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Pharmaceutical Compositions

Field of the Invention

This invention relates to pharmaceutical compositions comprising iron oxy-hydroxide in high loading in a form suitable for oral administration, and in particular for administration as an oral delivery system either as dosage forms for intact swallowing (e.g. film-coated) or as dosage forms capable of rapid disintegration, as well as methods of production thereof.

Background

In patients with chronic renal insufficiency, a pathologically increased serum phosphate level occurs due to the decrease in the glomerular filtration rate. The secondary hyperparathyroidism which sets in therewith must be considered as one of the causes of the occurrence of renal osteopathy. Attempts are normally made to maintain the phosphate balance in equilibrium by dialysis or by the administration of oral phosphate adsorbers which suppress the resorption of foodstuff phosphates in the gastrointestinal tract, or by the combination of both methods, but with the current state of the art this is either not efficient enough, is not economic, or is burdened with side effects.

Recently new and effective phosphate adsorbers based on iron oxy-hydroxide, in particular containing beta-iron oxy-hydroxide stabilised by a stabilization agent such as a carbohydrate and/or humic acid, have been described (EP 0 868 125). These adsorbents show superior phosphate adsorption capacity from aqueous solutions, for example for the adsorption of inorganic phosphates and phosphates bonded to

foodstuffs (EP 0 868 125) and have been shown to be efficient oral phosphate binders in the treatment of hyperphosphataemia (Neophrol. Dial. Transplant 14, 863, 1999).

To achieve maximum efficiency while maintaining good patient compliance, it is desirable that such adsorbers can be administered in high dosages. However, phosphate adsorbers with high iron loadings are still not available. Factors, such as ease of administration in general, unacceptable taste, as well as storage and stability problems, limit the applicability of currently available phosphate binders.

WO 2006/000547 of the present applicant discloses a process for preparing an iron-sulfate based phosphate adsorbent, which may be used for preventing and treating hyperphosphatemic conditions. Described are iron oxy hydroxide compositions which are prepared form ferric sulphate and/or nitrate containing a stabilising agent selected from humic acid and carbohydrates and which have an iron content of at most 20.3 to 22.3 % by weight. These compositions are obtained by rotary evaporation. No specific oral formulations such as tablets are disclosed. It is explained that the iron compositions can be formulated to tablets or other oral formulations together with usual excipients and adjuvants. This means that tablets obtained from the iron oxy hydroxide compositions can have an iron content of at most 20 % (w/w) corresponding to 32 % (w/w) iron oxy-hydroxide.

EP 1 757 299 of the present applicant describes iron(III) carbohydrate complex compounds and there use for orally or parenterally treating iron deficiency in patients having chronic inflammatory bowel disease. In the document reference is made to Maltofer® film tablets containing 100 mg iron(III). The iron content of the tablet is16 % by weight corresponding to 25.6 % w/w iron oxy-hydroxide. The preparation is intended for treating iron deficiency, that is, for liberating iron(III), contrary to phosphate adsorbents as defined in the present invention. No drying procedure is described.

WO 92/01458 discloses oxy-iron compounds, in particular iron oxides, iron hydroxides and iron oxy hydroxides which are formulated as a therapeutic dosage form for use as a phosphate adsorber. No specific oral formulations are disclosed, and no specific iron loading is mentioned. Further, no excipients and manufacturing methods are specifically disclosed, but reference is made to "acceptable methods and excipients". It is said that each oral dose may contain 50 mg to about 500 mg or more of oxy-iron compound. According to the state of the art tablets containing 500 mg oxy-iron compounds, which are necessary in order to achieve a desired degree of phosphate adsorption, would be of such an enormous size that they could not be swallowed by the patient. The document does not disclose anything as to obtaining a high iron loading.

US 5,514,281 discloses polynuclear iron oxy hydroxides bound to a support such as saponified divinylethylene urea vinylacetate copolymer, Lewatit R®, silica, glasses and organic porous supports modified with dextran. The maximum iron loading of a support carrying iron(III) is reported to be 29.3 % by dry weight. The product is formed from a dry support, which is swelled, and it may not be dried thereafter since otherwise removal of phosphate from the dialysate would not work at all. None of the examples in US 5,514,281 describes a dry / tablet formulation for oral administration. The examples given describing adsorbents are all meant for extracorporal use and none of the supports used for their production is applicable for medicinal use. The preparation of an oral formulation is only described as "pressed into powder for...". These products are developed to release iron.

For a wide range of drugs, oral dosage forms such as tablets are clearly the preferred form of delivery. This is due to a high level of patient acceptability and compliance (because they provide an accurate dosage and are easy to administer) as well as advantageous characteristics during and after manufacture, such as they typically show

satisfactory physical and chemical stability, are convenient for packing, shipping and administering and offer advantages in manufacturing speed and cost.

However, oral dosage forms need carefully designed disintegration characteristics to achieve the desired bioavailability for the incorporated drug, i.e. dissolution must precede absorption, in case of immediate release tablets should disintegrate rapidly after ingestion in order to facilitate dissolution of the drug. Moreover, the drug loading of conventional tablet formulations is often limited due to potential gastrointestinal irritation (caused by locally high concentration) and/or patient compliance (which limits size and shape to achieve easy swallowing).

These limitations have prevented the development of an effective oral delivery system for iron oxy-hydroxide as phosphate binder with high loadings.

Applicants have now found that iron oxy-hydroxide (hereinafter also referred to as active agent), and in particular iron oxy-hydroxide containing beta-iron oxy-hydroxide, and in particular further containing a carbohydrate and/or humic acid that may act as a stabilization agent as described in EP 0 868 125 B1, can be successfully formulated in form of an oral delivery system with high loadings (hereinafter also called pharmaceutical compositions or compositions of the invention), preferably either as dosage forms for intact swallowing (e. g. film-coated) or as dosage forms capable of rapid disintegration (either in the oral cavity or in a small amount of liquid prior to ingestion). Thus the pharmaceutical compositions of the invention are able to achieve both high loadings and suitable disintegration characteristics while maintaining a minimal size and thus are able to overcome the drawbacks of currently known formulations.

The inventive compositions have a low iron release rate of below 2.5 % w/w, which is essential for phosphate adsorbers. In contrast thereto, compositions used for treating iron deficiency have a high iron release rate and thus are completely different form the inventive compositions.

Furthermore it was found that the pharmaceutical compositions of the invention can be preferably obtained through conventional molding or tabletting methods, more preferably direct compression tabletting methods, in the presence of one or more excipients fulfilling for example the functions of binder and/or filler and/or disintegrant in one.

It was further found that any disagreeable taste associated with the active agent, if administered as dosage forms capable of disintegration in the oral cavity, can be eliminated using suitable taste-masking agents, sweeteners and/or taste-enhancing agents.

Further it was found that favourable tablet formulations with a particularly high iron-oxy-hydroxide-load can be obtained, if they are comprised of substantial amounts of a flowable powder that has been prepared by spray-drying an aqueous suspension of the ingredients.

Summary of the Invention

It is an object of the invention to provide pharmaceutical compositions comprising iron oxy-hydroxide in a form suitable for oral administration, in particular as an oral delivery system with high loadings, preferably either as dosage forms for intact swallowing (e.g. film-coated) or as dosage forms capable of rapid disintegration (either in the oral cavity or in a small amount of liquid prior to ingestion).

In a preferred embodiment the iron oxy-hydroxide-containing pharmaceutical composition comprises one or more carbohydrates and/or humic acid, preferably a carbohydrate such as a mono- di- or polysaccharide, preferably saccharose (sucrose), starch, agarose, dextran, dextrin, cellulose and derivatives of each of these. Those

carbohydrates and/or humic acid may act as a stabilization agent as described in EP 0 868 125 B1. Apart from this or in addition to this the carbohydrate(s) and/or humic acid may act as a binder and/or filler and/or disintegrant.

In yet another embodiment the compositions of the invention comprise one or more taste-masking and/or coloring additives such as flavouring agents, sweeteners, taste-enhancing agents, colorants, and the like.

Depending on the intended use of the tablet, i.e. whether it is for intact swallowing or rapid disintegration (in the oral cavity or in a small amount of liquid prior to ingestion), such as e.g. a chewable tablet, usual excipients, such as superdisintegrants, glidants, lubricants, antioxidants compression aids and the like may be added if desired. The tablet may be coated with usual film-forming agents, if desired.

In another embodiment, the pharmaceutical compositions of the invention are in any dosage form suitable for oral administration and in particular include tablets and pills, either in a form for intact swallowing (e.g. film-coated) or in a form capable of rapid disintegration (either in the oral cavity after ingestion or in a small amount of liquid prior to ingestion), including a chewable form, dry powders, granules, capsules or sachets containing these, granules, wafers, films, lozenges, and the like.

It is a further object of the invention to provide methods for formulating an oral delivery system according to the invention, in particular an oral delivery system either as dosage forms for intact swallowing (e.g. film-coated) or as dosage forms capable of rapid disintegration (either in the oral cavity or in a small amount of liquid prior to ingestion), comprising iron oxy-hydroxide in high loadings, by means of conventional molding or tabletting methods, preferably direct compression tabletting methods.

Detailed Description of the Invention

Thus, in a first aspect the present invention is directed to pharmaceutical compositions comprising iron oxy-hydroxide as an active agent in high loadings and in a form suitable for oral administration showing the desired disintegration characteristics.

In particular, the present invention is directed to such orally administrable, pharmaceutical compositions with high loadings of the active agent, either as dosage forms for intact swallowing (e.g. film-coated) or as dosage forms capable of rapid disintegration (either in the oral cavity or in a small amount of liquid prior to ingestion).

As indicated hereinabove, the term "active agent" as used herein includes iron(III)-oxy-hydroxide. Iron(III)-oxy-hydroxide or iron(III)-oxide-hydroxide is usually referred to as FeO(OH) or $Fe_2O_3 \times H_2O$. Such iron oxy-hydroxides to be used in accordance with the present invention are usually formed upon hydrolysis and precipitation in aqueous iron(III)-salt solutions (see, for example, Römpp Lexikon Chemie, 10. Auflage, 1997; U. Schwertmann, R. M. Cornell "Iron Oxides in the Laboratory", VCH Verlagsgesellschaft mbH, 1991, Seiten 95 - 100). The term "iron oxy-hydroxide" as used herein thus includes, in particular, alpha, beta, gamma, and delta FeOOH and mixtures thereof. Preferably, the iron oxy-hydroxide comprises beta FeOOH optionally in admixture with other iron oxy-hydroxide(s).

Iron oxy-hydroxides to be used in accordance with the present invention are preferably prepared by adding a base to an aqueous iron(III)-salt solution as described in EP 0868125 B1, and subsequent drying.

Preferably iron oxy-hydroxide stabilized by a stabilization agent is used.

The wording "iron oxy-hydroxide, which is stabilized by a stabilization agent" includes preferably an iron oxy-hydroxide together with a stabilization agent, which includes in particular carbohydrates and humic acid. As described in EP 0868125 B1 such stabilization agent usually is

not bound as a complex compound to the iron oxy-hydroxide, which means for example that a water-soluble stabilization agent can be removed by washing the stabilized iron oxy-hydroxide with water. As further described in EP 0868125 B1 the stabilization agent is supposed to stabilize the iron oxy-hydroxide against ageing, thereby preserving its phosphate adsorption capacity. This means that a stabilized iron oxy-hydroxide in general has a higher phosphate adsorption capacity (as measured in EP 0868125 B1) compared to a non-stabilized iron oxy-hydroxide. In a accordance with the present invention a preferred "iron oxy-hydroxide, which is stabilized by a stabilization agent" comprises beta iron oxy-hydroxide stabilized as described in EP 0868125 B1 with at least one carbohydrate and/or humic acid.

Generally, due to their chemical nature the iron oxy-hydroxides used and administered in accordance with the present invention essentially are not absorbed by the human body, i.e. they are essentially non-bioabsorbable.

Accordingly the term "stabilization agent" as used herein includes preferably at least one carbohydrate and/or humic acid, in particular, as described in EP 0868125 B1. In one embodiment, the at least one carbohydrate is soluble and includes at least one mono-, di- or polysaccharide, such as agarose, dextran, dextrin, dextran derivatives, cellulose and cellulose derivatives, saccharose (sucrose), maltose or lactose preferably saccharose (sucrose), dextrin or starch.

The term "starch" as used herein includes any conventionally used starch products (such as potato starch, corn starch, rice starch, tapioca starch) in native, pregelatinized, degraded, modified, and derivatized forms, preferably suitable for direct compression, and mixtures thereof.

Preferred products include native and pregelatinized starch, such as in a mixture having a ratio (native:pregelatinized) in the range of 10:1 to 0.5:1, preferably in the range of 3:1 to 0.5:1 more preferably in the range of 2:1 to 1:1. The use of a mixture of native and pregelatinized

starch has turned out be particularly advantageous in the manufacture of a tablet with high iron loading, since it allows the preparation of a stabilized pre-mixture which can be compressed to a suitable tablet either directly or with a very small amount of further excipients.

In one specific embodiment the stabilization agent of choice may be present in an amount of 1.0 to 50 % (w/w), preferably 5.0 to 30 % (w/w).

All % weights (w/w) throughout this description are expressed in relation to the total weight of the pharmaceutical composition, if not indicated otherwise.

The term "high loading" as used herein indicates that the iron oxy-hydroxide is present in an amount of 10 to 80 % (w/w), more preferably 30 to 65 % (w/w).

The content of iron oxy-hydroxide is calculated as approximately 1.6 x content of iron.

Thus, the values mentioned above correspond to a content of iron of 6 to 50 % w/w, more preferably 19 to 41 % (w/w).

In preferred embodiments of the invention even higher iron loadings are realized, namely more than 50 % (w/w) to 90 % (w/w) iron oxy-hydroxide, preferably 56 % - 65 % (w/w) corresponding to 31 to 56 % (w/w), preferably 35 % to 41 % (w/w) iron.

Or else, the iron oxy-hydroxide is preferably present in an amount of > 300 mg per dosage form, more preferably 300 to 2000 mg per dosage form. It is understood that the amount of active agent depends on the intended administration route, i.e. the amount present in tablets for intact swallowing film coated e.g. film-coated) are preferably 350 to 850 mg whereas the amount present in oral dosage forms capable of rapid disintegration (either in the oral cavity or in a small amount of liquid prior to ingestion) are preferably 700 to 1700 mg.

In addition to the active agent, conventional pharmaceutical compositions typically contain a number of additional inactive ingredients known as excipients and/or additives. In particular when the amount of active agent required to accomplish a desired therapeutic, nutritive or chemical effect is very small, the presence of inert diluents, fillers, binders, excipients and disintegrants, lubricants, glidants, and sweeteners, taste masking agents, colorants, and the like usually is critical to ensure the practicality and convenience of making oral dosage forms to achieve accurate and effective administration of the active agent.

In contrast, in case of orally administered pharmaceutical compositions having high loadings of active agent, as in the present invention, such additional inactive ingredients are minimized, since the size of an orally administered pharmaceutical composition is a critical feature for achieving good patient compliance.

As explained above, a carbohydrate such as a mono- di- or polysaccharide, preferably saccharose (sucrose), starch, agarose, dextran, dextrin, cellulose and derivativesof each of these, more preferably saccharose (sucrose), dextrin or starch may, apart from or in addition to its stabilizing effect on the iron-oxy hydroxide, act as a binder and/or filler and/or disintegrant in the pharmaceutical composition of the present invention.

Thus, a preferred composition of the invention may comprise iron oxy-hydroxide inthe amounts specified above, a stabilization agent of choice in an amount of 1.0 to 50 % (w/w), preferably 5.0 to 30 % (w/w), and an excipient of choice, different from the stabilizing agent, in an amount of 1.0 to 50 % (w/w), preferably 5.0 to 30 % (w/w), each expressed in relation to the total weight of the composition.

In another embodiment the compositions of the invention comprise one or more taste-masking and coloring additives such as flavouring agents,

sweeteners, taste-enhancing agents, colorants, and the like, which are typically used for oral dosage forms.

Taste-masking agents, such as a taste-enhancing agent, flavouring agent, and/or natural or unnatural sweetener, including intense sweetener, are incorporated into oral dosage forms, such as chewable dosage forms, to give them a more pleasant taste or to mask an unpleasant one.

Typical sweeteners include, but are not limited to, a sugar which is dextrose, sucrose, fructose, lactose, confectionery sugar, powdered sugar, or is a polyol which is sorbitol (e.g. Neosorb), xylitol, maltitol, maltose and polydextrose, or a mixture thereof. Typical intense sweeteners may include, but not be limited to, aspartame, sucralose, acesulfamine K, and/or saccharin derivatives, or a mixture thereof. Further suitable sweeteners or taste-enhancing agents include glycosides such as neohesperidin dihydrochalcone (neohesperidin DC or NHDC), glycyrrhizin, glutamate, and the like. The latter may be used in very small quantities and thus may hereinafter also be called taste-enhancing agents. All the above are suitable to be used alone or as mixtures with other sweeteners and/or flavouring agents. These substances insure great lingering of the sweet taste and cover any undesired aftertaste. Preferred sweeteners and/or taste-enhancing agents include glycosides such as neohesperidin dihydrochalcone.

In one embodiment the sweetener of choice may be present in an amount of 0.01 to 2.5 % (w/w), preferably 0.1 to 1.5 % (w/w), most preferably 0.2 to 1.0 % (w/w), in relation to the total weight of the composition.

The taste-enhancing agent of choice may be present in an amount of 0.1 to 50 ppm, preferably 1 to 10 ppm, most preferably 1 to 5 ppm, in relation to the total weight of the composition.

Typical flavouring agents include any natural and unnatural flavouring agent suitable for pharmaceutical applications, such as flavouring agents derived from a spice, fruit or fruit juice, vegetable or vegetable juice, and the like, for example flavours based on cocoa, caramel, vanilla, apple, apricot, berry (e.g. blackberry, red currant, black currant, strawberry, raspberry, woodberry, etc.), mint, panettone, honey, nut, malt, cola, verveine (verbena) or any combination thereof, such as for example caramel/vanilla, fruit/cream (e.g. strawberry/cream)and the like.

In one embodiment the flavouring agent of choice may be present in an amount of 0.01 to 10 % (w/w), preferably 0.1 to 5 % (w/w), most preferably 0.1 to 1 % (w/w), in relation to the total weight of the composition.

Thus, another composition of the invention may comprise iron oxy-hydroxide in the amounts specified above, a stabilization agent of choice in an amount of 1.0 to 50 % (w/w), preferably 5.0 to 30 % (w/w), an excipient of choice, different from the stabilization agent, in an amount of 1.0 to 50 % (w/w), preferably 5.0 to 30 % (w/w), and taste-enhancing agent of choice, which may be present in an amount of 0.1 to 50 ppm, preferably 1 to 10 ppm, most preferably 1 to 5 ppm, and/or a flavouring agent of choice, which may be present in an amount of 0.01 to 10 % (w/w), preferably 0.1 to 5 % (w/w), most preferably 0.1 to 1 % (w/w), each in relation to the total weight of the composition.

In yet another embodiment excipients, such as superdisintegrants, glidants, lubricants, antioxidants and the like may be added to the compositions of the invention if desired, depending on the intended use of the tablet, i.e. whether it is for intact swallowing or rapid disintegration (in the oral cavity or in a small amount of liquid prior to ingestion).

Thus in a particular embodiment the compositions of the invention may further comprise a superdisintegrant.

The term "superdisintegrant" as used herein refers to a group of disintegration agents well-known to a person skilled in the art, which can be used in a fractional amount of normal disintegrants to obtain the same effect of facilitating the disintegration or "breakup" of the dosage form after administration. Suitable examples include but are not limited to cross-linked polyvinylpyrrolidones (commercially available as Kollidon® CL and Polyplasdone® XL), particularly crospovidone®, modified starches, particularly sodium starch glycolate (commercially available under the trade names Primojel® and Explotab®), Starch 1500, modified celluloses, particularly croscarmellose sodium (cross-linked sodium carboxymethylcellulose, commercially available under the trade name Ac-Di-Sol), LHPC (Low substituted hydroxypropylcellulose) and Veegum®. Preferred examples for use in the tablet according to the invention include cross-linked polyvinylpyrrolidones and modified starches, particularly sodium starch glycolate.

According to the invention, the superdisintegrant will be present in the tablet in an amount of 0.1 to 10 % (w/w), preferably 0.5 to 8 % (w/w), more preferably 2.5 to 6 % (w/w), in relation to the total weight of the composition. The superdisintegrant may be a single superdisintegrant or a combination of superdisintegrants or may be used in combination with one or more common disintegrants, such as for example starches, methylcellulose, calcium carboxymethylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, pregelatinized starch, clays, cellulose, powdered cellulose, pregelatinized starch, sodium alginate, alginic acid, guar gum, magnesium aluminum silicate, polacrilin potassium, and the like.

Thus, another composition of the invention may comprise iron oxy-hydroxide in the amounts specified above, a stabilization agent of choice in an amount of 1.0 to 50 % (w/w), preferably 5.0 to 30 % (w/w), an excipient of choice, different from the stabilization agent, in an

amount of 1.0 to 50 % (w/w), preferably 5.0 to 30 % (w/w), said excipient comprising a superdisintegrant in an amount of 0.1 to 10 %, preferably 0.5 to 8 % (w/w), more preferably 2.5 to 6 % (w/w), and a taste-enhancing agent of choice in an amount of 0.1 to 50 ppm (w/w), preferably 1 to 10 ppm (w/w), more preferably 1 to 5 ppm (w/w), and/or a flavouring agent of choice in an amount of 0.01 to 10 % (w/w), preferably 0.1 to 5 % (w/w), more preferably 0.1 to 1 % (w/w), all weight ranges are in relation to the total weight of the composition.

In yet another embodiment the compositions of the invention may further comprise a glidant and/or lubricant.

The term "glidant" and/or "lubricant" as used herein refers to a group of additives that are used to facilitate tablet manufacture by achieving suitable flowability, compressability, and the like. Examples of suitable glidants include, but are not limited to, magnesium oxide, magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type I, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, polyethylene glycol, talcum, zinc stearate, silica derivatives, such as colloidal silica (e.g. Aerosil®) pyrogenic silica, hydrated sodium silicoaluminate, colloidal silicon dioxide, and mineral oil and light mineral oil.

Preferred glidants include magnesium oxide, magnesium stearate, talcum, colloidal silica.

In one embodiment the glidant of choice may be present in an amount of 0.01 to 10 % (w/w), preferably 0.1 to 5 % (w/w), most preferably 1 to 2 % (w/w), in relation to the total weight of the composition.

Further additives specifically used for oral dosage forms capable of rapid disintegration in the oral cavity, may include salivating agents (compounds that are able to stimulate production of saliva) to ease swallowing. These are in general pharmaceutically acceptable acids, for

example citric acid, malic acid, tartrate, or the compounds Optamint® and Optaflow®. Care has to be taken that iron release is not increased by the use of such acidic compounds, e.g. citric acid, and the amount of these substances therefore has to chosen suitably. In one embodiment the acid of choice may be present in an amount of 0.01 to 10 % (w/w), preferably 0.1 to 5 % (w/w), most preferably 2 to 5 % (w/w), in relation to the total weight of the composition.

As mentioned hereinabove, the pharmaceutical compositions are in a form suitable for oral administration for the selective removal of inorganic phosphate, and in particular for administration as an oral delivery system either as film-coated dosage forms for intact swallowing or as dosage forms capable of disintegration (in the oral cavity or in a small amount of liquid prior to ingestion).

Thus, the pharmaceutical composition of the invention include any dosage form suitable for oral administration and in particular may include tablets and pills, either in a form for intact swallowing (e.g. film-coated) or in a form capable of rapid disintegration (either in the oral cavity after ingestion or in a small amount of liquid prior to ingestion), including a chewable form, dry powders, granules, capsules or sachets containing these granules, wafers, lozenges, and the like. The form for intact swallowing may be film-coated, if desired.

Preferred dosage forms include tablets and pills, either in a form for intact swallowing (e.g. film-coated) in or in a chewable form, granules and capsules or sachets containing these granules, and lozenges.

In the case of orally administrable dosage forms, if desired film-coated, these are swallowed intact and disintegration takes place in the stomach, whereupon the active agent is released for adsorption of phosphate to reduce its systemic uptake.

The term "film-coated" as used herein relates to a mixture of pharmaceutically acceptable excipients which is typically applied to a

compressed tablet, beads, granules, or particles of active ingredient that are compressed into tablets. Alternatively it may also be combined with, mixed with or otherwise added to the active agent. It is understood that the coating chosen must be compatible with the active agent. It is further understood that a person skilled in the art will know how to manipulate the coating to achieve disintegration in the stomach by choosing the excipients which make up the coating, its type, and/or its thickness.

In a preferred embodiment the film coating is applied to a pharmaceutical composition comprising the iron oxy-hydroxide and at least one excipient in compressed form.

Suitable polymers for film-coating according to the present invention are soluble at pH of from about 1.2 to about 5, such as for example hydroxypropylmethylcellulose (HPMC) alone and/or in combination with hydroxypropylcellulose (HPC), carboxymethylcellulose, methylcellulose, ethylcellulose, acrylic resins, and polyvinylpyrrolidone and gelatin or other commercially available film-coating preparations such as Dri-Klear® (Crompton & Knowles Corp., Mahwah, N.J.) or Opadry® (Colorcon, West Point Pa.).

The preferred film coating of this invention is comprised of a commercial film-coating product designed for aqueous film coating containing the water-soluble, film-forming resin, hydroxypropyl methylcellulose and polyethylene glycol (or other suitable plasticizing agents such as propylene glycol or glycerine) and optionally containing titanium dioxide (or other colorant or opacifying agent). Such a product is commercially available under the trade name Opadry® White (Colorcon, West Point, Pa.).

A suitable blend for coating may comprise 0 to about 20% w/w titanium dioxide or colorant, about 5 to about 95% w/w hydroxypropyl methylcellulose, and 0 to about 25% w/w polyethylene glycol. The most

preferred embodiment comprises 10.5% non-water additives, of which 7.5% is Opadry®, in relation to the total weight of the coating.

This blend for coating may further comprise flavoring agents, taste-masking agents and salivating agents as defined hereinabove, in small amounts such as for example 0.1 to 1.0 % (w/w), preferably 0.1 to 0.4 % based on the weight of the total blend for coating. The preferred flavoring and/or taste-masking agent may be selected from the group of agents as defined hereinabove. The preferred amount is readily determined by balancing the goal of adding an amount sufficient to mask the core tablet taste and provide a distinct, characteristic and pleasing taste, and the goal of keeping the tablet from being too much like a candy product. The desired strength of the flavoring and/or taste-masking agent may vary depending on the type of tablet and the intended recipients and the identity of the flavouring and/or taste-masking agent.

The amount of coating deposited on the tablet is typically in the range of from about 1.0% to about 6.0 % weight gain, preferably from 2.0% to 4.0% weight gain, which means the weight gain of the tablet upon coating relative to the weight of the uncoated tablet.

In the case of orally administrable, rapidly disintegrating dosage forms, disintegration takes place immediately upon administration allowing to quickly release the active agent or forming small particles containing the active agent in the oral cavity. Suitable disintegration rates range from 1 second to 3 minutes. A preferred disintegration time is typically less than 30 seconds, measured according to standard European Pharmacopeia testing method.

Thus in one embodiment, the formulation is a tablet made by standard tabletting techniques, such as direct compression, and dry granulation, comprising iron oxy-hydroxide, a stabilization agent, an excipient (different from the stabilization agent), including, in particular, one or

more sweeteners, taste-enhancing agents, flavouring agents, superdisintegrants, glidants, antioxidants and the like. Wet processing techniques must be avoided. This is due to the fact that in case of using organic solvents, typically isopropanol, solvent remains in the granulate after drying which might not be compatible with the product specification. In case of using water as a solvent for wet granulation, iron release from the product is increased which should be avoided under any circumstances for the inventive phosphate adsorber compositions. Extrusion techniques may cause problems in that, when using high loadings of iron, small hard balls are formed which are not suitable for the invention since they hardly show any phosphate adsorbing properties.

In dry granulation, powdered components are typically mixed prior to being compacted, also called pre-compression, to yield hard slugs which are then ground and sieved before the addition of other ingredients and final compression.

Preferably, the compositions of the invention are made by direct compression, which may be considered to be the simplest and the most economical process for producing tablets.

In a preferred embodiment of the invention the compositions of the invention are made by mixing most of the ingredients (more than 50 %, preferably more than 70 %, and more preferably more than 90 % up to 100 % of the total weight of the ingredients), for example those of the ingredients presented in table 1, in the form of an aqueous suspension (amount of dry substance, for example, 1 to 50% (w/w), preferably 10 to 40% (w/w), more preferably 20 to 30% (w/w)), subjecting said suspension to known spray-drying processes under conventional conditions of exposure to hot gases such as air or preferably nitrogen to temperatures of from 135 °C to 200 °C to obtain a flowable powder, which is optionally subsequently mixed with additional ingredients (e.g. as shown in Table 2) and subsequently directly compressed under a range of compression forces such as from 10 to 20 kN to obtain a tablet.

Preferably, the suspension contains 3 to 9 % (w/w) of iron, more preferably 4 to 8 % (w/w), most preferably 6 % (w/w).

Care has to be taken that the diameter and the height of the spray drying column are sufficiently large. Further, the temperature has to be chosen in a range that the excipients and other ingredients neither melt nor caramelize. Both of these processed do not lead to a dry powder but to a solid melt, which is unsuitable for the present invention.

Preferably, the flowable powder, before tabletting, is first compacted using dry compacting in order to reduce the amount of fine powder (dust) and to homogenize the particle size. In doing this a hardness of the obtained tablets in the range of 25 to 400 N is achieved. The compression force is adjusted in a range that the hardness of the tablets obtained from the compacted mixture is 50 to 100 N for chewable tablets, and 100 to 200 N in case of coated tablets or swallowing tablets. If these ranges are used, the disintegration time of the obtained tablets is within the specification required by Ph. Eur..

It has been found surprisingly that, in particular, due to this method the amount of excipients required to obtain tablets with suitable properties, for example in respect to tablet strength, disintegration behaviour etc. can be reduced, whereby pharmaceutical compositions, in particular, in tablet form can be produced having a high load of iron oxy hydroxide.

It is understood that the exact amounts of ingredients will determine the size and depth of the tablet. Tablets capable of rapid disintegration (either in the oral cavity, i.e. chewing tablets, or in a small amount of liquid prior to ingestion) can have any geometrical shape, such as round, square, triangular, etc. Typically they are round and have preferably a diameter of 15 to 30 mm, most preferably 20 mm and a height of 2 to 8 mm, preferably 4 to 6 mm. Film coated tablets for intact swallowing are typically in oblong form, for example about 19 mm in length, 10 mm in width and 8 mm in height. These examples are merely illustrative and by no means limiting. A person skilled in the art will know to choose the

appropriate forms depending on the amount of total ingredients. Compression should be sufficient to hold the ingredients together during dose administration, while allowing easy disintegration in the oral cavity. Typically 10 to 20 kN are used.

In another embodiment, the pharmaceutical composition is in form of granules suitable for disintegration in the oral cavity or rapid dissolution in small amounts of water. The granules may be prepared by high shear granulation or preferably fluidized bed granulation or (dry) mixing processes. As pointed out above, wet techniques using solvents must be avoided. The granules may be filled in capsules or sachets for storage and administration to the oral cavity.

In a further embodiment, as an alternative to spry-drying, the pharmaceutical composition can be provided in form of a wafer. The wafer may be formed by compressing a powder, lyophilizing a cake, or evaporating a suspension, emulsion or gel. Alternatively, the mixed dry materials could be flattened or compressed in a compression machine or between rollers to form the powder e.g. into a sheet that may be cut to an appropriate size that can be inserted in the oral cavity. In one embodiment, the wafer is formed by suspending the active agent, solvent, binding agent or other additives in a solvent such as water. A predetermined amount of the suspension is placed in wells in a plastic mold and lyophilized in the wells to remove the water and form a wafer.

As mentioned hereinabove, the compositions of the invention are indicated for use in the known indications of essentially non-bioabsorbable iron oxy-hydroxide, particularly for the selective removal of inorganic phosphate such as in the treatment of hyperphosphataemia.

Therefore, in a further aspect the invention provides a composition of the invention for use in the treatment of hyperphosphataemia.

In another aspect the invention provides a method for treating hyperphosphataemia comprising administering a composition of the invention to a patient in need thereof.

In yet another aspect the invention provides the use of a composition of the invention in the preparation of a medicament for the treatment of hyperphosphataemia.

The utility of the compositions of the invention may be observed in standard clinical tests.

The exact amount of iron oxy-hydroxide and composition to be administered depends on several factors, for example the severity of the illness, the desired duration of treatment and the like.

The invention is explained in more detail by means of the following specific, non-limiting examples:

Examples

Direct compression was performed using a standard tabletting press at a compression force of 10 to 20 kN. Spraydrying processes were performed at a temperature of 135 to 200 °C.

Tablet Test Methods:

Tablet hardness and disintegration time was determined according to standard European Pharmacopeia testing methods.

Example 1: Preparation of stabilized iron oxy-hydroxide premixture

A stabilized iron oxy-hydroxide premixture was prepared by mixing amounts/ratios of an iron oxy-hydroxide suspension (prepared according to EP 0 868 125 B1) with the excipients according to Table 1. This suspension was subjected to spray-drying at 135 to 200 °C to obtain a premixture in form of a flowable powder. This premixture was subjected to direct compression to obtain a tablet, the composition of which is shown in Table 1.

Table 1:

	Ex. 1a	Ex. 1b	Ex. 1c	Ex. 1d	Ex. 1e
Component	mg	mg	mg	mg	mg
Fe-OOH	800	800	800	800	800
Saccharose[1)]	800	800	800	800	-
Native starch[2)]	-	533	400	533	-
Pregelatinised starch[3)]	800	267	400	267	-
Polyplasdone® XL[4)]	-	-	-	120	-
Dextrin[2)]	-	-	-	-	1600
Water[5)]	8400	8400	8400	8400	8400
Disintegration time (seconds)	nd	nd	nd	35	nd

[1)] stabilizer
[2)] filler/disintegrant
[3)] stabilizer/binder/filler/disintegrant
[4)] superdisintegrant
[5)] water is not present anymore in the premixture after drying, except a re-maining portion of approx. 5% of the dry weight (total of other components)

Example 2: Preparation of tablets

A dry mixture was prepared by mixing the ingredients according to table 2 and subjected to direct compression to obtain a tablet.

Table 2 :

	Ex. 2a	Ex. 2b	Ex. 2c	Ex. 2d
component	mg	mg	mg	mg
Premixture (according to Example 1a-d)	2500 (1a)	2500 (1b)	2500 (1c)	2500 (1d)
Flavour of choice	15	15	15	15
NHDC	0.025	0.025	0.025	0.025
Aerosil®	25	25	25	25
Mg-stearate	12.5	12.5	12.5	12.5
Explotab®	-	12.5	200	-
Polyplasdone® XL	-	-	-	50

Example 3: Film-coating of tablets

Tablets obtained according to Example 2, but with only 50% of the amounts, were compressed into oblong form and subsequently film-coated (weight gain from 2 to 5%) by mixing the ingredients according to the following table:

Table 3:

component	mg
Opadry® II White	83.4
Optaflow® WA	1.7
Apricot aroma	1.7

Example 4: Granules

The powder obtained according to Example 1e was wet granulated using high shear granulation with isopropanol as granulating liquid by adding

the ingredients according to the following table:

Table 4:

component	mg
Premixture (Ex. 1e)	2500
Neosorb® (Sorbitol)	1060
Polyvinylpyrrolidon	200
Xanthan	37.5

Example 5: Preparation of a final instantly dispersable granulate for filling into sachets or stickpacks:

A dry mixture was prepared by mixing the ingredients according to the following table and subjected to subsequent filling into sachets or stickpacks.

Table 5:

Component	mg
Granules (Ex. 4, variants obtained from different base materials)	3797.5
Aspartam	15
Flavour*	70
citric acid	155

* "refreshing flavour" such as cola, verveine, blackberry

Example 6: Preparation of a final instantly dispersable granulate for filling into sachets or stickpacks:

A dry mixture was prepared by mixing the ingredients according to the

following table and subjected to subsequent filling into sachets or stickpacks:

Example 7: Preparation of flowable powders

9.6 kg FeOOH (corresponding to 6.0 kg Fe) was supended in water together with the amounts of excipients and adjuvants shown in Table 7a. 100 kg of the suspension was subjected to spray-drying. The iron loading of the obtained powders is given in Table 7b.

Table 7a:

Product	Amount of FeOOH [kg]	Sucrose [kg]	PST[1] [kg]	Dextrin [kg]	Lycatab®[2] [kg]
a	9.6	8.9	5.9		3.0
b	9.6	6.9			
c	9.6			6.9	
d	9.6	2.0	2.0	2.9	
e	9.6	1.7	1.7	1.7	1.7
f	9.6	3.0	2.1	0.9	0.9
g	9.6	3.4	2.3		1.1

[1] potato starch
[2] pregelatinised starch, available from Roquette

Table 8:

Product	Fe [% w/w]	FeOOH (Fe x 1.6) [% w/w]	LOD[1] (approx.) [%w/w]	Total amount of product [kg]
a	20-22	33,6	4	28.6
b	34-36	56	4	17.1
c	34-36	56	4	17.1
d	34-36	56	4	17.1
e	34-36	56	4	17.1
f	34-36	56	4	17.1
g	34-36	56	4	17.1

[1] Loss on drying, determined by a halogen moisture analyzer (constant mass; change in mass not more than 1mg per 180 seconds).

Example 8: Tabletting of the obtained flowable powders

The product obtained in Examples 7a) to g) were mixed with the ingredients shown in Table 9a, and tablets were formed of the obtained mixtures. The Fe content, Fe release at pH 3 and phosphate adsorption of the obtained tablets are given in Table 9b.

The Fe release was measured according to European Pharmacopeia chapter 2.9.3 using standard dissolution equipment and parameters as described in the monograph. The test medium was water, pH 3 was adjusted using hydrochloric acid. Samples were taken after 2h and iron content analyzed by titration.

Phosphate adsoprtion was measured as described in WO 2006/000547 by dissolving the obtained tablet in a defined amount of phosphate solution of a specific concentration, adjusting the pH to 3, reacting for 2 hours at 37°C, centrifugation, decanting and measuring the phosphate content via ionic chromatography or photometric determination.

Table 9a:

Component	Amount [% w/w]
Flowable powder 7a) - 7g)	98-93, without coating 98 to 95 %
Aroma including taste masking agent (neohesperidine dihydrochalcone)	0.2-1
Lubricant/glidant/flow aid	total 0.5-2
Compression aid (ProSolv®)	0.5-2
Optionally coating	max. 3

Table 9b:

product	Flowable powder used	Fe loading [% w/w]	Fe release at pH 3 [% w/w)	Phosphate absorption [mg P/mg Fe]
8a	7a	19.5	1.8	0.314
8b	7b	34.7	3.4	0.319
8c	7c	36.7	0.5	0.241
8d	7d	35.9	0.4	0.216
8e	7e	36.3	0.6	0.229
8f	7f	36.2	0.2	0.219
8g	7g	37.5	0.2	0.170

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Claims

1. Pharmaceutical composition comprising iron oxy-hydroxide in high loading, in a form suitable for oral administration.

2. Pharmaceutical composition comprising iron oxy-hydroxide in high loading, in a form suitable for oral administration as film-coated dosage forms for intact swallowing or as dosage forms capable of disintegration in the oral cavity.

3. The composition according to claims 1 or 2, wherein the composition contains at least one carbohydrate and/or humic acid.

4. The composition according to claim 3, wherein the carbohydrate is selected from the group consisting of a mono-, di- or polysaccharide, such as agarose, dextran, dextrin, dextran derivatives, cellulose and cellulose derivatives, saccharose, maltose, and lactose, preferably saccharose, dextrin, and starch.

5. The composition according to any preceding claim wherein the iron oxy-hydroxide is containing beta iron oxy-hydroxide.

6. The composition of any preceding claim wherein iron oxy-hydroxide is present in an amount of 10 to 80 % (w/w), preferably 30 to 65 % (w/w), expressed in relation to the total weight of the composition.

7. The composition of any preceding claim wherein the carbohydrate and/or humic acid are present in a total amount of 1 to 50 % (w/w), preferably 5 to 30 % (w/w), expressed in relation to the total weight of the composition.

8. The composition of any preceding claim further comprising one or more flavouring agents, sweeteners, taste-enhancing agents, and/or coloring agents.

9. The composition of claim 8, wherein the sweetener is natural or unnatural sweetener selected from a sugar, a polyol, aspartame, sucralose, acesulfamine K, and/or saccharin and the taste-enhancing agent is selected from glycosides such as neohesperidin dihydrochalcone, glycyrrhizin, glutamate.

10. The composition of claim 8 or 9, wherein the sweetener is present in an amount of 0.01 to 2.5 % (w/w), and the taste-enhancing agent in an amount of 0.1 to 10 ppm, each expressed in relation to the total weight of the composition.

11. The composition of claim 8, wherein the flavouring agent is present in an amount of 0.01 to 10 % (w/w), preferably 0.1 to 5 % (w/w), most preferably 0.1 to 1 % (w/w), expressed in relation to the total weight of the composition.

12. The composition of any preceding claim further comprising one or more excipients, such as superdisintegrants, glidants, antioxidants.

13. The composition of claim 12, wherein the superdisintegrant is selected from the group consisting of cross-linked polyvinylpyrrolidones, modified starches, and modified celluloses.

14. The composition of claims 12 or 13, wherein the superdisintegrant is present in an amount of 0.1 to 10 % (w/w), preferably 0.5 to 8 % (w/w), more preferably 2.5 to 6 % (w/w), expressed in relation to the total weight of the composition.

15. The composition of claim 12, wherein the glidant is selected from the group consisting of magnesium stearate, silica derivatives, such as colloidal silica, pyrogenic silica, hydrated sodium silicoaluminate, colloidal silicon dioxide, talcum and mixtures thereof, preferably magnesium stearate, colloidal silica or talcum.

16. The composition of claims 12 or 15, wherein the glidant is present in an amount of 0.01 to 10 % (w/w), preferably 0.1 to 5 % (w/w), expressed in relation to the total weight of the composition.

17. The composition of any preceding claim comprising iron oxy-hydroxide in an amount of 10 to 80 % (w/w), at least one carbohydrate and/or humic acid in a total amount of 1.0 to 50 % (w/w), optionally one or more excipients in a total amount of 1.0 to 50 % (w/w), one or more taste-enhancing agents in a total amount of 0.1 to 10 ppm, and/or one or more flavouring agents in a total amount of 0.01 to 10 % (w/w), each expressed in relation to the total weight of the composition.

18. The composition of claim 17 comprising one or more

superdisintegrants in a total amount of 0.1 to 10 % by weight(w/w).

19. The composition of any preceding claim in form a form for intact swallowing or in a form capable of rapid disintegration such as chewable tablets or pills, dry powders, granules, capsules or sachets containing these granules, wafers, or lozenges.

20. Use of the compositions of any preceding claim for the manufacture of a medicament for the treatment of hyperphosphataemia.

21. Use of the compositions of any preceding claim for the manufacture of a medicament for the treatment of patients with chronic renal insufficiency.

22. A method for preparing the composition according to any preceding claim in form of a tablet by direct compression or dry granulation.

23. A method for preparing the composition according to any preceding claim in form of a tablet, wherein an aqueous suspension, comprising at least 90 % (w/w) of the ingredients based on the total weight of the final composition, is prepared, which is then subjected to spray-drying to obtain a flowable powder, which is optionally mixed with the remaining ingredients and subsequently compressed to obtain a tablet.

24. A tablet, as obtainable by the method of claim 23.

25. A tablet comprising iron oxy-hydroxide in an amount of 40 to 65 % (w/w), saccharose in an amount of 5 to 30 % (w/w), and starch in an

amount of 5 to 30 % (w/w), expressed in relation to the total weight of the tablet composition, excluding the weight of an optionally present tablet coating.