

Description

This invention relates to iron compounds for use in pharmaceutical compositions for the treatment of iron deficiency anaemia.

An adequate supply of iron to the body is an essential requirement for tissue growth in both man and animals. Although there is normally an ample amount of iron in the diet, the level of absorption of iron from food is generally low so that the supply of iron to the body can easily become critical under a variety of conditions. Iron deficiency anaemia is commonly encountered in pregnancy and may also present a problem in the newly born, particularly in certain animal species such as the pig. Moreover, in certain pathological conditions there is a maldistribution of body iron leading to a state of chronic anaemia. This is seen in chronic diseases such as rheumatoid arthritis, certain haemolytic diseases and cancer.

Although a wide range of iron compounds is already marketed for the treatment of iron deficiency anaemia, the level of iron uptake by the body from these compounds is often quite low thereby necessitating the administration of relatively high dosage levels of the compound. The administration of high dose, poorly absorbed, iron complexes may cause siderosis of the gut wall and a variety of side effects such as nausea, vomiting, constipation and heavy malodorous stools.

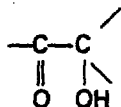
The present invention relates to a group of hydroxypyrrone iron complexes which we have identified as being of particular value for use at relatively low dosage levels in the treatment of iron deficiency anaemia. The hitherto unrecognised value of these complexes in such a context, as shown by *in vivo* experiments, is unexpected in view of the well known need for improved iron compounds for the treatment of iron deficiency anaemia. This is particularly so as among the hydroxypyrrones whose iron complexes are of the most interest for use in the present invention is a significant number of compounds which are naturally occurring materials, or are readily derivable from such materials, and which have been known for some time to be capable of forming iron complexes. In particular, Kidani *et al*, Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo, 1970, 18, 16 (Chemical Abstracts, 1971, 75, 115362k) describe the preparation of the 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-2-methyl-4-pyrone and provide details of its electronic and infrared spectra, whilst Gerard *et al*, Journal of Chemical Research (S), 1980, 314 (Chemical Abstracts, 1981, 94, 24201h) also describe this complex and various hydroxo complexes of 3-hydroxy-2-methyl-4-pyrone and iron(III) and report upon their spectra.

An added advantage of the present invention is that several of the hydroxypyrrones used to form the iron complexes to which the invention relates have previously been used in foodstuffs thereby indicating their non-toxic nature and the consequent suitability for pharmaceutical use of their iron complexes. Although certain of the iron complexes themselves have also previously been proposed for use in foodstuffs, as colouring agents, it had never previously been appreciated that they have any therapeutic use and the conditions proposed for the use of such complexes as colouring agents would not generally be such as to lead to any significant physiological effect.

Accordingly the present invention comprises an iron complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for use in therapy.

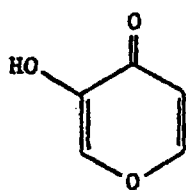
The iron complexes of use in the present invention preferably contain iron in the ferric state. Although the use of complexes containing iron in the ferrous state may be considered, such complexes tend to be less stable and are thus of less interest. The iron complexes are preferably neutral and this is conveniently achieved by complexing with a ferric cation the appropriate number of anions derived from the hydroxypyrrone (through the conversion $\text{OH} \rightarrow \text{O}^-$) necessary to produce neutrality. Preferred iron complexes of use in the present invention are thus the neutral 3:1 complexes containing three hydroxypyrrone anions complexed with a ferric cation.

The substituted 3-hydroxy-4-pyrones may carry more than one type of aliphatic hydrocarbon group but this is not usual and, indeed, substitution by one rather than two or three aliphatic hydrocarbon groups is preferred. The term aliphatic hydrocarbon group is used herein to include both acyclic and cyclic groups which may be unsaturated or saturated, the acyclic groups having a branched chain or especially a straight chain. Groups of from 1 to 4 carbon atoms and particularly of 1 to 3 carbon atoms are of most interest. Saturated aliphatic hydrocarbon groups are preferred, these being either cyclic groups such as the cycloalkyl groups cyclopropyl and especially cyclohexyl or, more particularly acyclic groups such as the alkyl groups n-propyl and isopropyl, and especially ethyl and methyl. Substitution at the 2- or 6- position is of especial interest although, when the ring is substituted by the larger aliphatic hydrocarbon groups, there may be an advantage in avoiding substitution on a carbon atom alpha to the

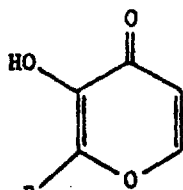


system. This system is involved in the complexing with iron and the close proximity of one of the larger aliphatic hydrocarbon groups may lead to steric effects which inhibit complex formation.

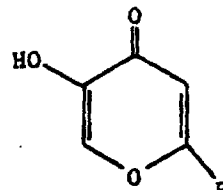
Examples of specific compounds whose iron complexes are of use in the present invention are shown by the following formulae (I), (II) and (III):—



(I)



(II)



(III)

in which R is a cycloalkyl or alkyl group, for example methyl, ethyl, n-propyl or isopropyl. Among these compounds 3-hydroxy-2-methyl-4-pyrone (maltol; II, $R=CH_3$) is of most interest, whilst 3-hydroxy-4-pyrone (pyromeconic acid; I), 3-hydroxy-6-methyl-4-pyrone (III, $R=CH_3$) and particularly 2-ethyl-3-hydroxy-4-pyrone (ethylpyromeconic acid; II, $R=C_2H_5$) are also of especial interest. For convenience the compound 3-hydroxy-2-methyl-4-pyrone is referred to in the following discussion under the name maltol.

In the case of certain of the hydroxypyrones referred to above, i.e. maltol, 3-hydroxy-6-methyl-4-pyrone and 2-ethyl-3-hydroxy-4-pyrone, the formation of an iron complex of the compound has been referred to in the literature, although it should be noted that the procedures described in the literature for the production of such complexes often would not provide complexes of a form which is preferred for use in the present invention and the only 3:1 complex reported is that of maltol. In the case of the other hydroxypyrones, all forms of the iron complexes are novel and are included, *per se*, by the present invention.

The iron complexes are conveniently prepared by the reaction of the hydroxypyrene and iron ions, the latter conveniently being derived from an iron salt, particularly a ferric halide and especially ferric chloride. The reaction is conveniently effected in a suitable mutual solvent and water may often be used for this purpose. If desired, however, an aqueous/organic solvent mixture may be used or an organic solvent, for example ethanol, methanol or chloroform and mixtures of these solvents together and/or with water where appropriate. In particular, methanol or especially ethanol may be used where it is desired to effect the separation of at least a major part of a by-product such as sodium chloride by precipitation whilst the iron complex is retained in solution.

It should be appreciated that the nature of the iron complex obtained by the reaction of a hydroxypyrene and iron ions will depend both on the proportion of these two reactants and upon the pH of the reaction medium. Thus, for the preparation of the 3:1 ferric complex, for example, the hydroxypyrene and the ferric salt are conveniently mixed in solution in a 3:1 molar proportion and the pH adjusted to a value in the range of 6 to 9, for example 7 or 8. If a similar excess of hydroxypyrene:iron is employed but no adjustment is made of the acidic pH which results on the admixture of the hydroxypyrene and an iron salt such as ferric chloride, then a mixture of the 2:1 and 1:1 complex will instead be obtained.

Reaction to form the iron complex is generally rapid and will usually have proceeded substantially to completion after 5 minutes at about 20°C, although a longer reaction time may be used if necessary. Following separation of any precipitated by-product such as sodium chloride in the case of certain solvent systems, the reaction mixture may conveniently be evaporated on a rotary evaporator or freeze dried to yield the solid iron complex. This may, if desired, be crystallised from a suitable solvent, for example water, an alcohol such as ethanol, or a solvent mixture, including mixtures containing an ether. The present invention thus further includes a process for the preparation of a neutral 3:1 hydroxypyrene:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, but excluding 3-hydroxy-2-methyl-4-pyrone, which comprises reacting said hydroxypyrene with ferric ions at a pH in the range of 6 to 9 to form the 3:1 complex and isolating said complex in the solid form.

Whilst for some uses it may be appropriate to prepare the iron complex in substantially pure form, i.e. substantially free from by-products of manufacture, in other cases, for example with a solid oral formulation as described hereinafter, the presence of by-products such as sodium chloride may be quite acceptable. In general, however, the neutral 3:1 hydroxypyrene:iron(III) complex is of particular interest in a form which is substantially free at least from those by-products which are complexes containing different proportions of hydroxypyrene and iron, in particular the 2:1 and 1:1 complexes. Accordingly the present invention includes an iron complex, for example the 3:1 hydroxypyrene:iron(III) complex, of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, but excluding 3-hydroxy-2-methyl-4-pyrone, when in a form substantially free from iron complexes of the hydroxypyrene containing other proportions of iron. As indicated hereinafter, it may be advantageous under some circumstances for the iron complex to be used in admixture with the free pyrene or a salt thereof containing a physiologically acceptable cation. It is possible to produce such a mixture by mixing the two components either in the solid form or in solution, followed by isolation of a solid mixture in the latter case when a solid composition is required. However, it may be more convenient to obtain such a mixture by reacting a molar proportion of the hydroxypyrene and iron ions of greater than 3:1. It should be stressed, however, that the conditions as well as the proportion of reactants used in the reaction are of importance if a mixture of the free pyrene and

the preferred neutral 3:1 complex is to be obtained. In particular, as indicated previously, the pH of the reaction mixture is particularly important and, because of this fact, certain prior art procedures concerned with the use of iron hydroxypyrrone complexes in food colouring, for example as described in US patent 4,018,907, substantially fail to yield the 3:1 complex even though an excess of the hydroxypyrrone is present, owing to the lack of pH control.

Certain hydroxypyrrones, such as maltol, are available commercially. With others, a convenient starting material in many instances consists of 3-hydroxy-4-pyrone which is readily obtainable by the decarboxylation of 2,6-dicarboxy-3-hydroxy-4-pyrone (meconic acid). Thus, for example, 3-hydroxy-4-pyrone may be reacted with an aldehyde to insert a 1-hydroxyalkyl group at the 2-position, which group may then be reduced to produce a 2-alkyl-3-hydroxy-4-pyrone. The preparation of 2-ethyl-3-hydroxy-4-pyrone, etc, by this route is described in the published US application serial number 310,141 filed Sept. 19, 1963 (series of 1960) referred to in US—A—3,376,317.

It will be appreciated that these are not the only routes available to these compounds and their iron complexes and that various alternatives may be used as will be apparent to those skilled in the art.

The iron complexes may be formulated with a physiologically acceptable diluent or carrier for use as pharmaceuticals for veterinary or human use in a variety of ways. However, compositions in which the diluent or carrier is other than a non-sterile solution in water and/or an organic solvent are generally preferred. Thus, the iron complexes may be applied as an aqueous, oily or emulsified composition incorporating a liquid diluent, which will, however, most usually be employed for parenteral administration and therefore may conveniently be sterile and pyrogen free. One form of composition of particular interest thus has the form of a sterile, injectable solution, suspension or emulsion. Oral administration is, however, more generally to be preferred for the treatment of iron deficiency anaemia in humans and the complexes of the present invention may be given by such a route. Although compositions incorporating a liquid diluent may be used for oral administration, it is preferred to use compositions incorporating a solid carrier, for example a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate. The iron complex will of course be present in such a preferred composition in solid form, which form is accordingly a preferred one for the complex, and such a solid composition may, for example, be presented in tablet form.

In the case of animals, compositions for parenteral administration are of greater interest than with humans. The problems of iron deficiency anaemia in newly born pigs arise primarily during the first three weeks or so of their life when a very rapid weight gain takes place. The iron complexes of the present invention may be used to treat piglets directly by a parenteral route but an alternative approach is to enhance the iron content of the milk on which the piglets are feeding by treating the mother pig using oral or parenteral administration, for example with an injectable slow release preparation.

Other forms of administration than by injection or through the oral route may also be considered in both human and veterinary contexts, for example the use of suppositories for human administration.

The present invention thus further includes a pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier, but excluding any liquid which is non-sterile and non-pyrogen free.

Compositions may be formulated in unit dosage form, i.e. in the form of discrete portions containing a unit dose, or a multiple or sub-unit dose. Whilst the dosage of hydroxypyrrone iron complex given will depend on various factors, including the particular compound which is employed in the composition, it may be stated by way of guidance that maintenance at a satisfactory level of the amount of iron present in the human body will often be achieved using a daily dosage, in terms of the iron content of the compound, which lies in a range from 0.1 to 100 mg and often in a range from 0.5 to 10 mg, for example 1 or 2 mg, veterinary doses being on a similar g/kg body weight ratio. However, it will be appreciated that it may be appropriate under certain circumstances to give daily dosages either below or above these levels. In general, the aim should be to provide the amount of iron required by the patient without administering any undue excess and the properties of the pharmaceutical compositions according to the present invention are particularly suited to the achievement of this aim. Similarly, the concentration of iron in the pharmaceutical composition in the form of the hydroxypyrrone complex may vary quite widely, for example over a range from 0.01 to 20% w/w. However, it is more usual for the concentration to exceed 0.01% w/w and it may often exceed 0.05 or 0.1% w/w, whilst a more usual limit for the upper end of the range is 13% w/w. A common range of concentration is 0.05 to 5% w/w, for example 0.2 to 0.5, 1 or 2% w/w.

Where desired, more than one hydroxypyrrone iron complex as described above may be present in the pharmaceutical composition or indeed other active compounds may be included in the composition, for example compounds having the ability to facilitate the treatment of anaemia, such as folic acid. Another additional component which may be included in the composition, if desired, is a source of zinc. Iron compounds used in the treatment of iron deficiency anaemia can inhibit the mechanism of zinc uptake in the body and this can cause serious side effects in the foetus when treating anaemia in a pregnant female. It is believed, however, that the iron complexes of the present invention have a further advantage in that they either do not have this effect or exhibit the effect at a lower level than the compounds at present used in the treatment of anaemia. Accordingly, it may often be the case that the level of zinc providing

compound added to the composition may not require to be high or, with preferred formulations of the iron complexes, may be dispensed with altogether.

The present invention thus further includes the use of an iron complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for the manufacture of a medicament for use in effecting an increase in the level of iron in a patient's blood stream.

We have found that the iron complexes described herein are particularly suited to the treatment of iron deficiency anaemia, both in humans and also in a veterinary context and particularly for the treatment of various mammalian species, especially pigs. Thus, the chelating agents which they contain, and particularly maltol, have a high affinity for iron ($\log \beta_3 = 30$ for maltol) but a lower affinity for copper (II), zinc (II), calcium and magnesium. Both the high affinity of maltol for iron and its low affinity for calcium are reflected in its K_{soi} value ($\log K_{soi}$ is defined as being equal to

$$\log \beta_{Fe(L)_n} + 21 - [pK_{sp} + n \log a_L (H+) + m \log a_L (Ca++)]$$

where $\log \beta_{Fe(L)_n}$ is the cumulative affinity constant of the ligand in question for iron (III), pK_{sp} is the negative logarithm of the solubility product for $Fe(OH)_3$ and has a value of 39, n and m are the number of hydrogen and calcium ions, respectively, which are bound to the ligand, and $a_L (H+)$ and $a_L (Ca++)$ are the affinities of the ligand for hydrogen and ions and calcium ions, respectively. In order to solubilise iron (III) hydroxide, $\log K_{soi}$ must be greater than 0. The value of K_{soi} for maltol is 8.0 and this is also sufficiently large to prevent appreciable competition from phytate, phosphate, thiols, and other potential ligands likely to occur in the intestinal lumen. In order to exchange iron efficiently with transferrin, the $\log K_{soi}$ value should be close to that of apotransferrin, which is 6.0, so that maltol is also suitable in this respect. Moreover, although the neutral 3:1 maltol:iron (III) complex is thermodynamically stable (thermodynamic stability constant = 30) it is also extremely labile and is therefore able to donate iron to high affinity sites, such as those found in apotransferrin. The half life for the exchange of iron (III) between the maltol complex and apotransferrin is 1 minute whereas, by contrast, the corresponding figure for the complex of EDTA with iron (III) is 4 days.

It will be appreciated, however, that in addition to possessing properties such as those described above from iron maltol, a compound which is to act as a source of iron through oral administration is required to show a high level of membrane permeability. An indication of the properties of a compound in this respect is provided by the value of the partition coefficient (K_{part}) obtained on partition between *n*-octanol and Tris hydrochloride (20 mM, pH 7.4); Tris representing 2-amino-2-hydroxymethylpropane 1,3-diol) at 20°C and expressed as the ratio (concentration of compound in organic phase)/(concentration of compound in aqueous phase). The value of K_{part} for the neutral 3:1 maltol:iron (III) complex is 0.5, which is well placed in the preferred range of 0.2 to 1.0 and compares favourably with the figures of 0.001 and 0.0015 for the EDTA:iron (III) complex and iron (III) ascorbate, respectively.

The value of the iron complexes of the present invention is confirmed by various *in vitro* and *in vivo* tests. Thus, their ability to permeate biological membranes is confirmed in practice by tests of the ability of the ^{59}Fe labelled iron complexes to permeate erythrocytes. Moreover, iron complexes of the present invention have been found to exhibit a high level of efficiency in promoting iron uptake, as measured in the rat small intestine, as compared with a range of other iron complexes currently marketed for the treatment of iron deficiency anaemia. *In vivo* experiments in the cat and rat have confirmed the value of iron maltol compounds as a source of iron, the iron uptake obtained either on intravenous administration or on direct administration into the small intestine being markedly superior to that obtained with commercially available iron compounds such as iron sulphate, iron EDTA and iron gluconate. It was found from these experiments that the iron was not excreted to any significant extent in the urine but became generally distributed throughout the body, the complexes donating iron to transferrin to an equilibrium level once they are present in the bloodstream.

Certain aspects of this formulation may enhance the activity of the complexes in particular contexts. Thus, although the neutral 3:1 ferric complexes are stable over a wide pH range from about 4 or 5 up to 10, they will dissociate at the pH values of less than 4 prevailing in the stomach to form a mixture of the 2:1 and 1:1 complex together with the free hydroxypyron, and it has been found that the blood levels of ^{59}Fe achieved on administration of the 3:1 complex into the small intestine are much higher than when administration is made into the stomach. However, when the stomach contents is flushed to the small intestine in *in vivo* cat experiments an increase of iron uptake occurs almost immediately. The undesirable effects of this dissociation on iron uptake may be countered by using one or more of the following procedures in the formulation of the iron complex. Firstly, one of several variations may be employed which avoid or reduce exposure of the iron complex to the acidic conditions of the stomach. Such approaches may range from a controlled release system, for example one based upon a polymer, which simply provides a delayed release of the complex, through a system which avoids dissociation under acidic conditions, for example by buffering, to a system which is pH sensitive and allows optimised release under alkaline conditions such as prevail in the small intestine. Specific examples of methods which may be used include the use of polymeric hydrogel formulations and liposome formulations.

A second approach to countering the effect of the acidic conditions prevailing in the stomach involves

formulation of the complex in the pharmaceutical composition together with the metal-free hydroxypyrrone from which it is derived or a salt thereof containing a physiologically acceptable cation. The dissociation of the neutral 3:1 ferric complex, for example, involves various equilibria between this complex, the 2:1 and 1:1 complexes, and the metal-free compound, so that the presence of the latter will inhibit this dissociation. Any proportion of the free compound can be advantageous in this context but little further advantage accrues from increasing the proportion beyond a certain level. A preferred range for the molar proportion of the free compound present in compositions according to the present invention is thus from 0 to 100 moles of free hydroxypyrrone:1 mole of iron complex, particularly of the neutral 3:1 iron (III) complex. Conveniently, a proportion of up to no more than 20, 30 or 50 moles:1 mole is used with a lower level of 1 or 2 moles:1 mole, although to obtain a marked effect upon dissociation of the iron complex a proportion of at least 5 or 10 moles:1 mole is usually employed. Thus a range of particular interest for the molar proportion of uncomplexed hydroxypyrrone:iron complex is from 1:1 to 100:1, for example from 5:1 to 50:1 or from 10:1 to 20:1. It will be appreciated that a solid mixture of the hydroxypyrrone and the corresponding 3:1 iron (III) complex in a proportion of from 1:1 to 100:1 is novel and that such novel mixtures are included by the present invention. The use of such a mixture is an important feature of the present invention since in principle it can enable one to obtain almost quantitative uptake of iron from the complex.

The use of an uncomplexed hydroxypyrrone or a salt thereof in admixture with its iron complex may also have another advantage in addition to the prevention of dissociation of the iron complex under acidic conditions. Thus, in certain pathological conditions there may be an excess of iron deposited at certain sites even though the patient exhibits an overall anaemia. In these patients the use of such a mixture has the advantage that the iron complex will remedy the overall anaemia whilst the free hydroxypyrrone will act to remove iron from pathological to physiological sites. However, although it is preferable for the hydroxypyrrone present in an iron donor to be rapidly metabolized in order that iron may be efficiently transferred to the binding proteins and eventually to the iron requiring mechanisms within the body, it is preferable for a hydroxypyrrone being used as an iron remover not to be rapidly metabolized so that it remains in the system, taking up iron, for an extended period. Thus, for example, maltol is rapidly metabolized and is therefore particularly suited for use as an iron complex, but for this same reason it is not appropriate for use in the free form. It is also the case that different compounds may function more efficiently either in the free form as an iron remover or in complex form as an iron donor for quite other reasons. Accordingly the present invention includes a mixture of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a different such 3-hydroxy-4-pyrone or a salt thereof containing a physiologically acceptable cation.

Alternatively, the different 3-hydroxy-4-pyrone may be replaced by a quite different form of iron chelating agent. Examples of such other iron chelating agents which may be used include the substituted 3-hydroxypyrid-2-ones and -4-ones and 1-hydroxypyrid-2-one and substituted 1-hydroxypyrid-2-ones (and salts of these various pyridones containing a physiologically acceptable cation) described in co-pending European Patent Applications 83301659.5 (0093498), 84301881.3 (0120669) and 84306437.9 (0138420).

When a free hydroxy-4-pyrone, hydroxypyrid-2-one, hydroxy-pyrid-4-one or salt thereof, or other iron chelating agent is present in admixture with the iron complex of a hydroxy-4-pyrone for the purpose of acting as an iron remover, then the amount of this agent used may be different than when a free hydroxypyrrone necessarily corresponding to that present in the iron complex is present primarily to prevent dissociation. Thus the daily dosage of the iron complex may be as above and the daily dosage of the free iron chelating agent, particularly when this is a hydroxy-pyrid-2- or -4-one or a 1-hydroxypyrid-2-one, may be that quoted in the co-pending applications referred to above, i.e. about 0.1 g to 5 g for human use, particularly 0.5 g to 2 g, from which it will be seen that the proportion of iron complex and free iron chelating agent used in such a context may extend across a wide range but preferred amounts of the free iron chelating agent tend to be higher than when this is necessarily a hydroxypyrrone.

In addition to the pharmaceutical uses of the iron complexes discussed above they are also of potential interest as a source of iron in various other contexts including cell and bacterial growth, plant growth, and the control of iron transport across membranes.

This invention is illustrated by the following Examples:—

EXAMPLES

Example 1

The preparation of iron maltol

A chloroform solution of maltol is mixed with a 1M solution of ferric chloride in ethanol to provide a 3:1 molar ratio of maltol:iron in the mixture. After 5 minutes at 20°C, a 10 molar excess of solid sodium carbonate is added and the mixture is stirred for 10 minutes. The mixture is then filtered and the solvent evaporated to give the neutral complex containing maltol and the ferric cation in 3:1 proportion. Recrystallisation of the 3:1 complex from ethanol gives wine red needle crystals in an essentially quantitative yield, m.p. 275°C, v_{max} (Nujol) ⁽¹⁾ 1600 cm^{-1} .

⁽¹⁾ Nujol is a Registered Trade Mark.

The use of an excess of maltol above the 3:1 molar ratio leads to an essential quantitative yield of a solid mixture of the excess maltol and the 3:1 iron maltol complex on rotary evaporation, this mixture not being deliquescent.

The partition coefficient K_{part} (concentration in n-octanol/concentration in aqueous phase) between n-octanol and Tris hydrochloride (20 mM, pH 7.4) of maltol and of its 3:1 iron complex is measured at 10^{-4} M by spectrophotometry. Acid washed glassware is used throughout and, following mixing for 1 minute, the aqueous/n-octanol mixture is centrifuged at 1000 g for 30 seconds. The two resulting phases are separated for a concentration determination by spectrophotometry on each. For maltol, the range 220–340 nm is used for the concentration determination whilst for the complex the range 340–640 nm is used. Typically, a value of 0.66 is obtained for maltol and of 0.50 for its iron complex, whilst comparative experiments on iron(III) EDTA and iron(III) ascorbate give much smaller values of 0.001 and 0.0015, respectively.

The ability of the iron complex of maltol to bind to haemoglobin is investigated by studying the elution profile of a ^{59}Fe label when a mixture of haemoglobin and the ^{59}Fe -labelled complex (at 1 mM concentration) in NaCl (130 mM) buffered to pH 7.4 by Tris hydrochloride is applied to a PD-10 column (Sephadex⁽¹⁾ G-10 gel permeation column — Pharmacia). Typically, no evidence is found for binding of the complex to haemoglobin which is an advantageous finding since such binding reduces availability of the iron.

The ability of the iron complex of maltol to bind to bovine serum albumen (BSA) is investigated through a similar procedure in which the complex is applied to a column with BSA rather than haemoglobin. The iron complex also shows little ability to bind to BSA.

⁽¹⁾ Sephadex is a Registered Trade Mark.

Example 2

In vitro tests on permeation of iron complexes into human erythrocytes

The accumulation of iron by human erythrocytes which are associated with the iron complex of maltol described in Example 1, and various other iron compounds by way of comparison, was studied by incubating the erythrocytes for 1 hour at 37°C in a medium consisting of the ^{59}Fe labelled iron compound in aqueous sodium chloride (130 mM) buffered to a pH of 7.4 by Tris hydrochloride. Following this period of incubation an aliquot of the erythrocyte/medium mixture was placed above a layer of silicone oil ($\rho = 1.06$) and the erythrocytes separated by centrifugation through the oil. The ^{59}Fe levels associated with the erythrocytes and the incubation medium were then counted and presented as a distribution ratio (concentration in erythrocytes/concentration in medium). The ratios obtained from the various iron compounds after incubation for 1 hour are shown in Table 1 where it will be seen that the uptake of iron is clearly much greater with the iron maltol complex than with the other compounds. Values of less than 0.1 are probably associated with binding to the external surface and do not represent transmembrane movement of iron. Moreover, although a period of 1 hour was employed in order to facilitate monitoring of the more slowly permeating iron compounds, the uptake of the iron maltol complex reached equilibrium at the level shown after about 15 minutes.

TABLE 1

Compound	Concentration (mM)	Distribution ratio
Fe^{III} (maltol) ₃	3	1.60
Fe^{II} gluconate	1	0.08
Fe^{III} ascorbate	1	0.12
Fe^{III} citrate	1	0.05
Fe^{III} EDTA	1	0.05

When the above described procedure was applied using ratios of maltol to iron of less than 3:1 larger apparent distribution ratios were observed than 1.60. However, this is explained by the non-specific binding of the positively charged 2:1 and 1:1 maltol: iron complexes to the surface of the erythrocytes which possesses a net negative charge, being rich in both phosphate and sulphate moieties. Experiments to determine the percentage of ^{59}Fe associated with erythrocyte ghosts after lysis confirm this hypothesis. In one experiment, lysis was initiated by a small volume of 10% v/v Triton ⁽¹⁾X100 and in a second experiment by a 10 fold excess of water. In each case the resulting ghosts were centrifuged through silicone oil

⁽¹⁾ Triton is a Registered Trade Mark.

($p = 1.02$) and, as will be seen from Table 2, very little of the 3:1 maltol:iron complex was found to be bound to the membranes, in contrast with the situation with the 2:1 and 1:1 complexes. Such binding is of course undesirable as the complex is likely to remain tightly bound to the membrane by electrostatic interactions and not be transmitted across it.

TABLE 2

Ratio of maltol:iron	Iron associated with with ghosts (%)	
	Triton lysis	Hypotonic lysis
0:1	100	—
1:1	55	63
2:1	22	39
3:1	<1	<5

Example 3

25 In vitro tests on permeation of rat jejunal sac by iron complexes

The iron uptake into the serosal space of the rat jejunal sac was compared for the iron complex of maltol described in Example 1 and various other iron compounds by way of comparison. Rats (male Sprague Dawley, 60 g) were killed and the jejunum removed, everted and cut into three segments (4 cm length). The segments were tied at both ends, filled with Krebs Ringer buffer (0.2 ml) and incubated in Krebs Ringer buffer containing the appropriate ^{59}Fe compound at 37°C for periods up to 90 minutes. The contents of the sac were counted for ^{59}Fe and measured spectrophotometrically.

The results obtained for the iron maltol complex and for 6 other iron compounds which are each contained in preparations marketed for the treatment of iron deficiency anaemia are shown in Table 3, the iron uptake for each at 15 and 60 minutes after the initiation of the experiment being shown relative to that for ferric chloride as 1. It will be seen that the iron maltol complex provides a level of iron uptake which is significantly higher than the levels observed for any of the 6 compounds in current use for the treatment of iron deficiency anamia. The uptake of the iron maltol complex was linear for a period of 90 minutes. Moreover, the uptake increased linearly as the concentration of the complex was increased over a range from 0.5 to 10 mM, so it does not show saturation kinetics and the process is thus non-facilitated and therefore should occur in all natural membranes.

TABLE 3

Compound	Relative iron uptake	
	15 minutes	60 minutes
FeCl_3	1	1
Fe^{III} (maltol) $_3$	40	5.8
Fe^{II} sulphate	2.4	1.4
Fe^{II} fumarate	4.0	1.8
Fe^{II} gluconate	1.6	0.8
Fe^{II} succinate	2.0	1.0
Fe^{III} ascorbate	0.4	0.8
Fe^{III} citrate	2.0	1.8

The procedure described above was used to compare the uptake of iron from buffer containing differing molar proportions of maltol:iron. The results obtained are presented in Table 4 which shows the amount of iron transferred via the maltol complex into the serosal contents of the sac, the basal uptake of iron measured in a control experiment being subtracted in each case. It will be seen that the amount of iron transferred in the case of a 3:1 molar proportion of maltol:iron (III) is much higher than in the other two cases and, moreover the low, but significant level of iron uptake observed in the case of a 2:1 ratio is attributed to the proportion of the 3:1 complex (containing 13% of the total iron) present under these conditions.

TABLE 4

Maltol/iron (molar ratio)	Iron uptake (n mole)
1:1	1.6
2:1	4.0
3:1	30.0

Example 4

In vivo test of action of iron compounds in the rat

The action of the iron complex of maltol described in Example 1 was compared with that of iron (II) sulphate, iron (III) EDTA (1:1 molar ratio) and iron (II) gluconate.

Groups of rats (300—350 g) were anaesthetised with nembutal (0.25 ml) and then with ether. A mid-line incision was made and the ^{59}Fe labelled sample [100 μg Fe, 3.7×10^6 becquerels (10 μCi)] was passed into the lumen of the duodenum via small incision. The abdominal wall was then closed with a suture. The animals were sacrificed 1, 2, 4 and 6 hours after the administration of the compound and the various organs were monitored for their ^{59}Fe content. The data is presented as histograms in Figures 1 to 4 which relate to iron maltol, iron sulphate, iron EDTA and iron gluconate, respectively, and show the levels of ^{59}Fe in cpm after various time intervals for the different organs, the data in each case representing a mean of the results for three individual animals. In the case of the data for blood and sternum (bone marrow) the counts given are cpm/ml and cpm/g respectively, whilst in all other cases they are the total cpm counts. The various histograms have been normalised and consequently are directly comparable.

A comparison between Figures 1 and 2 shows that the neutral 3:1 maltol:iron (III) complex is markedly superior to iron (II) sulphate for the introduction of iron via the rat intestine. The gut washings (which contain non-absorbed iron) show a much lower level of counts for the maltol complex, and the counts associated with the gut wall, liver, blood, bone marrow and spleen are correspondingly greater. It is clear from Figure 1 that ^{59}Fe associated with maltol enters the intestine wall very rapidly and from there it is efficiently removed by the blood supply. Iron is deposited in the bone marrow continuously throughout the 6 hour period at an apparently constant rate.

The maltol complex is also more efficient than iron (III) EDTA as shown by Figure 3. With the later complex, the gut washings remain high for 4 hours and may be presumed to decrease only due to the effect of natural bowel movements translocating material from the portion under investigation to lower portions of the intestine. The levels in the intestine wall and blood are extremely low. Although iron is transferred to both bone marrow and spleen, this is at reduced rates as compared to those obtained with the maltol complex. As shown by Figure 4, iron (II) gluconate proved more effective than the sulphate or the EDTA complex, although deposition in the gut wall was less than that observed with the maltol complex. The decrease was reflected in the lower levels of ^{59}Fe in both bone marrow and the spleen, the difference being particularly marked after 6 hours. In view of the much higher levels of ^{59}Fe trapped in the intestine wall in the case of the maltol complex, it may be predicted that this compound facilitates a more prolonged supply of iron than iron (II) gluconate.

This test illustrates the superiority of the neutral 3:1 maltol:iron (III) complex as compared with three commonly used "soluble iron" preparations for the movement of iron across the rat jejunal wall into the blood circulation, the iron maltol being very rapidly removed from the lumen of the intestine.

Example 5

In vivo test of action of iron complexes in the cat

The action of the iron complex of maltol described in Example 1, was compared with that of iron (III) EDTA (1:1 molar ratio) which is one of the iron compounds currently marketed for the treatment of iron deficiency anaemia. Cats were anaesthetised with chloralase (60 mg/kg) and pentobarbitone sodium (60 mg/kg) (i.p.), having been kept free of food for 18 hours. In each animal the trachea was cannulated to maintain a clear airway and allow positive pressure artificial respiration if necessary. The left femoral vein

was cannulated for the intravenous administration of drugs and physiological saline solution. Arterial blood pressure was monitored by a Washington pressure transducer through a cannula inserted into the femoral artery of the right hind leg. Arterial blood samples were taken at appropriate intervals from a short cannula inserted into an external carotid artery. Body temperature was monitored with a rectal thermometer. Each animal was given heparin (1000 iu/kg) as anticoagulant and additional small amounts

pentobarbitone sodium if needed to maintain a satisfactory level of anaesthesia. In those animals where the iron compounds were to be administered into the duodenum, a mid-line incision was made in the abdomen to reveal the intestines. A cannula was then inserted through a small cut such that its tip rested approximately 5 cm below the opening of the bile duct. The cannula was then sutured in place and the abdominal wall closed with stitches.

The iron maltol complex (100 µg Fe) alone (3:1 molar ratio of maltol:iron) and together with a large excess of maltol (40:1 molar ratio of maltol:iron) was injected intravenously in separate experiments and 0.25 ml samples of blood were taken at intervals. The apparent volume of distribution of the compound was calculated by extrapolation of the log-linear blood concentration curve to zero. (The volume corresponds to a value between that of the total extracellular space of the animal and the blood volume.) Elimination of ^{59}Fe from the blood followed first order kinetics with a rate constant of $-0.022/\text{minute}$ in the presence and absence of excess maltol, as illustrated in Figure 5 which shows the ^{59}Fe level in the blood in cpm/0.25 ml plotted against time in the case of one typical experiment of each type in an individual cat.

The distribution of ^{59}Fe in the tissues of the animal after the same intravenous experiment to which Figure 5 relates (the lower end of the ordinate in this Figure represents the background level) was investigated and the typical results are shown in Table 5. The amount of ^{59}Fe administered in this experiment was 1.48×10^5 becquerels (4 µCi) or 2.2×10^6 cpm. It will be seen that approximately 10% of the dose was located in the combined tissue of the heart, liver and spleen. As less than 0.2% of the dose was located in the urine, the bulk (approximately 90%) of the ^{59}Fe was almost certainly directed to the bone marrow and extremely high levels were found to be located in the sternum.

As indicated previously, the maltol complex is able to donate iron rapidly to transferrin and it is hypothesised that such an exchange occurs as soon as the complex is delivered to the plasma; and that the initial plateau (represented in Figure 5 by a dotted line) represents saturation of the plasma transferrin pool with ^{59}Fe . When there is net donation of ^{59}Fe from the plasma into the organs of the animal, the blood levels of radioactivity begin to fall, the major route of transfer of iron bound to transferrin being to the bone marrow, liver and spleen. Binding of ^{59}Fe to transferrin prevents its excretion in the urine.

TABLE 5
(Iron maltol, i.v.)

Tissue	Total tissue weight (g)	Sample weight (g)	Net ^{59}Fe content (cpm/g)	Net total ^{59}Fe content (cpm)
Heart	14.4	0.91	490	7,056
Liver	105	1.3	510	53,550
Spleen	8.4	0.86	14,890	125,076
Kidney	12.2	1.05	546	6,661
Skeletal muscle	—	1.85	0	0
Sternum (bone marrow)	—	1.2	3,200	—
Urine	—	1	152	<3,000

Identical experiments carried out with ^{59}Fe labelled iron (III) EDTA gave a entirely different picture as will be seen for the results of a typical experiment illustrated in Figure 6 (in which the lower end of the ordinate represents the background level) and Table 6 (the amount of ^{59}Fe administered in this experiment was 7.4×10^4 becquerels (2 µCi) but the figures given in the table have been adjusted to correspond to a dosage of 2.2×10^6 cpm in order to facilitate comparison with Table 5). In this experiment the radioactivity in the blood showed no initial plateau. Instead, loss of radioactivity followed at least a two-component

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process such that a large amount found its way to the urine rather than to the tissues. The rate constant of the elimination from the blood of the linear phase of the regression was 0.023/minute. The concentration of radioactivity in the kidney and urine, and not in the bone marrow or spleen, would indicate that iron in this form does not appear to be able to attach to transferrin in the plasma and protect itself from urinary excretion. The combined tissue of heart, liver and spleen contained only 1% of the original dose at the end of the experiment, whereas the urine contained over 50%. This is in accord with the fact that EDTA does not exchange iron with transferrin rapidly.

TABLE 6
(Iron EDTA, i.v.)

Tissue	Total tissue weight (g)	Sample weight (g)	Net ⁵⁹ Fe content (cpm/g)	Net total ⁵⁹ Fe content (cpm)
Heart	15.5	1.01	209	3,248
Liver	75	1.21	261	19,600
Sternum (bone marrow)	—	0.28	1,164	—
Spleen	11.2	0.89	162	1,814
Kidney	19.2	1.47	1,134	21,770
Skeletal muscle	—	2.59	95	—
Urine	19 ml	2 ml	62,156	1,180,900

The iron maltol complex (100 µg Fe) was also administered to the duodenum of the cat in the presence of a 40 fold excess of maltol followed by 5 ml of 150 ml Tris hydrochloride buffer (pH 7.4). In this case the ⁵⁹Fe content of the blood, as shown in Figure 7, reaches a maximum level 2 hours after the initial administration (the readings start at about 300 cpm/0.5 ml which represents the background reading). The distribution of ⁵⁹Fe in the tissues of the animal after the same duodenal experiment to which Figure 7 relates were investigated and the typical results are shown in Table 7. The amount of ⁵⁹Fe administered in this experiment was 3.7×10^5 becquerels (10 µCi) or 5.327×10^6 cpm into a 2.9 kg cat. It will be seen that the distribution of the ⁵⁹Fe after 4 hours was similar to that after intravenous infusion, with low levels in the kidney and urine and high levels in both the spleen and bone marrow.

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TABLE 7
(Iron maltol, per duodenum)

Tissue	Total tissue weight (g)	Sample weight (g)	Net ⁵⁹ Fe content (cpm/g)	Net total ⁵⁹ Fe content (cpm)
Heart	14	0.633	50	1,106
Liver	81	1.45	400	32,400
Spleen	12.7	1.19	3,783	48,047
Kidney	14.4	0.835	79	1,138
Sternum (bone marrow)	10	1.26	790	7,905
Bile	5 ml	1 ml	2,200	11,000
Urine	10 ml	1 ml	22	220

When ⁵⁹Fe labelled iron (III) EDTA was administered duodenally in the same manner, the plasma levels of radioactivity hardly exceeded the background level and are therefore not illustrated in a Figure. The distribution of ⁵⁹Fe in the tissues of the animal after the same duodenal experiment were investigated and the typical results are shown in Table 8. The amount of ⁵⁹Fe administered in this experiment was 3.7×10^5 becquerels (10 μ Ci) or 2.65×10^6 cpm into a 2.9 kg cat. It will be seen that, although some ⁵⁹Fe entered the tissues, rather low levels were detected in the spleen and bone marrow (sternum) whereas a large proportion of the dose was located in the urine.

TABLE 8
(Iron EDTA, per duodenum)

Tissue	Total tissue weight (g)	Sample weight (g)	Net ⁵⁹ Fe content (cpm/g)	Net total ⁵⁹ Fe content (cpm)
Heart	15.3	1.18	188	2,878
Liver	59.3	0.78	499	29,574
Kidney	11.3	0.90	1,762	19,913
Spleen	4.4	0.42	200	880
Sternum (bone marrow)	—	0.78	917	—
Skeletal muscle	—	1.48	117	—
Urine	15 ml	5 ml	36,306	544,596

Example 6

Polymer formulation of iron maltol

A solution of ferric chloride (concentration between 1 and 5% w/v), together with maltol in a weight ratio of 8 parts by weight of maltol to 1 part by weight of ferric chloride, is prepared in a 4.5:4.5:1 v/v/v

mixture of chloroform:methanol:water. Sodium carbonate is added in a 10 molar excess over the iron content in order to remove hydrochloric acid and the precipitated NaCl and Na₂CO₃ are filtered off. The preparation is contacted with a cross-linked polyethylene glycol hydrogel material to effect take up of the solution by the polymer and provide a polymer formulation of iron maltol in the presence of excess maltol.

Claims

1. An iron complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for use in therapy.
2. A complex according to Claim 1, in which the or each aliphatic hydrocarbon group is of 1 to 4 carbon atoms.
3. A complex according to Claim 1 or 2, in which the or each aliphatic hydrocarbon group is an acyclic group.
4. A complex according to Claim 1 or 2, in which the or each aliphatic hydrocarbon group is a cycloalkyl or alkyl group.
5. A complex according to Claim 1, being a complex of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different substituents, selected from methyl, ethyl, n-propyl and isopropyl.
6. A complex according to Claim 5, in which the or each substituent is a methyl group.
7. A complex according to any of Claims 1 to 6, in which the substituted 3-hydroxy-4-pyrone has a single substituent at the 2- or 6-position.
8. A complex according to any of the preceding claims, being a neutral 3:1 hydroxypyrrone:iron(III) complex.
9. A complex according to Claim 1, being the neutral 3:1 hydroxy-pyrone:iron(III) complex of 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-6-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone.
10. A complex according to Claim 1, being the neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-2-methyl-4-pyrone.
11. A complex according to Claim 1, being the neutral 3:1 hydroxypyrrone:iron(III) complex of 2-ethyl-3-hydroxy-4-pyrone.
12. A neutral 3:1 complex according to any of Claims 8 to 11, being substantially free from complexes containing other proportions of the hydroxypyrrone and iron(III).
13. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier, but excluding any liquid which is non-sterile and non-pyrogen free.
14. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable solid carrier.
15. A pharmaceutical composition according to Claim 14, which is adapted for oral administration.
16. A pharmaceutical composition according to Claim 15 in table form.
17. A pharmaceutical composition according to Claim 14 in suppository form.
18. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent, said composition being of a sterile injectable form.
19. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier, said composition being of a delayed release form.
20. A pharmaceutical composition according to Claim 19, which is adapted for release of the iron complex in the small intestine rather than in the stomach.
21. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier, said composition being of a form resistant to dissociation under aqueous acidic conditions.
22. A pharmaceutical composition according to Claim 21, which is adapted for dissociation under aqueous alkaline conditions.

mixture of chloroform:methanol:water. Sodium carbonate is added in a 10 molar excess over the iron content in order to remove hydrochloric acid and the precipitated NaCl and Na₂CO₃ are filtered off. The preparation is contacted with a cross-linked polyethylene glycol hydrogel material to effect take up of the solution by the polymer and provide a polymer formulation of iron maltol in the presence of excess maltol.

Claims

1. An iron complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for use in therapy.
2. A complex according to Claim 1, in which the or each aliphatic hydrocarbon group is of 1 to 4 carbon atoms.
3. A complex according to Claim 1 or 2, in which the or each aliphatic hydrocarbon group is an acyclic group.
4. A complex according to Claim 1 or 2, in which the or each aliphatic hydrocarbon group is a cycloalkyl or alkyl group.
5. A complex according to Claim 1, being a complex of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different substituents selected from methyl, ethyl, n-propyl and isopropyl.
6. A complex according to Claim 5, in which the or each substituent is a methyl group.
7. A complex according to any of Claims 1 to 6, in which the substituted 3-hydroxy-4-pyrone has a single substituent at the 2- or 6-position.
8. A complex according to any of the preceding claims, being a neutral 3:1 hydroxypyrrone:iron(III) complex.
9. A complex according to Claim 1, being the neutral 3:1 hydroxy-pyrone:iron(III) complex of 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-6-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone.
10. A complex according to Claim 1, being the neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-2-methyl-4-pyrone.
11. A complex according to Claim 1, being the neutral 3:1 hydroxypyrrone:iron(III) complex of 2-ethyl-3-hydroxy-4-pyrone.
12. A neutral 3:1 complex according to any of Claims 8 to 11, being substantially free from complexes containing other proportions of the hydroxypyrrone and iron(III).
13. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier, but excluding any liquid which is non-sterile and non-pyrogen free.
14. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable solid carrier.
15. A pharmaceutical composition according to Claim 14, which is adapted for oral administration.
16. A pharmaceutical composition according to Claim 15 in table form.
17. A pharmaceutical composition according to Claim 14 in suppository form.
18. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent, said composition being of a sterile injectable form.
19. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier, said composition being of a delayed release form.
20. A pharmaceutical composition according to Claim 19, which is adapted for release of the iron complex in the small intestine rather than in the stomach.
21. A pharmaceutical composition comprising a physiologically effective amount of a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier, said composition being of a form resistant to dissociation under aqueous acidic conditions.
22. A pharmaceutical composition according to Claim 21, which is adapted for dissociation under aqueous alkaline conditions.



23. A pharmaceutical composition according to any of Claims 13 to 22, in which the or each aliphatic hydrocarbon group is of 1 to 4 carbon atoms.
24. A pharmaceutical composition according to any of Claims 13 to 23, in which the or each aliphatic hydrocarbon group is an acyclic group.
25. A pharmaceutical composition according to any of Claims 13 to 23, in which the or each aliphatic hydrocarbon group is a cycloalkyl or alkyl group.
26. A pharmaceutical composition according to any of claims 13 to 22, in which the complex is of a 3-hydroxy-4-pyrone wherein one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different substituents selected from methyl, ethyl, n-propyl and isopropyl.
27. A pharmaceutical composition according to Claim 26, in which the or each substituent is a methyl group.
28. A pharmaceutical composition according to any of Claims 13 to 27, in which the substituted 3-hydroxy-4-pyrone has a single substituent at the 2- or 6-position.
29. A pharmaceutical composition according to any of Claims 13 to 22, in which the complex is of 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-6-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone.
30. A pharmaceutical composition according to any of Claims 13 to 22, in which the complex is of a 3-hydroxy-2-methyl-4-pyrone.
31. A pharmaceutical composition according to any of Claims 13 to 22, in which the complex is of 2-ethyl-3-hydroxy-4-pyrone.
32. A pharmaceutical composition according to any of Claims 13 to 31, in which the neutral 3:1 complex is substantially free from complexes containing other proportions of the hydroxypyrrone and iron(III).
33. A pharmaceutical composition according to Claim 32, in which the iron complex is in substantially pure form.
34. A pharmaceutical composition according to any of Claims 13 to 33, which contains an iron chelating agent as an additional active component thereof.
35. A pharmaceutical composition according to Claim 34, in which the iron chelating agent is uncomplexed 3-hydroxy-4-pyrone or an uncomplexed 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or a salt thereof containing a physiologically acceptable cation.
36. A pharmaceutical composition according to Claim 35, which comprises a complexed hydroxypyrrone together with the same hydroxypyrrone or a salt thereof in uncomplexed form.
37. A pharmaceutical composition according to Claim 36, which comprises the neutral 3:1 iron complex of 3-hydroxy-2-methyl-4-pyrone and uncomplexed 3-hydroxy-2-methyl-4-pyrone or a salt thereof.
38. A pharmaceutical composition according to Claim 36 or 37, in which the molar proportion of uncomplexed hydroxypyrrone:iron(III) complex is from 1:1 to 100:1.
39. A pharmaceutical composition according to any of Claims 13 to 38, which contains folic acid as an additional active component thereof.
40. A pharmaceutical composition according to any of Claims 13 to 39 in unit dosage form.
41. A pharmaceutical composition according to any of Claims 13 to 40 for human use.
42. A neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, but excluding 3-hydroxy-2-methyl-4-pyrone.
43. A complex according to Claim 42, being the neutral 3:1 iron(III) complex of 3-hydroxy-4-pyrone, 3-hydroxy-6-methyl-4-pyrone or 2-ethyl-3-hydroxy-4-pyrone.
44. A complex according to Claim 42, being the neutral 3:1 iron(III) complex of 2-ethyl-3-hydroxy-4-pyrone.
45. A complex according to Claim 42, 43 or 44, being substantially free from iron complexes containing other proportions of the hydroxy-pyrone and iron(III).
46. A mixture in the solid form of (a) a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms; and (b) the same hydroxypyrrone, or a salt thereof containing a physiologically acceptable cation, in uncomplexed form; the molar proportion of uncomplexed hydroxypyrrone:iron complex being from 1:1 to 100:1.
47. The mixture of (a) a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms; and (b) an iron chelating agent other than the particular hydroxypyrrone which is present in the complex, in uncomplexed form.
48. A mixture of (a) a neutral 3:1 hydroxypyrrone:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms; and (b) a different hydroxypyrrone being 3-hydroxy-4-pyrone or a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or a salt thereof containing a physiologically acceptable cation, in uncomplexed form.



49. A mixture according to Claim 46, 47 or 48, in which the complex is of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different substituents selected from methyl, ethyl, n-propyl and isopropyl.
50. A mixture according to Claim 46, 47 or 48, in which the complex is of 3-hydroxy-4-pyrone, 3-hydroxy-2-methyl-4-pyrone, 3-hydroxy-6-methyl-4-pyrone, or 2-ethyl-3-hydroxy-4-pyrone.
51. A pharmaceutical composition comprising a complex according to any of Claims 42 to 45 or a mixture according to any of Claims 47 to 50, together with a physiologically acceptable diluent or carrier.
52. A process for the preparation of a neutral 3:1 hydroxypyron:iron(III) complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, but excluding 3-hydroxy-2-methyl-4-pyrone, which comprises reacting the hydroxypyron with ferric ions at a pH in the range of 6 to 9 to form the 3:1 complex and isolating said complex in the solid form.
53. A process according to Claim 52, in which the complex is as defined in any of Claims 43 to 45.
54. The use of an iron complex of 3-hydroxy-4-pyrone or of a 3-hydroxy-4-pyrone in which one or more of the hydrogen atoms attached to ring carbon atoms are replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for the manufacture of a medicament for use in effecting an increase in the level of iron in a patient's bloodstream.
55. The use of a complex according to Claim 54, in which the complex is as defined in any of Claims 1 to 12.

Patentansprüche

1. Eisenkomplex von 3-Hydroxy-4-pyron oder 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ring kohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zur Verwendung in der Therapie.
2. Komplex nach Anspruch 1, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe 1 bis 4 Kohlenstoffatome aufweist.
3. Komplex nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine acyclische Gruppe ist.
4. Komplex nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine Cycloalkyl- oder Alkylgruppe ist.
5. Komplex nach Anspruch 1, nämlich ein Komplex von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch die gleichen oder verschiedene Substituenten, ausgewählt aus Methyl, Ethyl, n-Propyl und Isopropyl, ersetzt sind.
6. Komplex nach Anspruch 5, dadurch gekennzeichnet, daß der oder jeder Substituent eine Methylgruppe ist.
7. Komplex nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das substituierte 3-Hydroxy-4-pyron einen einzigen Substituenten in 2- oder 6-Position hat.
8. Komplex nach einem der vorstehenden Ansprüche, nämlich ein neutraler 3:1-Hydroxypyron:Eisen(III)-Komplex.
9. Komplex nach Anspruch 1, nämlich der neutrale 3:1-Hydroxypyron:Eisen(III)-Komplex von 3-Hydroxy-4-pyron, 3-Hydroxy-2-methyl-4-pyron, 3-Hydroxy-6-methyl-4-pyron oder 2-Ethyl-3-hydroxy-4-pyron.
10. Komplex nach Anspruch 1, nämlich der neutrale 3:1-Hydroxypyron:Eisen(III)-Komplex von 3-Hydroxy-2-methyl-4-pyron.
11. Komplex nach Anspruch 1, nämlich der neutrale 3:1-Hydroxypyron:Eisen(III)-Komplex von 2-Ethyl-3-hydroxy-4-pyron.
12. Neutraler 3:1-Komplex nach einem der Ansprüche 8 bis 11, dadurch gekennzeichnet, daß er im wesentlichen von Komplexen frei ist, die andere Verhältnismengen von Hydroxypyron und Eisen(III) enthalten.
13. Arzneimittel, dadurch gekennzeichnet, daß es eine physiologisch wirksame Menge eines neutralen 3:1-Hydroxypyron:Eisen(III)-Komplexes von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit einem physiologisch annehmbaren Verdünnungsmittel oder Träger, jedoch unter Ausschluß irgendeiner Flüssigkeit, die nicht steril und nicht pyrogenfrei ist, enthält.
14. Arzneimittel, dadurch gekennzeichnet, daß es eine physiologisch wirksame Menge eines neutralen 3:1-Hydroxypyron:Eisen(III)-Komplexes von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit einem physiologisch annehmbaren festen Träger enthält.
15. Arzneimittel nach Anspruch 14, dadurch gekennzeichnet, daß es für die orale Verabreichung ausgebildet ist.
16. Arzneimittel nach Anspruch 15 in Tablettenform.



17. Arzneimittel nach Anspruch 14 in Suppositorienform.

18. Arzneimittel, dadurch gekennzeichnet, daß es eine physiologisch wirksame Menge eines neutralen 3:1-Hydroxypyron:Eisen(III)-Komplexes von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit einem physiologisch annehmbaren Verdünnungsmittel enthält, wobei das Arzneimittel in steriler injizierbarer Form vorliegt.

19. Arzneimittel, dadurch gekennzeichnet, daß es eine physiologisch wirksame Menge eines neutralen 3:1-Hydroxypyron:Eisen(III)-Komplexes von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatom ersetzt sind, zusammen mit einem physiologisch annehmbaren Verdünnungsmittel oder Träger enthält, wobei das genannte Arzneimittel in Retardform vorliegt.

20. Arzneimittel nach Anspruch 19, dadurch gekennzeichnet, daß es für die Freisetzung des Eisen-Komplexes im kleinen Darm anstelle im Magen ausgebildet ist.

21. Arzneimittel, dadurch gekennzeichnet, daß es eine physiologisch wirksame Menge eines neutralen 3:1-Hydroxypyron:Eisen(III)-Komplexes von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit einem physiologisch annehmbaren Verdünnungsmittel oder Träger enthält, wobei das genannte Arzneimittel in einer Form vorliegt, die gegenüber einer Dissoziation unter wäßrigen sauren Bedingungen beständig ist.

22. Arzneimittel nach Anspruch 21, dadurch gekennzeichnet, daß es für die Dissoziation unter wäßrigen alkalischen Bedingungen ausgebildet ist.

23. Arzneimittel nach einem der Ansprüche 13 bis 22, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe 1 bis 4 Kohlenstoffatome aufweist.

24. Arzneimittel nach einem der Ansprüche 13 bis 23, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine acyclische Gruppe ist.

25. Arzneimittel nach einem der Ansprüche 13 bis 23, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine Cycloalkyl- oder Alkylgruppe ist.

26. Arzneimittel nach einem der Ansprüche 13 bis 22, dadurch gekennzeichnet, daß der Komplex von einem 3-Hydroxy-4-pyron ist, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch die gleichen oder verschiedene Substituenten, ausgewählt aus Methyl, Ethyl, n-Propyl und Isopropyl, ersetzt sind.

27. Arzneimittel nach Anspruch 26, dadurch gekennzeichnet, daß der oder jeder Substituent eine Methylgruppe ist.

28. Arzneimittel nach einem der Ansprüche 13 bis 27, dadurch gekennzeichnet, daß das substituierte 3-Hydroxy-4-pyron einen einzigen Substituenten in 2- oder 6-Position aufweist.

29. Arzneimittel nach einem der Ansprüche 13 bis 22, dadurch gekennzeichnet, daß der Komplex von 3-Hydroxy-4-pyron, 3-Hydroxy-2-methyl-4-pyron, 3-Hydroxy-6-methyl-4-pyron oder 2-Ethyl-3-hydroxy-4-pyron ist.

30. Arzneimittel nach einem der Ansprüche 13 bis 22, dadurch gekennzeichnet, daß der Komplex von 3-Hydroxy-2-methyl-4-pyron ist.

31. Arzneimittel nach einem der Ansprüche 13 bis 22, dadurch gekennzeichnet, daß der Komplex von 2-Ethyl-3-hydroxy-4-pyron ist.

32. Arzneimittel nach einem der Ansprüche 13 bis 31, dadurch gekennzeichnet, daß der neutrale 3:1-Komplex im wesentlichen von Komplexen frei ist, die andere Verhältnismengen von Hydroxypyron und Eisen(III) enthalten.

33. Arzneimittel nach Anspruch 32, dadurch gekennzeichnet, daß der Eisenkomplex in im wesentlichen reiner Form vorliegt.

34. Arzneimittel nach einem der Ansprüche 13 bis 33, dadurch gekennzeichnet, daß es ein Eisen-Chelierungsmittel als weitere aktive Komponente davon enthält.

35. Arzneimittel nach Anspruch 34, dadurch gekennzeichnet, daß das Eisen-Chelierungsmittel nichtkomplexiertes 3-Hydroxy-4-pyron oder ein nichtkomplexiertes 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, oder ein Salz davon, das ein physiologisch annehmbares Kation enthält, ist.

36. Arzneimittel nach Anspruch 35, dadurch gekennzeichnet, daß es ein komplexiertes Hydroxypyron zusammen mit dem gleichen Hydroxypyron oder einem Salz davon in unkomplexierter Form enthält.

37. Arzneimittel nach Anspruch 36, dadurch gekennzeichnet, daß es den neutralen 3:1-Eisenkomplex von 3-Hydroxy-2-methyl-4-pyron und nichtkomplexiertes 3-Hydroxy-2-methyl-4-pyron oder ein Salz davon enthält.

38. Arzneimittel nach Anspruch 36 oder 37, dadurch gekennzeichnet, daß das Molverhältnis von nichtkomplexiertem Hydroxypyron:Eisen(III)-Komplex 1:1 bis 100:1 beträgt.

39. Arzneimittel nach einem der Ansprüche 13 bis 38, dadurch gekennzeichnet, daß es Folsäure als weitere aktive Komponente davon enthält.



40. Arzneimittel nach einem der Ansprüche 13 bis 39, dadurch gekennzeichnet, daß es in Einheitsdosisform vorliegt.

41. Arzneimittel nach einem der Ansprüche 13 bis 40 für die Verwendung in der Humantherapie.

42. Neutraler 3:1-Hydroxypyron:Eisen(III)-Komplex von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenwasserstoffatomen ersetzt sind, jedoch ausgenommen 3-Hydroxy-2-methyl-4-pyron.

43. Komplex nach Anspruch 42, nämlich der neutrale 3:1-Eisen(III)-Komplex von 3-Hydroxy-4-pyron, 3-Hydroxy-6-methyl-4-pyron oder 2-Ethyl-3-Hydroxy-4-pyron.

44. Komplex nach Anspruch 42, nämlich der neutrale 3:1-Eisen(III)-Komplex von 2-Ethyl-3-hydroxy-4-pyron.

45. Komplex nach Anspruch 42, 43 oder 44, dadurch gekennzeichnet, daß er im wesentlichen von Eisenkomplexen frei ist, die andere Verhältnismengen von Hydroxypyron und Eisen(III) enthalten.

46. Ein Gemisch in fester Form aus (a) einem neutralen 3:1-Hydroxypyron:Eisen(III)-Komplex von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, und (b) das gleiche Hydroxypyron oder ein Salz davon, das ein physiologisch annehmbares Kation enthält, in nichtkomplexierter Form enthält, wobei das Molverhältnis von nichtkomplexiertem Hydroxypyron:Eisen(III)-Komplex 1:1 bis 100:1 beträgt.

47. Gemisch aus (a) einem neutralen 3:1-Hydroxypyron:Eisen(III)-Komplex von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, und (b) einem anderen Eisen-Chelierungsmittel als das jeweilige Hydroxypyron, das in dem Komplex vorhanden ist, in nichtkomplexierter Form.

48. Gemisch aus (a) einem neutralen 3:1-Hydroxypyron:Eisen(III)-Komplex von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, und (b) einem davon verschiedenen Hydroxypyron, nämlich 3-Hydroxy-4-pyron oder 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist oder einem Salz davon, das ein physiologisch annehmbares Kation enthält, in nichtkomplexierter Form.

49. Gemisch nach Anspruch 46, 47 oder 48, dadurch gekennzeichnet, daß der Komplex von einem 3-Hydroxy-4-pyron ist, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch die gleichen oder verschiedene Substituenten, ausgewählt aus Methyl, Ethyl, n-Propyl und Isopropyl, ersetzt sind.

50. Gemisch nach Anspruch 46, 47 oder 48, dadurch gekennzeichnet, daß der Komplex von 3-Hydroxy-4-pyron, 3-Hydroxy-2-methyl-4-pyron, 3-Hydroxy-6-methyl-4-pyron oder 2-Ethyl-3-hydroxy-4-pyron ist.

51. Arzneimittel, dadurch gekennzeichnet, daß es einen Komplex nach einem der Ansprüche 42 bis 45 oder ein Gemisch nach einem der Ansprüche 47 bis 50 zusammen mit einem physiologisch annehmbaren Verdünnungsmittel oder Träger enthält.

52. Verfahren zur Herstellung eines neutralen 3:1-Hydroxypyron:Eisen(III)-Komplexes von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, jedoch ausgenommen von 3-Hydroxy-2-methyl-4-pyron, dadurch gekennzeichnet, daß man das Hydroxypyron mit Eisen(III)-Ionen bei einem pH-Wert im Bereich von 6 bis 9 umsetzt, um den 3:1-Komplex zu bilden, und daß man den genannten Komplex in der festen Form isoliert.

53. Verfahren nach Anspruch 52, dadurch gekennzeichnet, daß der Komplex wie in einem der Ansprüche 43 bis 45 definiert ist.

54. Verwendung eines Eisen-Komplexes von 3-Hydroxy-4-pyron oder von 3-Hydroxy-4-pyron, bei dem eines oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome angefügt sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zur Herstellung eines Arzneimittels zur Verwendung bei der Bewirkung einer Erhöhung des Eisenspiegels im Blutstrom des Patienten.

55. Verwendung des Komplexes nach Anspruch 54, dadurch gekennzeichnet, daß der Komplex wie in einem der Ansprüche 1 bis 12 definiert ist.

Revendications

1. Complexe de fer de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur les atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, pour utilisation en thérapeutique.
2. Complexe selon la revendication 1, dans lequel le ou chaque groupe hydrocarboné aliphatique comporte 1 à 4 atomes de carbone.



3. Complexe selon la revendication 1 ou 2, dans lequel le ou chaque groupe hydrocarboné aliphatique est un groupe acyclique.
4. Complexe selon la revendication 1 ou 2, dans lequel le ou chaque groupe hydrocarboné aliphatique est un groupe cycloalkyle ou alkyle.
5. Complexe selon la revendication 1, qui est un complexe d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par des substituants identiques ou différents choisis parmi un groupe méthyle, éthyle, n-propyle et isopropyle.
6. Complexe selon la revendication 5, dans lequel le ou chaque substituant est un groupe méthyle.
7. Complexe selon l'une quelconque des revendications 1 à 6, dans lequel la 3-hydroxy-4-pyrone substituée comporte un seul substituant en position 2 ou 6.
8. Complexe selon l'une quelconque des revendications précédentes, qui est un complexe neutre à 3:1 hydroxypyrrone:fer(III).
9. Complexe selon la revendication 1, qui est le complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone, de la 3-hydroxy-2-méthyl-4-pyrone, de la 3-hydroxy-6-méthyl-4-pyrone ou de la 2-éthyl-3-hydroxy-4-pyrone.
10. Complexe selon la revendication 1, qui est le complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-2-méthyl-4-pyrone.
11. Complexe selon la revendication 1, qui est le complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 2-éthyl-3-hydroxy-4-pyrone.
12. Complexe neutre à 3:1 selon l'une quelconque des revendications 8 à 11, qui est essentiellement dépourvu de complexes contenant d'autres proportions de l'hydroxypyrrone et du fer(III).
13. Composition pharmaceutique comprenant une quantité physiologiquement efficace d'un complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique comportant 1 à 6 atomes de carbone, avec un diluant, véhicule ou excipient physiologiquement acceptable, mais à l'exclusion de tout liquide qui n'est pas stérile et n'est pas dépourvu de pyrogènes.
14. Composition pharmaceutique comprenant une quantité biologiquement efficace d'un complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un group hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec un support solide physiologiquement acceptable.
15. Composition pharmaceutique selon la revendication 14, qui est destinée à une administration orale.
16. Composition pharmaceutique selon la revendication 15, sous forme de comprimés.
17. Composition pharmaceutique selon la revendication 14, sous forme de suppositoires.
18. Composition pharmaceutique comprenant une quantité physiologiquement efficace d'un complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone de noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec un diluant physiologiquement acceptable, ladite composition étant sous forme stérile injectable.
19. Composition pharmaceutique comprenant une quantité physiologiquement efficace d'un complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un group hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec un diluant, excipient ou support physiologiquement acceptable, ladite composition étant sous forme à libération retardée.
20. Composition pharmaceutique selon la revendication 19, qui est destinée à libérer le complexe de fer dans l'intestin grêle plutôt que dans l'estomac.
21. Composition pharmaceutique comprenant une quantité physiologiquement acceptable d'un complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec un diluant ou véhicule ou support physiologiquement acceptable, ladite composition étant sous une forme résistant à la dissociation dans des conditions aqueuses acides.
22. Composition pharmaceutique selon la revendication 21, qui est destinée à se dissocier dans des conditions aqueuses alcalines.
23. Composition pharmaceutique selon l'une quelconque des revendications 13 à 22, dans laquelle le ou chaque groupe hydrocarboné aliphatique comporte 1 à 4 atomes de carbone.
24. Composition pharmaceutique selon l'une quelconque des revendications 13 à 23, dans laquelle le ou chaque groupe hydrocarboné aliphatique est un groupe acyclique.
25. Composition pharmaceutique selon l'une quelconque des revendications 13 à 23, dans laquelle le ou chaque groupe hydrocarboné aliphatique est un groupe cycloalkyle ou alkyle.
26. Composition pharmaceutique selon l'une quelconque des revendications 13 à 22, dans laquelle le



complexe dérive d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par des substituants identiques ou différents choisis parmi un groupe méthyle, éthyle, n-propyle et isopropyle.

27. Composition pharmaceutique selon la revendication 26, dans laquelle le ou chaque substituant est un groupe méthyle.

28. Composition pharmaceutique selon l'une quelconque des revendications 13 à 27, dans laquelle la 3-hydroxy-4-pyrone substituée comporte un seul substituant sur la position 2 ou 6.

29. Composition pharmaceutique selon l'une quelconque des revendications 13 à 22, dans laquelle le complexe dérive de la 3-hydroxy-4-pyrone, de la 3-hydroxy-2-méthyl-4-pyrone, de la 3-hydroxy-6-méthyl-4-pyrone ou de la 2-éthyl-3-hydroxy-4-pyrone.

30. Composition pharmaceutique selon l'une quelconque des revendications 13 à 22, dans laquelle le complexe dérive de la 3-hydroxy-2-méthyl-4-pyrone.

31. Composition pharmaceutique selon l'une quelconque des revendications 13 à 22, dans laquelle le complexe dérive de la 2-éthyl-3-hydroxy-4-pyrone.

32. Composition pharmaceutique selon l'une quelconque des revendications 13 à 31, dans laquelle le complexe neutre à 3:1 est essentiellement dépourvu de complexes contenant d'autres proportions de l'hydroxypyrrone et du fer(III).

33. Composition pharmaceutique selon la revendication 32, dans laquelle le complexe de fer est sous forme essentiellement pure.

34. Composition pharmaceutique selon l'une quelconque des revendications 13 à 33, qui contient un agent de chélation du fer à titre de composant actif supplémentaire.

35. Composition pharmaceutique selon la revendication 34, dans laquelle l'agent de chélation du fer est la 3-hydroxy-4-pyrone non complexée ou une 3-hydroxy-4-pyrone non complexée dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) à des atomes de carbone du noyau est ou sont remplacé(s) par des groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un sel de ce composé contenant un cation physiologiquement acceptable.

36. Composition pharmaceutique selon la revendication 35, qui comprend une hydroxypyrrone complexée avec la même hydroxypyrrone ou un de ses sels sous forme non complexée.

37. Composition pharmaceutique selon la revendication 36, qui comprend le complexe neutre à 3:1 de fer de la 3-hydroxy-2-méthyl-4-pyrone et la 3-hydroxy-2-méthyl-4-pyrone non complexée ou un de ses sels.

38. Composition pharmaceutique selon la revendication 36 ou 37, dans laquelle la proportion molaire entre l'hydroxypyrrone non complexée et le complexe de fer(III) se situe entre 1:1 et 100:1.

39. Composition pharmaceutique selon l'une quelconque des revendications 13 à 38, qui contient de l'acide folique comme composant actif supplémentaire.

40. Composition pharmaceutique selon l'une quelconque des revendications 13 à 39, sous forme de doses unitaires.

41. Composition pharmaceutique selon l'une quelconque des revendications 13 à 40, destinée à l'administration à des êtres humains.

42. Complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, mais à l'exclusion de la 3-hydroxy-2-méthyl-4-pyrone.

43. Complexe selon la revendication 42, qui est le complexe neutre à 3:1 de fer(III) de la 3-hydroxy-4-pyrone, de la 3-hydroxy-6-méthyl-4-pyrone ou de la 2-éthyl-3-hydroxy-4-pyrone.

44. Complexe selon la revendication 42, qui est le complexe neutre à 3:1 de fer(III) de la 2-éthyl-3-hydroxy-4-pyrone.

45. Complexe selon la revendication 42, 43 ou 44, qui est essentiellement dépourvu de complexes de fer contenant d'autres proportions de l'hydroxypyrrone et du fer(III).

46. Mélange sous forme solide de (a) un complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur les atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone; et (b) de la même hydroxypyrrone, ou d'un de ses sels contenant un cation physiologiquement acceptable, sous forme non complexée; la proportion molaire de l'hydroxypyrrone non complexée au complexe de fer se situant entre 1:1 et 100:1.

47. Mélange de (a) un complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone; et (b) d'un agent de chélation du fer autre que l'hydroxypyrrone particulière qui est présente dans le complexe, sous forme non complexée.

48. Mélange de (a) un complexe neutre à 3:1 hydroxypyrrone:fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone; et (b) d'une hydroxypyrrone différente, qui est la 3-hydroxy-4-pyrone ou une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou



sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un de ses sels contenant un cation physiologiquement acceptable, sous forme non complexée.

49. Mélange selon la revendication 46, 47 ou 48, dans lequel le complexe dérive d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par des substituants identiques ou différents choisis parmi un groupe méthyle, éthyle, n-propyle et isopropyle.

50. Mélange selon la revendication 46, 47 ou 48, dans lequel le complexe dérive de la 3-hydroxy-4-pyrone, de la 3-hydroxy-2-méthyl-4-pyrone, de la 3-hydroxy-6-méthyl-4-pyrone, ou de la 2-éthyl-3-hydroxy-4-pyrone.

51. Composition pharmaceutique comprenant un complexe selon l'une quelconque des revendications 42 à 45 ou un mélange selon l'une quelconque des revendications 47 à 50, avec un diluant, véhicule ou support physiologiquement acceptable.

52. Procédé pour la préparation d'un complexe neutre à 3:1 hydroxypyron:2 fer(III) de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, mais à l'exclusion de la 3-hydroxy-2-méthyl-4-pyrone, qui comprend la réaction de l'hydroxypyron avec des ions ferriques à un pH compris entre 6 et 9 pour former le complexe à 3:1, et l'isolement dudit complexe sous forme solide.

53. Procédé selon la revendication 52, dans lequel le complexe est tel que défini dans l'une quelconque des revendications 43 à 45.

54. Utilisation d'un complexe de fer de la 3-hydroxy-4-pyrone ou d'une 3-hydroxy-4-pyrone dans laquelle un ou plusieurs des atomes d'hydrogène fixé(s) sur des atomes de carbone du noyau est ou sont remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, pour la fabrication d'un médicament destiné à servir à réaliser une augmentation du taux du fer dans le courant de la circulation sanguine d'un patient.

55. Utilisation d'un complexe selon la revendication 54, dans laquelle le complexe est tel que défini dans l'une quelconque des revendications 1 à 12.

