Material

FIELD

The present invention relates to granules containing water-insoluble inorganic solids, particularly mixed metal compounds, having pharmaceutical activity, as phosphate binders. It also extends to methods of manufacture of the granules and their use in unit doses for oral administration.

BACKGROUND

Various ailments may lead to high phosphate concentrations in the blood in animals, particularly warm-blooded animals such as humans. This can lead to a number of physiological problems, such as deposition of calcium phosphate.

In patients with kidney failure who are being treated by regular haemodialysis, phosphate concentrations in the blood plasma can rise dramatically and this condition, known as hyperphosphataemia, can result in calcium phosphate deposition in soft tissue. Plasma phosphate levels may be reduced by oral intake of inorganic and organic phosphate binders.

Classes of inorganic solid phosphate binders are disclosed in WO 99/15189. These include alkali treated inorganic sulphates, such as calcium sulphate, and mixed metal compounds which are substantially free from aluminium and which have a phosphate binding capacity of at least 30% by weight of the total weight of phosphate present, over a pH range of from 2-8, as measured by the phosphate binding test as described therein. The inorganic solids are water insoluble and are primarily intended for oral administration.

Typically such mixed metal compounds may contain iron (III) and at least one of magnesium, calcium, lanthanum and cerium. Preferably they also contain at least one of hydroxyl and carbonate anions and optionally additionally, at least one of sulphate, chloride and oxide.

Mixed metal compounds such as described in WO 99/15189 present particular problems in the formulation of unit dosages containing them. In part, these problems arise from the fact that the compounds need to be dosed in relatively large amounts. This means that in order for a unit dose to be of a size which does not make it too difficult to swallow, assisting with patient compliance, the inclusion level of the active ingredient needs to be quite high, leaving very little formulation space for excipients.

There is a need for unit doses containing such inorganic solid phosphate binders which include high levels of the pharmaceutically active ingredient yet which maintain physical integrity and stability on storage. There is also a need for such unit doses to disintegrate in order to release the solid inorganic phosphate binder in the stomach and to give rapid phosphate binding, but not to disintegrate excessively in the mouth or oesophagus resulting in an unpleasant taste and potential lack of patient compliance. There is also a need for processing routes for forming the solid inorganic phosphate binders into unit doses without problems caused by poor flowability of the material and yet without excessive hindering of the rate of phosphate binding for the material.

SUMMARY OF INVENTION

Thus, a first aspect of the present invention provides a granular material comprising (i) at least 50% by weight based on the weight of the granular material of solid water-insoluble mixed metal compound capable of binding phosphate of formula (I):

$M^{II}_{1-x}M^{III}_{x}(OH)_2A^{n-}_{y}.zH_2O$ (I)

where M^{II} is at least one of magnesium, calcium, lanthanum and cerium; M^{III} is at least iron(III); A^{n-} is at least one n-valent anion; $x = \Sigma ny$; $0 < x \leq 0.67$, $0 < y \leq 1$, and $0 \leq z \leq 10$; (ii) from 3 to 12% by weight based on the weight of the granular material of non-chemically bound water, and (iii) no greater than 47% by weight based on the weight of the granular material of excipient.

A second aspect of the invention provides a unit dose for oral administration comprising a water-resistant capsule containing granules according to the first aspect of the invention.

A third aspect of the invention provides a unit dose for oral administration comprising a compacted tablet of granules according to the first aspect of the invention. Preferably, the tablet is coated with a water-resistant coating.

The solid water-insoluble inorganic compound capable of binding phosphate is referred to herein as an "inorganic phosphate binder" or as “binder”.

References herein to "granules" equally apply to the "granular material" of the present invention.

It has been found that surprisingly, for such granules for use in unit doses, the level of water is critical in maintaining the physical integrity of the granules, and of unit doses prepared from the granules during storage. Correct levels of water provide good phosphate binding when the granules are ingested, without excessive break-up of the granules or of tablets formed from the granules in the mouth. It has also been found that such granules bind phosphate rapidly.

It has also been found that by providing the compound of formula I is a granular form rather that as a powder the flowability problems of powders and the storage stability problems of powder based tablets are overcome while the advantages of such systems with regard to rapid disintegration are maintained. Fine particle size, for example as found in powders, results in very poor flowability of the powder resulting in poor tablet compression (tablets too soft and not homogenous), poor storage stability and problems with equipment loading. Surprisingly, we have found that by first increasing the particle size of the finely divided particulate by granulation of the mixture of compound of formula I with excipients, drying the granules to a controlled moisture content and reducing the granule size back down again to a more finely divided particulate (such as the 'small' particle size distribution of Table 7) we can obtain suitable phosphate binding granules without requiring substantial increased levels of excipients

whilst enabling operation of tablet compression machines typically capable of commercial production rates (for example from 10,000 to 150,000 tablets/hour) and compression into a suitably shaped tablet of a compact size which is not too difficult to swallow. In contrast, typical tablet formulations such as those disclosed in US4415555 or US4629626 Miyata et al of hydrotalcite materials resulted in formulations comprising less than 50% of the active compound and/or requiring hydrothermal treatment of the hydrotalcite to increase storage stability of the tablets.

The water content of the granules of the present invention is expressed in terms of the content of non-chemically bound water in the granules. This non-chemically bound water therefore excludes chemically bound water. Chemically bound water may also be referred to as structural water.

The amount of non-chemically bound water is determined by pulverizing the granules, heating at 105°C for 4 hours and immediately measuring the weight loss. The weight equivalent of non-chemically bound water driven off can then be calculated as a weight percentage of the granules.

It has been found that if the amount of non-chemically bound water is less than 3% by weight of the granules, tablets formed from the granules become brittle and may break very easily. If the amount of non-chemically bound water is greater than 10% by weight of the granules, disintegration time of the granules and of tablets prepared from the granules increases, with an associated reduction in phosphate binding rate and the storage stability of the tablet or granules becomes unacceptable leading to crumbling on storage.

By water-insoluble phosphate binder, it is meant that the binder has a solubility in distilled water at 25°C of 0.5g /litre or less, preferably 0.1g/litre or less, more preferably 0.05g/litre or less.

The water-resistant capsule of the second aspect of the invention is suitably a hard gelatine capsule. For the water-resistant capsule, by water-resistant it is meant that on storage for 4 weeks at 40°C and 70% relative humidity, the water

uptake of the unit dose, (i.e. the capsule containing the granules of the first aspect of the invention), due to moisture content change is preferably less than 10% more preferably less than 5% by weight of the unit dose. Such capsules have the advantage of helping stabilise the moisture content of the granules on storage

The tablets of third aspect of the invention preferably have a water-resistant coating in order to inhibit moisture ingress into the tablet or moisture loss from the tablet on storage. However, the water resistant coating must allow break-up of the tablet after a suitable time following ingestion such that the inorganic solid phosphate binder can be effective in the gut of the patient. By water-resistant it is meant that on storage for 4 weeks at 40°C and 70% relative humidity, the water uptake of the coated tablet due to moisture content change is preferably less than 10% more preferably less than 5% by weight of the coated tablet. In a preferred aspect by water-resistant it is meant that on storage for 12 months at 25°C and 60% relative humidity, the water uptake of the coated tablet due to moisture content change is preferably less than 10% more preferably less than 5% by weight of the coated tablet. In a further preferred aspect by water-resistant it is meant that on storage for 12 months at 30°C and 65% relative humidity, the water uptake of the coated tablet due to moisture content change is preferably less than 10% more preferably less than 5% by weight of the coated tablet. In a preferred aspect by water-resistant it is meant that on storage for 6 months at 40°C and 75% relative humidity, the water uptake of the coated tablet due to moisture content change is preferably less than 10% more preferably less than 5% by weight of the coated tablet.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

PHOSPHATE BINDERS

By binding of phosphate ions, it is meant that the phosphate ions are removed from solution and are immobilised in the atomic structure of the water-insoluble inorganic solid phosphate binder.

Suitable water-insoluble inorganic solids for binding phosphate ions from solution (hereinafter also called inorganic phosphate binders or as binders for brevity) are disclosed for instance in WO 99/15189 and include sulphates such as calcium sulphate, which has been alkali treated, mixtures of different metal salts and mixed metal compounds as described below. Preferred water-insoluble inorganic solids for use as phosphate binders in the tablets of the invention are mixed metal compounds.

Because of their water-insolubility, it is preferred if the inorganic phosphate binders used in the tablets of the invention are in a finely divided particulate form such that an adequate surface area is provided over which phosphate binding or immobilisation can take place. Suitably, the inorganic phosphate binder particles have a weight median particle diameter (d_{50}) of from 1 to 20 micrometres, preferably from 2 to 11 micrometres. Preferably, the inorganic phosphate binder particles have a d_{90} (i.e. 90% by weight of the particles have a diameter less than the d_{90} value) of 100 micrometres or less.

MIXED METAL BINDERS

The present invention provides a granular material comprising (i) at least 50% by weight based on the weight of the granular material of solid mixed metal compound capable of binding phosphate of formula (I):

$$M^{II}_{1-x}M^{III}_{x}(OH)_2A^{n-}_{y}.zH_2O \qquad (I)$$

where M^{II} is at least one of magnesium, calcium, lanthanum and cerium; M^{III} is at least iron(III); A^{n-} is at least one n-valent anion; $x = \Sigma ny$; $0 < x \leq 0.67$, $0 < y \leq 1$, and $0 \leq z \leq 10$; (ii) from 3 to 12% by weight based on the weight of the granular material of non-chemically bound water, and (iii) no greater than 47% by weight based on the weight of the granular material of excipient. The present invention further provides a unit dose for oral administration comprising a water-resistant capsule containing the granular material. The present invention yet further provides a unit dose for oral administration comprising a compacted tablet of the granular material. Preferably, the tablet is coated with a water-resistant coating.

A preferred inorganic phosphate binder is solid water-insoluble mixed compound of formula (I):

$M^{II}_{1-x}M^{III}_{x}(OH)_2A^{n-}_{y}.zH_2O$ (I)

where M^{II} is at least one bivalent metal; M^{III} is at least one trivalent metal; A^{n-} is at least one n-valent anion; $x = \Sigma ny$ and x, y and z fulfil $0 < x \leq 0.67$, $0 < y \leq 1$, $0 \leq z \leq 10$.

In one preferred aspect $0.1 < x$, such as $0.2 < x$, $0.3 < x$, $0.4 < x$, or $0.5 < x$. In one preferred aspect $0 < x \leq 0.5$. It will be understood that $x = [M^{III}]/([M^{II}] + [M^{III}])$ where $[M^{II}]$ is the number of moles of M^{II} per mole of compound of formula I and $[M^{III}]$ is the number of moles of M^{III} per mole of compound of formula I.

In one preferred aspect $0 < y \leq 1$. Preferably $0 < y \leq 0.8$. Preferably $0 < y \leq 0.6$. Preferably $0 < y \leq 0.4$. Preferably $0.05 < y \leq 0.3$. Preferably $0.05 < y \leq 0.2$. Preferably $0.1 < y \leq 0.2$. Preferably $0.15 < y \leq 0.2$.

In one preferred aspect $0 \leq z \leq 10$. Preferably $0 \leq z \leq 8$. Preferably $0 \leq z \leq 6$. Preferably $0 \leq z \leq 4$. Preferably $0 \leq z \leq 2$. Preferably $0.1 \leq z \leq 2$. Preferably $0.5 \leq z \leq 2$. Preferably $1 \leq z \leq 2$. Preferably $1 \leq z \leq 1.5$. Preferably $1 \leq z \leq 1.4$. Preferably $1.2 \leq z \leq 1.4$. Preferably z is approximately 1.4.

Preferably, $0 < x \leq 0.5$, $0 < y \leq 1$, and $0 \leq z \leq 10$.

It will be appreciated that each of the preferred values of x, y and z may be combined. Thus any combination of each of the values listed in the table below are specifically disclosed herein and may be provided by the present invention.

x	y	z
$0.1 < x$	$0 < y \leq 0.8$	$0 \leq z \leq 10$
$0.2 < x$	$0 < y \leq 0.6$	$0 \leq z \leq 8$
$0.3 < x$	$0 < y \leq 0.4$	$0 \leq z \leq 6$
$0.4 < x$	$0.05 < y \leq 0.3$	$0 \leq z \leq 4$

$0.5 < x$	$0.05 < y \leq 0.2$	$0 \leq z \leq 2$
$0 < x \leq 0.67$	$0.1 < y \leq 0.2$	$0.1 \leq z \leq 2$
$0 < x \leq 0.5$	$0.15 < y \leq 0.2$	$0.5 \leq z \leq 2$
		$1 \leq z \leq 2$
		$1 \leq z \leq 1.5$
		$1 \leq z \leq 1.4$
		$1.1 \leq z \leq 1.4$

In the above formula (I), when A represents more than one anion, the valency (n) of each may vary. "Σny" means the sum of the number of moles of each anion multiplied by its respective valency.

In formula (I), M^{II} is preferably selected from Mg (II), Zn (II), Fe (II), Cu (II), Ca (II), La (II) and Ni(II). Of these, Mg is especially preferred. M^{III} is preferably selected from Mn(III), Fe(III), La(III), Ni (III) and Ce(III). Of these, Fe(III) is especially preferred. Herein, (II) means a metal in a divalent state and (III) means a metal in a trivalent state.

A^{n-} is preferably selected from one or more of carbonate, hydroxycarbonate, oxo-anions (eg. nitrates, sulphate), metal-complex anion (eg. ferrocyanide), polyoxo-metalates, organic anions, halide, hydroxide and mixtures thereof. Of these, carbonate is especially preferred.

Preferably, the compound comprises less than 200g/kg of Aluminium, more preferably less than 100g/kg, even more preferably less than 50g/kg expressed as weight of aluminium metal per weight of compound.

More preferably, only low levels of aluminium are present such as less than 10g/kg, preferably less than 5 g/kg.

Even more preferably, the compound is free from aluminium (Al). By the term "free from aluminium" it is meant that the material termed "free from aluminium"

comprises less than 1g/kg, more preferably less than 500mg/kg, even more preferably less than 200mg/kg, most preferably less than 120mg/kg expressed as weight of elemental aluminium per weight of compound.

Suitably the compound contains iron(III) and at least one of Magnesium, Calcium, Lanthanum or Cerium, more preferably at least one of Magnesium, Lanthanum or Cerium, most preferably Magnesium.

Preferably, the compound comprises less than 100g/kg of calcium, more preferably less than 50g/kg, even more preferably less than 25g/kg expressed as weight of elemental calcium per weight of compound.

More preferably, only low levels of calcium are present such as less than 10g/kg, preferably less than 5 g/kg.

Even more preferably, the compound is free from calcium. By the term "free from calcium" it is meant that the material termed "free from calcium" comprises less than 1g/kg, more preferably less than 500mg/kg, even more preferably less than 200mg/kg, most preferably less than 120mg/kg expressed as weight of elemental calcium per weight of material.

Preferably, the binder compound is free from calcium and free from aluminium.

The final unit dose, comprising granules and any other material making up the final unit dose, as a whole, is also preferably free from aluminium and/or preferably free from calcium, using the definitions as detailed above.

Preferably the solid mixed metal compound comprises at least some material which is a Layered Double Hydroxide (LDH). More preferably, the mixed metal compound of formula (I) is a layered double hydroxide. As used herein, the term "Layered Double Hydroxide" is used to designate synthetic or natural lamellar hydroxides with two different kinds of metallic cations in the main layers and interlayer domains containing anionic species. This wide family of compounds is

sometimes also referred to as anionic clays, by comparison with the more usual cationic clays whose interlamellar domains contain cationic species. LDHs have also been reported as hydrotalcite-like compounds by reference to one of the polytypes of the corresponding [Mg-Al] based mineral.

A particularly preferred mixed metal compound contains at least one of carbonate ions, and hydroxyl ions .

A particularly preferred compound contains as M^{II} and M^{III}, magnesium and iron (III) respectively.

The solid mixed metal compound or compounds may be suitably made by co-precipitation from a solution, e.g. as described in WO 99/15189, followed by centrifugation or filtration, then drying, milling and sieving. The mixed metal compound is then rewetted again as part of the wet-granulation process and the resulting granules dried in a fluid-bed. The degree of drying in the fluid-bed is used to establish the desired water content of the final tablet.

Alternatively, mixed metal compound may be formed by heating an intimate mixture of finely divided single metal salts at a temperature whereby solid-solid reaction can occur, leading to mixed metal compound formation.

The solid mixed metal compound of formula (I) may be calcined by heating at temperatures in excess of 200 °C in order to decrease the value of z in the formula. In this case, it may be necessary to add water after calcination and prior to incorporation of the solid mixed metal compound in the granules in order to achieve the desired non-chemically bound water content of the granules.

It will be appreciated by those skilled in the art that the water provided by zH_2O in formula (I) may provide part of the 3 to 12% by weight of non-chemically bound water (based on the weight of the granular material). One skilled in the art may readily determine the value of z based on standard chemical techniques. Once the material of the present invention has been provided the amount of the non-

chemically bound water may then also be readily determined in accordance with the procedure described herein.

By mixed metal compound, it is meant that the atomic structure of the compound includes the cations of at least two different metals distributed uniformly throughout its structure. The term mixed metal compound does not include mixtures of crystals of two salts, where each crystal type only includes one metal cation. Mixed metal compounds are typically the result of coprecipitation from solution of different single metal compounds in contrast to a simple solid physical mixture of 2 different single metal salts. Mixed metal compounds as used herein include compounds of the same metal type but with the metal in two different valence states e.g. Fe(II) and Fe(III) as well as compounds containing more than 2 different metal types in one compound.

The mixed metal compound may also comprise amorphous (non-crystalline) material. By the term amorphous is meant either crystalline phases which have crystallite sizes below the detection limits of x-ray diffraction techniques, or crystalline phases which have some degree of ordering , but which do not exhibit a crystalline diffraction pattern and/or true amorphous materials which exhibit short range order, but no long-range order.

The compound of formula I is preferably formed with no aging or hydrothermal treatment to avoid the crystals of the compound growing in size and to maintain a high surface area over which phosphate binding can take place. The unaged compound of formula I is also preferably maintained in a fine particle size form during the post-synthesis route to maintain good phosphate binding.

PHOSPHATE BINDING

Any reference herein to phosphate binding capacity means phosphate binding capacity as determined by the following method, unless otherwise specified.

40mmoles/litre Sodium Phosphate solution (pH 4) is prepared and treated with the phosphate-binder. The filtered solution of the treated phosphate solution is then diluted and analysed by ICP-OES for phosphorus content.

Reagents used for this method are: Sodium Dihydrogen Phosphate Monohydrate (BDH, AnalaR™ grade), 1M hydrochloric acid, AnalaR™ water), standard phosphorous solution (10,000µg/ml, Romil Ltd), sodium chloride (BDH).

Specific apparatus used are: Rolling hybridisation incubator or equivalent (Grant Boekal HIW7), 10ml blood collection tubes, Reusable Nalgene screw cap tubes (30ml/50ml), 10ml disposable syringes, 0.45µm single use syringe filter, ICP-OES (inductively coupled plasma - optical emission spectrometer).

Phosphate solution is prepared by weighing 5.520 g (+/-0.001 g) of sodium di-hydrogen phosphate followed by addition of some AnalaR™ water and transferring to a 1ltr volumetric flask.

To the 1 litre volumetric flask is then added 1 M HCl drop-wise to adjust the pH to pH 4 (+/-0.1) mixing between additions. The volume is then accurately made up to one litre using AnalaR™ water and mixed thoroughly.

NaCl solution is prepared by accurately weighing out 5.85g (+/- 0.02g) of NaCl and quantitatively transferring into a 1 litre volumetric flask after which the volume is made up with AnalaR™ water and mixed thoroughly.

Calibration Standards are prepared by pipetting into 100 ml volumetric flasks the following solutions:

Flask No.	1	2	3	4
Identification	Blank	Std 1	Std 2	Std 3
NaCl solution	10 ml	10 ml	10 ml	10 ml
10000ppm P Std	0ml	4ml (400ppm)	2ml (200ppm)	1ml (100ppm)

The solutions are then made up to volume with AnalaR™ water and thoroughly mixed. These solutions are then used as calibration standards for the ICP-OES apparatus. The phosphate binder samples are then prepared in accordance with the procedure described hereafter and measured by ICP-OES. The ICP-OES results are initially expressed as ppm but can be converted to mmol using the equation: mmol = (reading ICP-OES in ppm / molecular weight of the analyte) x 4 (dilution factor).

Aliquots of each test sample, each aliquot containing 0.5g of the phosphate binder, are placed into 30ml screw top Nalgene tubes. If the test sample is a unit dose comprising 0.5g of the phosphate binder, it may be used as such. All samples are prepared in duplicate. 12.5ml aliquots of the Phosphate solution are pipetted into each of the screw top tubes containing the test samples and the screw cap fitted. The prepared tubes are then placed into the roller incubator pre heated to 37°C and rotated at full speed for a fixed time such as 30 minutes (other times may be used as shown in the Examples).The samples are subsequently removed from the roller incubator, filtered through a 0.45µm syringe filter, and 2.5ml of filtrate transferred into a blood collection tube. 7.5 ml of AnalaR™ water is pipetted into each 2.5ml aliquot, and mixed thoroughly. The solutions are then analysed on the ICP-OES.

The phosphate binding capacity is determined by: phosphate binding (%) =100 - (T/S x 100)

where

T = Analyte value for phosphate in solution after reaction with phosphate binder.

S = Analyte value for phosphate in solution before reaction with phosphate binder.

Suitably, the water-insoluble inorganic solid phosphate binders used in the granules of the present invention provide a phosphate binding capacity for the material as measured by the above method of at least 30% after 30 minutes, preferably at least 30% after 10 minutes, more preferably at least 30% after 5 minutes. Preferably the water-insoluble inorganic solid phosphate binders used in the tablets of the present invention have a phosphate binding capacity as measured by the above method of at least 40% after 30 minutes, preferably at least 30% after 10 minutes, more preferably at least 30% after 5 minutes. Even more preferably the water-insoluble inorganic solid phosphate binders used in the tablets of the present invention have a phosphate binding capacity as measured by the above method of at least 50% after 30 minutes, preferably at least 30% after 10 minutes, more preferably at least 30% after 5 minutes.

The pH of the phosphate binding measurement may be varied by use of addition of either 1M HCl or NaOH solution. The measurement may then be used to asses the phosphate binding capacity at varying pH values.

Suitably, the water-insoluble inorganic solid phosphate binders used in the tablets of the present invention have a phosphate binding capacity at a pH from 3 to 6, preferably at a pH from 3 to 9, more preferably at a pH from 3 to 10, most preferably at a pH from 2 to 10, as measured by the above method, of at least 30% after 30 minutes, preferably at least 30% after 10 minutes, more preferably at least 30% after 5 minutes.

Preferably the water-insoluble inorganic solid phosphate binders used in the tablets of the present invention have a phosphate binding capacity at a pH from 3 to 4, preferably from 3 to 5, more preferably from 3 to 6 as measured by the above method of at least 40% after 30 minutes, preferably at least 40% after 10 minutes, more preferably at least 40% after 5 minutes.

Even more preferably the water-insoluble inorganic solid phosphate binders used in the tablets of the present invention have a phosphate binding capacity at a pH from 3 to 4, preferably from 3 to 5, more preferably from 3 to 6, as measured by the above method, of at least 50% after 30 minutes, preferably at least 50% after 10 minutes, more preferably at least 50% after 5 minutes.
It will be understood that it is desirable to have high phosphate binding capability over as broad a pH range as possible.

An alternate method of expressing phosphate binding capacity using the method described above is to express the phosphate bound by the binder as mmol of Phosphate bound per gram of binder.

Using this description for phosphate binding, suitably, the water-insoluble inorganic solid phosphate binders used in the tablets of the present invention have a phosphate binding capacity at a pH from 3 to 6, preferably at a pH from 3 to 9, more preferably at a pH from 3 to 10, most preferably at a pH from 2 to 10 as measured by the above method of at least 0.3 mmol/g after 30 minutes, preferably at least 0.3 mmol/g after 10 minutes, more preferably at least 0.3 mmol/g after 5 minutes. Preferably the water-insoluble inorganic solid phosphate binders used in the tablets of the present invention have a phosphate binding capacity at a pH from 3 to 4, preferably from 3 to 5, more preferably from 3 to 6 as measured by the above method of at least 0.4 mmol/g after 30 minutes, preferably at least 0.4 mmol/g after 10 minutes, more preferably at least 0.4 mmol/g after 5 minutes. Even more preferably the water-insoluble inorganic solid phosphate binders used in the tablets of the present invention have a phosphate binding capacity at a pH from 3 to 4, preferably from 3 to 5, more preferably from 3 to 6 as measured by the above method of at least 0.5 mmol/g after 30 minutes, preferably at least 0.5 mmol/g after 10 minutes, more preferably at least 0.5 mmol/g after 5 minutes.

GRANULES

The granules of the present invention comprise at least 50%, preferably at least 60%, more preferably at least 70% most preferably at least 75%, by weight inorganic phosphate binder.

The granules of the present invention comprise from 3 to 12% by weight of non-chemically bound water, preferably from 5 to 10% by weight.

The remainder of the granules comprises a pharmaceutically acceptable carrier for the phosphate binder, chiefly an excipient or blend of excipients, which provides the balance of the granules. Hence the granules may comprise no greater than 47% by weight of excipient. Preferably the granules comprise from 5 to 47 % by weight of excipient, more preferably from 10 to 47 % by weight of excipient, more preferably from 15 to 47 % by weight of excipient.

GRANULE SIZE

Suitably, at least 95% by weight of the granules have a diameter less than 1180 micrometres as measured by sieving.

Preferably, at least 50% by weight of the granules have a diameter less than 710 micrometres as measured by sieving.

More preferably, at least 50% by weight of the granules have a diameter from 106 to 1180 micrometres, preferably from 106 to 500 micrometres.

Even more preferably, at least 70% by weight of the granules have a diameter from 106 to 1180 micrometres, preferably from 106 to 500 micrometres.

Preferably the weight median particle diameter of the granules is from 200 to 400 micrometres.

Larger granules can lead to unacceptably slow phosphate binding. Too high a proportion of granules less than 106 micrometres in diameter can lead to the

problem of poor flowability of the granules. Preferably, at least 50% by weight of the granules have a diameter greater than 106 micrometres as measured by sieving, more preferably at least 80% by weight.

GRANULE INGREDIENTS

Suitable excipients which may be included in the granules include conventional solid diluents such as, for example, lactose, starch or talcum, as well as materials derived from animal or vegetable proteins, such as the gelatins, dextrins and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes; sugars such as mannitol, dextrose, galactose and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminium silicates; and amino acids having from 2 to 12 carbon atoms such as a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

The term excipient herein also includes auxiliary components such as tablet structurants or adhesives, disintegrants or swelling agents.

Suitable structurants for tablets include acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxypropylmethylcellulose, kaltodectrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.

Suitable disintegrants include cross-linked disintegrants. For example, suitable disintegrants include cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high molecular weight hydroxypropylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene copolymer,

polymethylmethacrylate, cross-linked polyvinylpyrrolidone (PVP) and high molecular weight polyvinylalcohols.

Cross-linked polyvinylpyrrolidone (also known as crospovidone, for example available as Kollidon CL-M™ ex BASF) is an especially preferred excipient for use in the tablets of the invention. Suitably, the granules of the tablets of the invention comprise from 1 to 15% by weight of cross-linked polyvinylpyrrolidone, preferably from 1 to 10%, more preferably from 2 to 8%. Preferably, the cross-linked polyvinylpyrrolidone has a d_{50} weight median particle size, prior to granulation of less than 50 micrometres (i.e. so-called B-type cross-linked PVP). Such material is also known as micronised crospovidone. It has been found that the cross-linked polyvinylpyrrolidone at these levels leads to good disintegration of the tablet but with less inhibition of phosphate binding of the inorganic phosphate binder as compared to some other excipients. The preferred sizes for the cross-linked polyvinylpyrollidone give reduced grittiness and hardness of the particles formed as the tablets disintegrate.

Another preferred excipient for use in the granules of the tablets of the invention is pregelatinised starch (also known as pregelled starch). Preferably, the granules comprise from 5 to 20% by weight of pregelled starch, more preferably 10 to 20%, even more preferably from 12 to 18% by weight. The pregelatinised starch at these levels improves the durability and cohesion of the tablets without impeding the disintegration or phosphate binding of the tablets in use. The pregelatinised starch is suitably fully pregelatinised, with a moisture content from 1 to 15% by weight and a weight median particle diameter from 100 to 250 micrometres. A suitable material is Lycotab™ - a fully pregelatinised maize starch available from Roquette.

A combined excipient including both pregelatinised starch and crospovidone is particularly preferred, as this combination of excipients gives the ability to reliably form compacted tablets of various shapes, good granule homogeneity and good disintegration characteristics from the granules of the invention.

The granules may also comprise preservatives, wetting agents, antioxidants, surfactants, effervescent agents, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents. Suitable colouring agents include red, black and yellow iron oxides and FD & C dyes such as FD & C blue No. 2 and FD & C red No. 40 available from Ellis & Everard. Suitable flavouring agents include mint, raspberry, liquorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape flavours and combinations of these. Suitable pH modifiers include sodium hydrogencarbonate (i.e. bicarbonate), citric acid, tartaric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame, acesulfame K and thaumatin. Suitable taste-masking agents include sodium hydrogencarbonate, ion-exchange resins, cyclodextrin inclusion compounds and adsorbates. Suitable wetting agents include sodium lauryl sulphate and sodium docusate. A suitable effervescent agent or gas producer is a mixture of sodium bicarbonate and citric acid.

GRANULATION

Granulation may be performed by a process comprising the steps of:

i) mixing the solid water-insoluble inorganic compound capable of binding phosphate with one or more excipients to produce a homogeneous mix,

ii) contacting a suitable liquid with the homogeneous mix and mixing in a granulator to form wet granules,

iii) optionally passing the wet granules though a screen to remove granules larger than the screen size,

iv) drying the wet granules to provide dry granules.

v) milling and/or sieving the dry granules.

Suitably the granulation is by wet granulation, comprising the steps of;

i) mixing the inorganic solid phosphate binder with suitable excipients to produce a homogeneous mix,

ii) adding a suitable liquid to the homogeneous mix and mixing in a granulator to form granules,

iii) optionally passing the wet granules though a screen to remove granules larger than the screen size,

iv) drying the granules.

v) milling and sieving the granules

Suitable liquids for granulation include water, ethanol and mixtures thereof. Water is a preferred granulation liquid.

The granules are dried to the desired moisture levels as described hereinbefore prior to their use in tablet formation or incorporation into a capsule for use as a unit dose.

LUBRICANT

Prior to tabletting the granules into a unit dose composition, it is preferred that the granules are blended with a lubricant or glidant such that there is lubricant or glidant distributed over and between the granules during the compaction of the granules to form tablets.

Typically the optimum amount of lubricant required depends on the lubricant particle size and on the available surface area of the granules. Suitable lubricants include silica, talc, stearic acid, calcium or magnesium stearate and sodium stearyl fumarate and mixtures thereof. Lubricants are added to the granules in a finely divided form, typically no particles greater than 40 micrometres in diameter (ensured typically by sieving).The lubricant is suitably added to the granules at a level of from 0.1 to 0.4%, preferably from 0.2 to 0.3% by weight of the granules. Lower levels can lead to sticking or jamming of the tablet die whereas higher levels may reduce the rate of phosphate binding or hinder tablet disintegration. Salts of fatty acids may be used as lubricants, such as calcium and/or magnesium stearate. A preferred lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate and mixtures thereof. It has been found that some lubricants, such as fatty acids, lead to pitting and loss of integrity in the coating layer of the tablets. It is thought that this may arise from

partial melting of the lubricant as the coating layer is dried. Hence it is preferred that the lubricant has a melting point in excess of 55°C.

TABLETS

The tablets of the third aspect of invention may be prepared by compressing granules, under high pressure, in order to form a tablet having the necessary crushing strength for the handling required during packaging and distribution. The use of granules formed from a granulated powder mixture improves flowability from storage hoppers to the tabletting press which in turn benefits the efficiency of tablet processing. The inorganic phosphate binders used in the tablets of the present invention typically have poor flowability properties at their desired particle size as detailed hereinbefore. Because it is desired that the tablets of the invention comprise high levels of inorganic phosphate binder, of the order of 50% or more by weight of the tablet, the inorganic phosphate binder must be formed into granules prior to tablet formation. A fine powder is apt to pack or "bridge" in the hopper, feed shoe or die, and thus tablets of even weight or even compression are not easily obtainable. Even if it were possible to compress fine powders to a satisfactory degree, air may be trapped and compressed, which may lead to splitting of the tablet on ejection. The use of granules helps to overcome these problems. Another benefit of granulation is the increase in bulk density of the final tablet when prepared from granules rather than from fine powder, reducing the size of the final tablet and improving the likelihood of patient compliance.

The tablets of the invention may be circular but are preferably generally bolus- or torpedo-shaped (also known as double convex oblong shaped tablet,) i.e. having an elongate dimension, in order to assist swallowing of larger doses. It may for example be in the form of a cylinder with rounded ends or elliptical in one dimension and circular in an orthogonal dimension, or elliptical in both. Some flattening of one or more parts of the overall shape is also possible.

Where the tablet is in the form of a tablet provided with a "belly-band", it is preferred if the width of the belly-band is 2mm or more. It has been found that smaller belly-bands can lead to insufficient coverage or chipping or loss of integrity of the water-resistant coating of the tablet.

The tablets of the second aspect of the invention preferably have a hardness from 5 to 30 kgf as measured using a Holland C50 tablet hardness tester.

WATER RESISTANT COATING

The tablets of the second aspect of the invention, once formed from the granules of the first aspect of the invention, are preferably provided with a water-resistant coating.

The water-resistant coating may be applied to the tablet by any of the usual pharmaceutical coating processes and equipment. For example, tablets may be coated by fluid bed equipment (for example a "Wurster" type fluid bed dryer) coating pans (rotating, side vented, convention etc), with spray nozzles or guns or other sprayer types or by dipping and more recent techniques including Supercell tablet coater from Niro PharmaSystems. Variations in available equipment include size, shape, location of nozzles and air inlets and outlets, air flow patterns and degree of instrumentation. Heated air may be used to dry the sprayed tablets in a way that allows continuous spraying while the tablets are being simultaneously dried. Discontinuous or intermittent spraying may also be used, but generally requires longer coating cycles. The number and position of nozzles may be varied, as needed depending on the coating operation and the nozzles(s) is preferably aimed perpendicularly or nearly perpendicular to the bed although other direction(s) of aim may be employed if desired. A pan may be rotated at a speed selected from a plurality of operating speeds. Any suitable system capable of applying a coating composition to a tablet may be used. Virtually any tablet is acceptable herein as a tablet to be coated. The term "tablet" could include tablet, pellet or pill. Typically the preferred tablet will be in a form sufficiently stable physically and chemically to be effectively coated in a system which involves

some movement of a tablet, as for example in a fluidized bed, such as in a fluidized bed dryer or a side vented coating pan, combinations thereof and the like. Tablets may be coated directly, i.e. without a subcoat to prepare the surface. Subcoats or topcoats may of course be used. If desired, the same or a similar coating application system can be employed for both a first or second or more coating applications. The coating composition is prepared according to the physical properties of its constituents, i.e. soluble materials are dissolved, insoluble materials are dispersed. The type of mixing used is also based on the properties of the ingredients. Low shear liquid mixing is used for soluble materials and high shear liquid mixing is used for insoluble materials. Usually the coating formulation consists of two parts, the colloidal polymer suspension and the pigment suspension or solution (eg red oxide or Quinoline yellow dye). These are prepared separately and mixed before use.

A wide range of coating materials may be used, for example, cellulose derivatives, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, polyethylene glycols, copolymers of styrene and acrylate, copolymers of acrylic acid and methacrylic acid, copolymers of methacrylic acid and ethylacrylate, copolymers of methyl methacrylate and methacrylate, copolymers of methacrylate and tertiary amino alkyl methacrylate, copolymers of ethylacrylate methyl methacrylate and quaternary amino alkyl methacrylate and combinations of two or more hereof. Preferably, salts of methacrylate copolymers are used, eg. butylated methacrylate copolymer (commercially available as Eudragit EPO).

The coating is suitably present as 0.05 to 10% by weight of the coated tablet, preferably from 0.5% to 7%. Preferably the coating material is used in combination with red iron oxide pigment (Fe_2O_3) (1% or more, preferably 2% or more by weight of the dried coating layer) which is dispersed throughout the coating material and provides an even colouring of the coating layer on the tablet giving a pleasant uniform appearance.

In addition to protecting the tablet core from moisture loss or ingress on storage, the water resistant coating layer also helps to prevent the rapid breakup of the

tablet in the mouth, delaying this until the tablet reaches the stomach. With this purpose in mind, it is preferred if the coating material has low solubility in alkaline solution such as found in the mouth, but more soluble in neutral or acid solution. Preferred coating polymers are salts of methacrylate copolymers, particularly butylated methacrylate copolymer (commercially available as Eudragit EPO). Preferably the coating layer comprises at least 30% by weight of a coating polymer, more preferably at least 40% by weight.

The water loss or uptake of coated tablets is suitably measured as detailed hereinbefore for the measurement of the non-chemically bound water content for granules. From a set of freshly prepared coated tablets, some are measured for non-chemically bound water immediately following preparation, and others are measured after storage as detailed above.

In another aspect, the invention provides a method for preparing a tablet according to the first aspect of the invention, the method comprising granulating a water-insoluble inorganic solid phosphate binder with a pharmaceutically acceptable excipient and optionally, any other ingredients, forming a tablet from the granules by compression and optionally applying a water- resistant coating to the tablet so formed.

CAPSULES

Suitable capsules for use in the second aspect of the invention are hard gelatine capsules, although other suitable capsule films may be used.

USE OF UNIT DOSES

For treatment of and prophylaxis of hyperphosphataemia, amounts of from 0.1 to 500, preferably from 1 to 200, mg/kg body weight of inorganic phosphate binder are preferably administered daily to obtain the desired results. Nevertheless, it may be necessary from time to time to depart from the amounts mentioned above, depending on the body weight of the patient, the animal species of the

patient and its individual reaction to the drug or the kind of formulation or the time or interval in which the drug is applied. In special cases, it may be sufficient to use less than the minimum amount given above, whilst in other cases the maximum dose may have to be exceeded. For a larger dose, it may be advisable to divide the dose into several smaller single doses. Ultimately, the dose will depend upon the discretion of the attendant physician. Administration before meals, e.g. within one hour before a meal is suitable. Alternatively, the dose may be taken with a meal.

A typical tablet of the invention for human adult administration may comprise from 1 mg to 5 g, preferably from 10 mg to 2 g, more preferably from 100 mg to 1 g, such as from 150 mg to 750 mg, from 200 mg to 750 mg or from 250 mg to 750 mg of water-insoluble inorganic solid phosphate binder.

Preferably the unit doses of the invention comprise at least 200 mg of a water-insoluble solid inorganic phosphate binder. Preferably the unit doses of the invention comprise at least 250 mg of a water-insoluble solid inorganic phosphate binder Preferably the unit doses of the invention comprise at least 300 mg of a water-insoluble solid inorganic phosphate binder. A more preferred unit dose comprises 500 mg of the phosphate binder. The preferred unit dose weight is less than 750 mg, more preferably less than 700 mg, to aid with patient compliance for oral dosage. A particularly preferred unit dose contains 200 mg (±20mg) of a water-insoluble solid inorganic phosphate binder. A particularly preferred unit dose contains 250 mg (±20mg) of a water-insoluble solid inorganic phosphate binder. A particularly preferred unit dose contains 300 mg (±20mg) of a water-insoluble solid inorganic phosphate binder. When the unit dose is a tablet, the preferred unit dose weight includes any optional coating.

The tablet forms may be packaged together in a container or presented in foil strips, blister packs or the like, e.g. marked with days of the week against respective doses, for patient guidance.

In the further aspects of the invention detailed below, granular material refers to the granules of the first aspect of the invention.

An aspect of the invention is the granular material for use in or as a medicine on humans or animals, particularly as a medicine for the binding of phosphate, more particularly for the treatment of hyperphosphataemia.

Another aspect is the use of the granular material in the manufacture of a medicament for use on animals or humans in the treatment or therapy of a condition or disease associated with adverse phosphate levels, particularly elevated plasma phosphate levels, particularly hyperphosphataemia.

Another aspect is a method for the treatment or therapy of a condition or disease associated with adverse phosphate levels, particularly elevated plasma phosphate levels, particularly hyperphosphataemia by oral administration of the granular material to humans or animals.

STORAGE

As discussed herein, we have found that the system of the present invention can provide tablets which are stable of over a period of at least 12 months (see Table7 for particle size of small and large granules) determined at 25 C /60RH and 30 C/65RH. Under more extreme storage conditions (40 C/75RH) the storage stability is at least 6 months for both granule types.

FURTHER ASPECTS

Further aspects of the present invention are described in the following numbered paragraphs:

1. Granules comprising at least 50% by weight of water-insoluble inorganic solid phosphate binder, from 3 to 12% by weight of non-chemically bound water and up to 47% by weight of excipient.

2. Granules according to paragraph 1 wherein the water-insoluble inorganic solid phosphate binder is a mixed metal compound.

3. Granules according to paragraph 2, wherein the mixed metal compound is a compound of formula (I):

$M^{II}_{1-x}M^{III}_{x}(OH)_2A^{n-}_{y}.zH_2O$ (I)

where M^{II} is at least one bivalent metal; M^{III} is at least one trivalent metal; A^{n-} is at least one n-valent anion; $x = \Sigma ny$ and x, y and z fulfil $0 < x \leq 0.67$, $0 < y \leq 1$, $0 \leq z \leq 10$.

4. Granules according to paragraph 3 wherein $x = \Sigma ny$ and x, y and z fulfil $0 < x \leq 0.5$, $0 < y \leq 1$, $0 \leq z \leq 10$.

5. Granules according to any one of paragraphs 2 to 4 wherein the mixed metal compound is free from Aluminium and contains the metals iron(III) and at least one of Magnesium, Calcium, Lanthanum or Cerium.

6. Granules according to any one of paragraphs 3 to 5 wherein the mixed metal compound of formula (I) is a layered double hydroxide.

7. Granules according to any one of paragraphs 3 to 6 wherein the mixed metal compound contains at least one of hydroxyl and carbonate ions and contains as the metals iron (III) and magnesium.

8. Granules according to any one of paragraphs 1 to 7, wherein the granules comprise from 5 to 15% by weight of polyvinyl pyrrolidone as an excipient.

9. Granules according to any one of paragraphs 1 to 8, comprising from 10 to 20% by weight of pregelatinised starch as an excipient.

10. Granules according to any one of paragraphs 1 to 9 wherein the granules have a diameter less than 1000 micrometers.

11. A unit dose for oral administration comprising a water resistant capsule containing granules according to any preceding paragraph.

12. A unit dose for oral administration comprising a compacted tablet of granules according to any of paragraphs 1 to 10.

13. A unit dose according to paragraph 12 further comprising a lubricant between the granules.

14. A unit dose according to paragraph 13 comprising magnesium stearate as lubricant between the granules.

15. A unit dose according to any one of paragraphs 12 to 14 coated with a water-resistant coating.

16. A unit dose according to paragraph 15 wherein the water-resistant coating comprises at least 30% by weight of a butylated methacrylate copolymer.

17. A unit dose according to any one of paragraphs 12 to 16 wherein the tablet is provided with a belly band having a width of 2mm or more.

18. A unit dose according to any one of paragraphs 11 to 17 comprising at least 300 mg of a water-insoluble inorganic solid phosphate binder.

1A. A granular material comprising

(i) at least 50% by weight based on the weight of the granular material of solid water-insoluble inorganic compound capable of binding phosphate,

(ii) from 3 to 12% by weight based on the weight of the granular material of non-chemically bound water, and

(iii) no greater than 47% by weight based on the weight of the granular material of excipient.

2A. A granular material according to paragraph 1A wherein the water-insoluble inorganic solid phosphate binder is a mixed metal compound.

3A. A granular material according to paragraph 2A, wherein the mixed metal compound is a compound of formula (I):

$$M^{II}_{1-x}M^{III}_{x}(OH)_2A^{n-}_{y}.zH_2O \qquad (I)$$

where M^{II} is at least one bivalent metal; M^{III} is at least one trivalent metal; A^{n-} is at least one n-valent anion; $x = \Sigma ny$; $0 < x \leq 0.67$, $0 < y \leq 1$, and $0 \leq z \leq 10$.

4A. A granular material according to paragraph 3A wherein $x = \Sigma ny$; $0 < x \leq 0.5$, $0 < y \leq 1$, and $0 \leq z \leq 10$.

5A. A granular material according to paragraph 3A or 4A wherein the mixed metal compound of formula (I) is a layered double hydroxide.

6A. A granular material according to any one of paragraphs 2A to 5A wherein the mixed metal compound contains at least one of hydroxyl and carbonate ions and contains as the metals iron (III) and magnesium.

7A. A granular material according to any one of paragraphs 1A to 6A wherein the water-insoluble inorganic compound is free from Aluminium.

8A. A granular material according to any one of paragraphs 1A to 7A wherein the water-insoluble inorganic compound contains iron(III) and at least one of Magnesium, Calcium, Lanthanum or Cerium.

9A. A granular material according to any one of paragraphs 1A to 8A, wherein the granular material comprises from 5 to 20% by weight of pregelatinised starch as excipient based on the weight of the granular material .

10A. A granular material according to any one of paragraphs 1 to 9A, comprising from 1 to 15% by weight of polyvinyl pyrrolidone as excipient based on the weight of the granular material.

11A. A granular material according to any one of paragraphs 1A to 10A wherein at least 95% by weight of the granules of the granular material have a diameter less than 1180 micrometers.

12A. A unit dose for oral administration comprising a water resistant capsule containing a granular material according to any one of paragraphs 1A to 11A.

13A. A unit dose for oral administration comprising a compacted tablet of a granular material according to any of paragraphs 1A to 11A.

14A. A unit dose according to paragraph 13A further comprising a lubricant between the granules.

15A. A unit dose according to paragraph 14A wherein the lubricant is or comprises magnesium stearate.

16A. A unit dose according to any one of paragraphs 13A to 15A coated with a water-resistant coating.

17A. A unit dose according to paragraph 16A wherein the water-resistant coating comprises at least 30% by weight of a butylated methacrylate copolymer.

18A. A unit dose according to any one of paragraphs 16A to 17A wherein the tablet has a belly band having a width of 2mm or more.

19A. A unit dose according to any one of paragraphs 12A to 18A wherein the solid water-insoluble inorganic compound capable of binding phosphate is present in an amount of at least 300 mg.

20A. A process for the preparation of a granular material as defined in any one of paragraphs 1A to 11A comprising the steps of:

i) mixing the solid water-insoluble inorganic compound capable of binding phosphate with one or more excipients to produce a homogeneous mix,

ii) contacting a suitable liquid with the homogeneous mix and mixing in a granulator to form wet granules,

iii) optionally passing the wet granules though a screen to remove granules larger than the screen size,

iv) drying the wet granules to provide dry granules.

v) milling and/or sieving the dry granules.

21A. A process according to paragraph 20A where in the liquid is selected from water, ethanol and mixtures thereof.

22A. A granular material according to any one of paragraphs 1A to 11A for use in medicine.

23A. Use of a granular material according to any one of paragraphs 1A to 11A in the manufacture of a medicament for binding of phosphate.

24A. Use of a granular material according to any one of paragraphs 1A to 11A in the manufacture of a medicament for use in the therapy of a condition or disease associated with phosphate levels.

25A. Use of a granular material according to any one of paragraphs 1A to 11A in the manufacture of a medicament for use in the therapy of a condition or disease associated with adverse phosphate levels.

26A. Use of a granular material according to any one of paragraphs 1A to 11A in the manufacture of a medicament for use in the therapy of a condition or disease associated with elevated plasma phosphate levels.

27A. Use of a granular material according to any one of paragraphs 1A to 11A in the manufacture of a medicament for use in the therapy of hyperphosphataemia.

The present invention will now be explained in more detail by way of the following non-limiting examples.

EXAMPLES

The phosphate binder used in the examples below was formed by the reaction of aqueous solutions of magnesium sulphate and ferric sulphate in the presence of sodium hydroxide and sodium carbonate. The synthesis reaction is described by:

$4MgSO_4 + Fe_2(SO_4)_3 + 12\ NaOH + Na_2CO_3 \rightarrow Mg_4Fe_2(OH)_{12}.CO_3.nH_2O + 7Na_2SO_4$. The precipitation was carried out at approximately pH 10.3 at ambient temperature (15-25 ^{0}C). The resulting precipitate was filtered, washed, dried, milled and then sieved such that all material is less than106 micron. The formula of the phosphate binder was: $Mg_4Fe_2(OH)_{12}.CO_3.nH_2O$ and had the following XRF composition: MgO = 29.0%, Fe_2O_3 = 28.7%, Mg:Fe mole ratio = 2:1. The XRF values take into account all water present in the phosphate binder. XRD showed that the phosphate binder was characterised by the presence of the poorly crystalline hydrotalcite type structure.

Table 1

Material \ Example	1	2	3	4	5	6	7
Granules							
Phosphate Binder	75.1	65.0	66.1	56.3	74.9	75.1	74.9
Pre-gelled Starch	14.1	14.0			9.4	14.1	9.4
Microcrystalline Cellulose			28.5	37.7			
Micronised Crospovidone	4.7	14.0			9.4	4.7	9.4
Water content (dried granules)	5.8	6.7	5.1	5.7	6.0	5.8	6.0
Lubricants used for tabletting							
Stearic acid	0.3	0.3	0.3	0.3	0.3		
Magnesium Stearate						0.3	0.3

All values in the tables are percentages by weight.

Granules were prepared using the formulations as detailed in Table 1. The dry blends were made in 125 ml batches by mixing the components in the Turbula powder blender for 5 minutes prior to granulation. The 125 gram batches of dry powder blend were granulated by the steady addition of purified water in a planar mixer until small, distinct granules were produced. Each of the powder blends required different amounts of water to granulate. Typical values of water used for granulation as weight percentage of dry powder weight are: example (1) -106 %, example (2) -111 %, example (3) -78 %, example (4) -83 %, example (5) -100 %,

example (6) -70-106 %, example (7) -78 %. Batches of granules made for each of the formulations were then combined and dried in a fluid bed drier at an air inlet temperature of 40 °C to a target moisture content of 4-6% w/w before being passed through a 1.18 mm aperture mesh to remove large granules.

The amount of water required to granulate varied dependent on phosphate binder moisture content, particle size distribution, feed-rate and degree of dispersion (water droplet size). Typically if water was used at less than 50% finer granules were obtained whereas excessive amounts of water (above 110%) resulted in lump formation. The preferred water amount was between 70 and 100%.

Tablets were made with hardnesses from 13 to 29 kgF as measured by a Holland C50 tablet hardness tester. Varying compaction pressures were used to give tablets of differing tablet hardness (as measured in Kg Force) as detailed in Table 2, from formulations 1 to 4. 0.3% stearic acid was used as a lubricant.

The disintegration time for the tablets was measured using a disintegration bath - Copley DTG 2000 IS.

The phosphate binding capacity in Table 2 was measured as detailed in the phosphate binding test described hereinbefore at pH = 4 and time = 30 minutes.

Friability was measured by tablet friability tester Erweka TA10

Results are shown in Table 2 for uncoated tablets prepared from granules of formulae 1, 2, 3 and 4 at three differing crush strengths (tablet hardness) (a,b and c) as indicated in the table.

Table 2

Example	Disintegration Time (sec)	P (%) Binding	Tablet Hardness (KgF)	Friability (%)
1a	25	61	13	0
1b	25	66	21	0
1c	50	64	25	0
2a	20	58	13	0
2b	40	60	21	0
2c	53	61	27	0
3a	15	65	16	0
3b	12	60	19	0
3c	15	61	29	0
4a	8	55	16	0
4b	12	57	21	0
4c	20	60	28	0

Table 3 shows the effect of the addition of a water-resistant coating comprising Eudragit EPO on tablets prepared from granules of the formulation of example 1.

The coating formulation is:

84.02% Purified water, 0.81% Sodium Dodecyl Sulphate, 8.08 % Butylated methacrylate Copolymer (Eudragit EPO), 1.21% Stearic acid, 2.09% Talc, 2.83% MgStearate, 0.64% Titanium dioxide, 0.32% Red iron oxide. The coating was dried after application using hot air at 48°C.

Coating levels disclosed herein are determined from the increase in tablet weight before and after application of the coating formulation and drying in hot-air at 48°C.

Table 3

Coating Level (% weight of coated tablet)	Disintegration Time (s)
0.69	45
2.34	45-59
2.83	51-63
4.39	80-140

From Table 3 it can be seen that a coating has the effect of delaying the disintegration of the tablets.

Table 4 shows the effect of different coating type and lubricants on the storage behaviour and tablet characteristics for tablets formed with a hardness of 10 to 15 kgF from the granules of examples 1, 5, 6 and 7. Tablets from examples 1 and 5 included 0.3% by weight stearic acid as lubricant. Tablets from examples 6 and 7 included 0.3% by weight of Magnesium Stearate as lubricant.

Table 4

Example	Disintegration Time(s)		Moisture content (%) (coated tablet)		Appearance (Visible Pitting)	
	initial	4 weeks	Initial	4 weeks	initial	4 weeks
Ex1 Eudragit	158	226	8.6	12.7	No	Yes
Ex 6 Eudragit	422	128	8.8	11.3	No	No
Ex 6 Opadry-AMB	107	49	8.5	10.8	No	Yes
Ex 5 Eudragit	139	14	7.7	11.5	No	Yes
Ex 7 Eudragit	122	62	9.6	11.9	No	No

Example	Disintegration Time(s)		Moisture content (%) (coated tablet)		Appearance (Visible Pitting)	
	initial	4 weeks	Initial	4 weeks	initial	4 weeks
Ex 7 Opadry-AMB	72	27	8.5	11.1	No	Yes

The Eudragit coating is as described above

The Opadry AMB coating has Opaglos 2 Sodium Carboxymethylcellulose replacing Eudragit EPO as coating polymer with other coating ingredients as for the Eudragit coating composition.

Note that the moisture content in Table 4 is that for the complete coated tablet and not for the granules.

Storage was carried out with the tablets openly exposed at 75°C and 40% relative humidity for 4 weeks.

From Table 4 it can be seen that the Opadry coating does not prevent pitting on storage with Mg Stearate lubricant, whereas the Eudragit does. Even the Eudragit does not prevent pitting with Stearic acid. Hence the optimal system is Mg Stearate lubricant with Eudragit Coating.

Table 5 shows the effect of granule size and moisture content on the tablet disintegration time of an uncoated tablet in water at pH 7 and in 0.1 Normal HCl both at 37°C. The formulation was as for example 6 (but with varying levels of moisture) The tablets were compacted to the same approximate hardness of 10-15 Kgf.

Table 5

Granule moisture(%)	Granule diameter (μm)	Disintegration Time (s) Water	Disintegration Time(s) 0.1N HCl	Comments
1.19	<425	16	20	Static charge dusty
1.19	<1180	34	41	Static charge dusty
7.01	<425	20	24	Good
7.01	<1180	46	51	Good
18.84	<425	1090	1214	Irregular tablet surface
18.84	<1180	784	976	Irregular tablet surface

The irregular tablet surface for the high moisture granules was due to excess material squeezing past the sides of the tablet die during compaction.

All granules were sieved such that less than 25% by weight of the granules had a diameter less than 106 micrometres by sieving.

From Table 5 it can be seen that increasing the granule size slows disintegration at granule moisture levels of 1.19 and 7.01 %, and that the moisture content has a marked effect on both disintegration time and tablet quality.

A similar effect was found for the effect of granule size on the retardation of phosphate binding. Tablets formed from granules according to example 6 having a diameter less than 1180 μm were compared for phosphate binding as a function of time against tablets formed from granules having a diameter less than 425 μm. The tablets were both compacted to a strength of 13 kg tablet hardness and were coated with 4.5% of dried Eudragit EPO water resistant coating. The tablets prepared from the smaller granules reached 80% of the equilibrium

phosphate binding after 10 minutes, whereas the tablets prepared from the larger granules took 30 minutes. The equilibrium phosphate binding is as measured after 120 minutes. The phosphate binding results were obtained according to the modified method as described hereafter.

Table 6 shows phosphate binding of coated tablets formed from granules according to Example 6 coated with Eudragit EPO in an amount of 4.5wt% based on the coated tablet, the granules having a diameter less than 425 micrometres.

Table 6, 7 and 8 show phosphate binding (expressed as mmol of phosphate bound per gram of solid inorganic phosphate binder) at various pH values for the solution in which binding was measured.

The results of Table 6, 7, and 8 were obtained by means of the phosphate binding method described hereinbefore, but with the following modifications: 1 tablet containing 0.5g of the phosphate binder was dispersed in 125ml of 4mmol/litre phosphate solution (as opposed to 12.5 ml of 40mmol/litre). The samples were then incubated in stoppered polypropylene conical flasks in a shaking water bath at 37°C and 200rpm for varying times. pH of the phosphate solution was varied using 1M NaOH or HCl solution. The calibration standards for the ICP-OEC were changed accordingly to take account of the lower phosphate concentration.

Table 6

	phosphate binding (mmol/g) at different times (minutes)			
pH/Time	**10**	**30**	**60**	**120**
3	0.44	0.54	0.56	0.59
4	0.44	0.5	0.53	0.55
9	0.25	0.33	0.35	0.38

Table 7 shows the effect of particle size distribution for the granules on various parameters. "Transport" refers to the ease of transfer from a hopper to the tablet

press in relation to jamming and bridging. The granules were formed according to example 6.The fine granules (A) were poor.

Phosphate binding was measured by means of the phosphate binding method described previously as for Table 6 at a pH of 4.

The Phosphate binding results for A,B, C and D were from tablets (uncoated) whereas the results for E were from the granules themselves.

Table 7

particle size	fine	small	large	large	medium
by sieving	A	B	C	D	E
(micrometres)					
0	100	100	100	100	100
53	32	94	98	92	96
106	25	83	96	87	91
250	9	49	90		76
500	3	0	71	51	47
710	1	0	46		17
1180	0	0	5	3	0
Transport	poor	good	good	good	good
Phosphate binding					
(minutes)					
10	0.52	0.42	0.33	0.3	
20		0.47	0.40		
30	0.54	0.50	0.44	0.4	0.42
45		0.51	0.47		
60	0.54	0.54	0.48	0.45	0.49
120	0.57	0.56	0.51	0.47	

Examples 1-7 in uncoated tablet form, and prepared from granules having a diameter less than 1180 micrometres, were also measured using the modified phosphate binding test as shown in Table 8 at pH = 4 and time =30 minutes.

Table 8

Example 1	Example 2	Example3	Example 6	Example 7
mmol PO4/g				
0.45	0.55	0.27	0.44	0.60

From Table 8 and comparison of example 2 with 3 it can be seen that example 3 has lower phosphate binding demonstrating the effect of hindering of phosphate binding by the presence of the microcrystalline cellulose and the advantage of using the preferred combination of pre-gelled starch and micronised crospovidone. This preferred combination of excipients maintained good phosphate binding as well as aiding the granulation process and showing good dispersion of the granules and tablets in water.

Material from coated tablets (containing 0.5g of binder) formed from granules according to example 6 having diameters less than 425 micrometres was found to have the following Langmuir constants: K1 (1/mmol)= 0.25 and K2 (mmol/g) =1.88.

Material from coated tablets (containing 0.5g of binder) formed from granules according to example 6 having diameters less than 1000 micrometres was found to have the following Langmuir constants: K1 (1/mmol)= 0.19 and K2 (mmol/g) =1.88.

K1 is the affinity constant and is an indication of the strength of phosphate binding while K2 is the capacity constant and is the maximum amount of phosphate that can be bound per unit weight of binder.

These Langmuir constants were determined by changing the phosphate concentration from 1 to 40 mmol/l and were calculated by performing linear regression on a plot of the unbound/bound phosphate versus the unbound phosphate measured at equilibrium. The initial pH of the phosphate solutions was pH = 4, temp = 37 Celsius and the selected equilibrium point was at a time t = 120 minutes.

All publications and patents and patent applications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in chemistry, biology or related fields are intended to be within the scope of the following claims.

CLAIMS

1. A granular material comprising

(i) at least 50% by weight based on the weight of the granular material of solid water-insoluble mixed metal compound capable of binding phosphate of formula (I):

$M^{II}_{1-x}M^{III}_{x}(OH)_2A^{n-}_{y}.zH_2O$ (I)

where M^{II} is at least one of magnesium, calcium, lanthanum and cerium;

M^{III} is at least iron(III);

A^{n-} is at least one n-valent anion; $x = \Sigma ny$; $0 < x \leq 0.67$, $0 < y \leq 1$, and $0 \leq z \leq 10$

(ii) from 3 to 12% by weight based on the weight of the granular material of non-chemically bound water, and

(iii) no greater than 47% by weight based on the weight of the granular material of excipient.

2. A granular material according to claim 1 wherein $x = \Sigma ny$; $0 < x \leq 0.5$, $0 < y \leq 1$, and $0 \leq z \leq 10$.

3. A granular material according to claim 1 or 2 wherein the mixed metal compound of formula (I) comprises a layered double hydroxide.

4. A granular material according to any one of claims 1 to 3 wherein the mixed metal compound contains at least one of hydroxyl and carbonate ions and contains as the metals iron (III) and magnesium.

5. A granular material according to any preceding claim, wherein the granular material comprises from 5 to 20% by weight of pregelatinised starch as excipient based on the weight of the granular material .

6. A granular material according to any one of claims 1 to 5, comprising from 1 to 15% by weight of cross linked polyvinyl pyrrolidone as excipient based on the weight of the granular material.

7. A granular material according to any one of claims 1 to 6 wherein the excipient comprises at least pregelatinised starch and crospovidone

8. A granular material according to any preceding claim wherein at least 95% by weight of the granules of the granular material have a diameter less than 1180 micrometers.

9. A unit dose for oral administration comprising a water resistant capsule containing a granular material according to any preceding claim.

10. A unit dose for oral administration comprising a compacted tablet of a granular material according to any of claims 1 to 8.

11. A unit dose according to claim 10 further comprising a lubricant between the granules.

12. A unit dose according to claim 11 wherein the lubricant is or comprises magnesium stearate.

13. A unit dose according to any one of claims 10to 12 coated with a water-resistant coating.

14. A unit dose according to claim 13 wherein the water-resistant coating comprises at least 30% by weight of a butylated methacrylate copolymer.

15. A unit dose according to claim 13 or 14 wherein the tablet has a belly band having a width of 2mm or more.

16. A unit dose according to any one of claims 9 to 15 wherein the solid water-insoluble inorganic compound capable of binding phosphate is present in an amount of at least 200 mg.

17. A process for the preparation of a granular material as defined in any one of claims 1 to 8 comprising the steps of:

i) mixing the compound of formula (I) with one or more excipients to produce a homogeneous mix,

ii) contacting a suitable liquid with the homogeneous mix and mixing in a granulator to form wet granules,

iii) optionally passing the wet granules though a screen to remove granules larger than the screen size,

iv) drying the wet granules to provide dry granules.

v) milling and/or sieving the dry granules.

18. A process according to claim 17 where in the liquid is selected from water, ethanol and mixtures thereof.

19. A granular material according to any one of claims 1 to 8 for use in medicine.

20. Use of a granular material according to any one of claims 1 to 8 in the manufacture of a medicament for binding of phosphate.

21. Use of a granular material according to any one of claims 1 to 8 in the manufacture of a medicament for use in the therapy of a condition or disease associated with phosphate levels.

22. Use of a granular material according to any one of claims 1 to 8 in the manufacture of a medicament for use in the therapy of a condition or disease associated with adverse phosphate levels.

23. Use of a granular material according to any one of claims 1 to 8 in the manufacture of a medicament for use in the therapy of a condition or disease associated with elevated plasma phosphate levels.

24. Use of a granular material according to any one of claims 1 to 8 in the manufacture of a medicament for use in the therapy of hyperphosphataemia.

25. A granular material as substantially hereinbefore described with reference to the Examples.

26. A unit dose as substantially hereinbefore described with reference to the Examples.

27. A process as substantially hereinbefore described with reference to the Examples.

28. A use as substantially hereinbefore described with reference to the Examples.