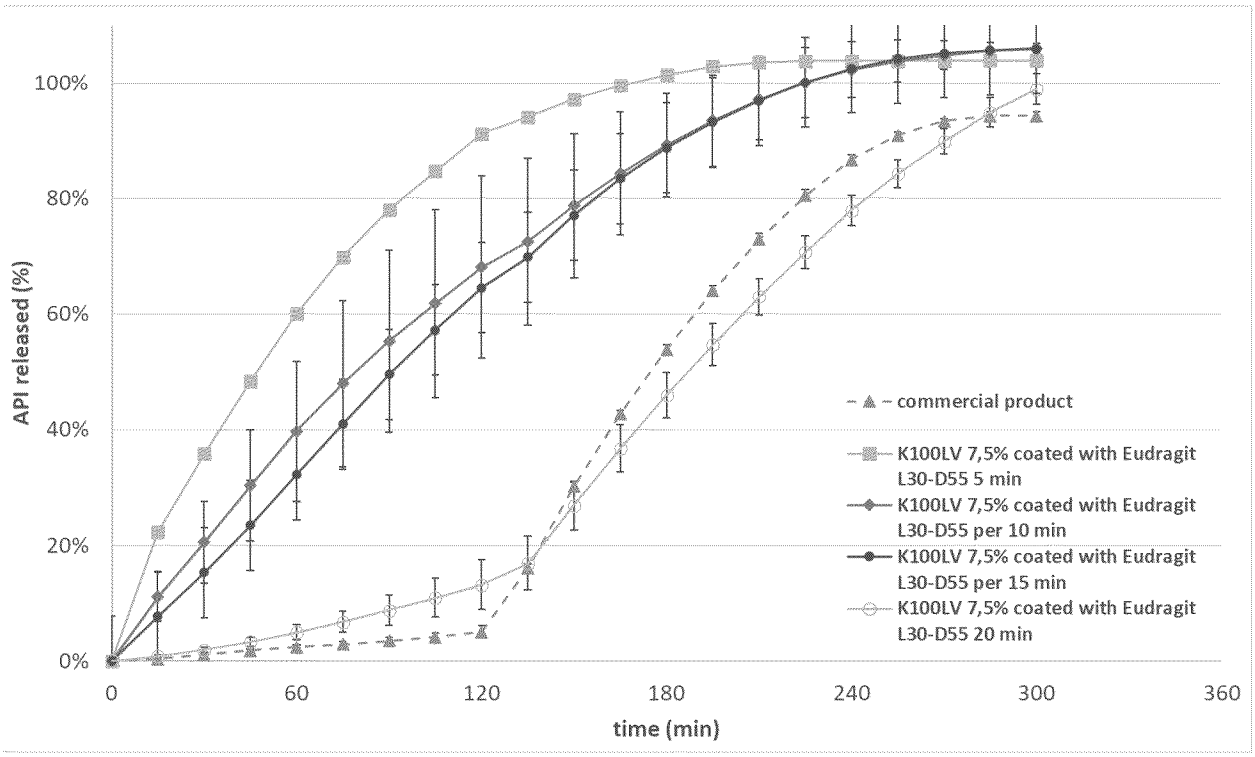


Figure 5

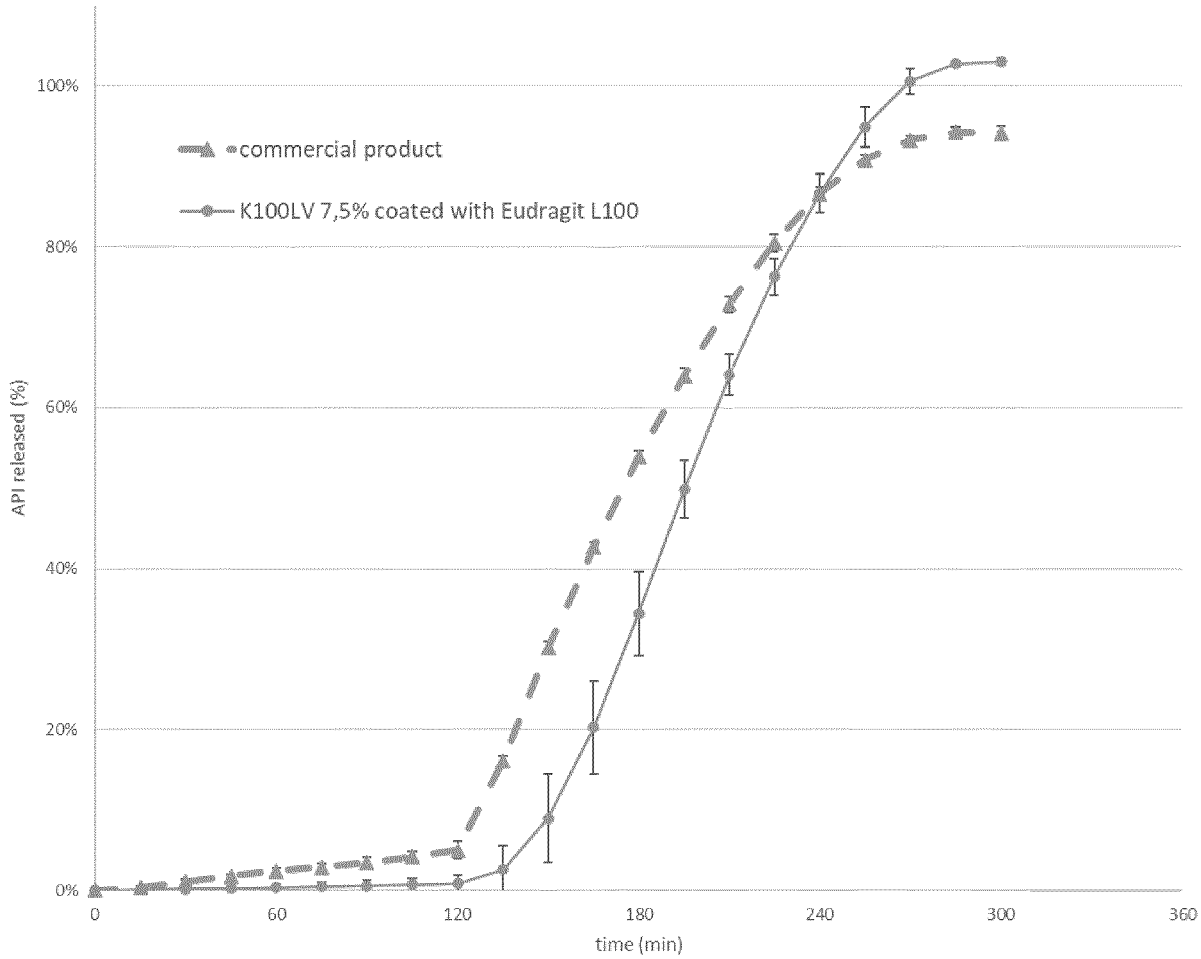
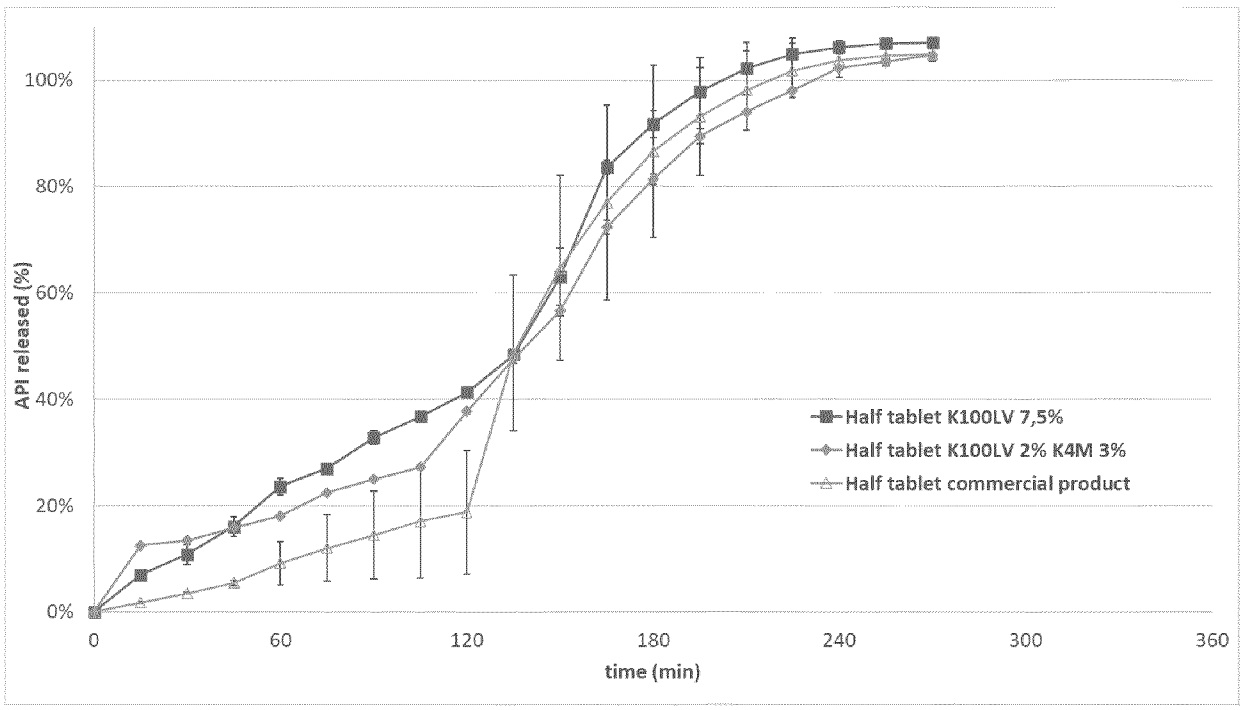


Figure 6



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/059303

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20
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

C. 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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Y	AGUILAR-DE-LEYVA ANGELA ET AL: "A new deferiprone controlled release system obtained by ultrasound-assisted compression", PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY, INFORMA HEALTHCARE, US, vol. 19, no. 6, 31 August 2014 (2014-08-31), pages 728-734, XP009518840, ISSN: 1097-9867, DOI: 10.3109/10837450.2013.829091 page 729, paragraph 4	1-20

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2023	15/06/2023

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

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	KAUL D ET AL: "Sustained release tablet formulation for a new iron chelator", JOURNAL DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 18, no. 9, 1 January 1992 (1992-01-01), pages 1023-1035, XP009539330, ISSN: 0363-9045 table 1 abstract -----	1-15

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/059303

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