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(54) **FORMES PHARMACEUTIQUES SOLIDES PAR VOIE BUCCALE RENFERMANT DE L'IFOSFAMIDE COMME MATIERE ACTIVE**

(54) **SOLID ORAL FORMS OF APPLICATION CONTAINING IFOSFAMIDE AS ACTIVE SUBSTANCE**

(57) Solid oral ifosfamide formulations are disclosed where the capsule mass substantially consists of the active substance ifosfamide and microcrystalline cellulase, or in the form of tablets which contain, in relation to one part by weight of ifosfamide, 0.1 - 1.0 parts by weight of tricalcium phosphate, and 0.04 - 0.4 parts by weight of polyethylene glycol as well as in addition, related to the weight of the tablet 5 - 60 % by weight of a filling and flow regulating agent, 1 - 10 % by weight of a disintegrant, 0.1 - 10 % by weight of an antiadhesion agent, and 0.1 - 80% by weight of a binding agent.

ABSTRACT OF THE DISCLOSURE

Solid oral ifosfamide formulations are disclosed where the capsule mass substantially consists of the active substance ifosfamide and microcrystalline cellulose, or in the form of tablets which contain, in relation to one part by weight of ifosfamide, 0.1 - 1.0 parts by weight of tricalcium phosphate, and 0.04 - 0.4 parts by weight of polyethylene glycol as well as in addition, related to the weight of the tablet 5 - 60 % by weight of a filling and flow regulating agent, 1 - 10 % by weight of a disintegrant, 0.1 - 10 % by weight of an antiadhesion agent, and 0.1 - 80% by weight of a binding agent.

Ifosfamide is the INN designation for 3-(2-chloroethyl) -2-(chloroethylamino)-tetrahydro-2H-1,3, 2-oxazophosphorin-2-oxide. Ifosfamide is an important cytostatically active medicinal active substance of the oxazaphosphorin type.

Ifosfamide is a white crystalline powder with a melting point of 48°C to 51°C and has strong hydroscopic properties. Ifosfamide already begins to sinter below the melting point and therefore has to be stored at temperatures that are as low as possible. It is also desirable to avoid contact with humidity whenever possible. Although ifosfamide dissolves to an extent of about 10 percent by weight in water, it is of only limited stability in aqueous solution.

Hitherto ifosfamide has only been registered in formulations for parenteral use. Ifosfamide is available in the form of a sterile crystallate which is filled in injection bottles in dosages of 200 mg to 2000 mg. Prior to application, the sterile crystallate must be dissolved in water for injection purposes, so that a 4% concentration is not exceeded. This solution is suitable for intravenous injection. For purposes of short intravenous infusion the ifosfamide solution is dissolved in 500 ml Ringer's solution or similar injection fluids. The duration of infusion is about 30 minutes, possibly 1 to 2 hours. In the case of the 24-hour infusion, the ifosfamide solution is, for example, dissolved in a total of 3 litres of 5% dextrose-sodium chloride solution.

There are many problems associated with the manufacture and processing of ifosfamide. The manufacture of sterile crystallized ifosfamide results in a product of changing physical characteristics. The variation in the free-flowing characteristics has a particularly deleterious effect on dosage accuracy during filling.

The processing of ifosfamide is further impaired by its hygroscopicity and low melting point. During longer storage periods the sterile crystallizate sinters and the speed of dissolution falls. As ifosfamide begins to sinter, the clarity of solution and the pH value of the solution decrease and a yellow discolouration develops. Therapeutic use is then generally no longer possible.

Apart from the difficulties in manufacturing the sterile crystallizate there are, above all, also serious disadvantages in use. Perenteral application can only be administered by specialized medical personnel. The patient has to be admitted to hospital as an inpatient or must at least attend hospital every day for treatment. This involves a great deal of time on the part of staff and patient.

The potential danger of the substance necessitates extensive protective measures for the staff during the manufacture of the sterile injection solution from the dry substance. Perenteral therapy is unpleasant for a patient since he has to submit to a painful puncture during application and is connected to an infusion apparatus for the duration of the infusion.

Because of all these disadvantages there has long been a need for an oral dosage form which eliminates the above disadvantages. Oral application could permit ambulant therapy. Oral intake of ifosfamide would be pleasant for the patient and would no longer constitute a risk for the medical personnel.

All attempts to develop a solid oral form have, however, hitherto failed because of the described physical-chemical properties of ifosfamide. It was not possible to prepare a medicinal form in soft gelatine capsules. The active substance appears to react with the capsule case,

becomes tanned and the capsule no longer dissolves in the gastric juice. Similarly, many attempts to develop a tablet have hitherto failed. The substance adhered to the die of the tabletting machine, the tablets were too soft and the active substance sometimes spurted in liquified form from the mould during compressing.

It has now surprisingly been found that ifosfamide can be filled into hard gelatine capsules in a mixture with microcrystalline cellulose. It is surprising to note that there is then no deleterious interaction between ifosfamide and the capsule case. Although the capsule case contains 12% to 15% of water (weight/weight) and although ifosfamide is both hygroscopic and moisture sensitive, the filled hard gelatine capsule proves capable of being stored for several years. After many years' storage, the capsule case still dissolves in the gastric juice within a few minutes.

For example, the ifosfamide capsules of the invention contain between 100 mg and 800 mg, preferably between 200 mg and 500 mg of ifosfamide.

The capsule mass substantially consists of ifosfamide and microcrystalline cellulose: the capsule mass optionally also containing small amounts of conventional flow regulators and antiadhesion agents. These flow regulators and antiadhesion agents may be used singly or in a mixture. The total amount of such additional flow regulating agents and antiadhesion agents related to 1 part by weight of ifosfamide is, for example, 0.001 to 0.1 parts by weight, preferably 0.01 to 0.04 parts by weight. It is, for example, possible to use flow regulators and antiadhesion agents that are for example listed in the following textbooks:

W.A. Ritschel, DIE TABLETTE, Editio Cantor Verlag, page 125, 1st edition 1966

Sucker, Fuchs, Speiser, PHARMAZEUTISCHE TECHNOLOGIE, G. Thieme Verlag, Stuttgart, page 334 to 336, 1st edition 1978

Münzel, Büchi, Schultz, GALENISCHES PRAKTIKUM, Wissenschaftliche Verlagsgesellschaft Stuttgart, page 731, 1st edition 1959

R. Voigt, LEHRBUCH DER PHARMAZEUTISCHEN TECHNOLOGIE, 4th edition, Verlag Chemie, Weinheim, page 195, 1st edition 1982

P.H. List, ARZNEIMITTELLEHRE, Wissenschaftliche Verlagsanstalt, Stuttgart, page 86, 1st edition 1976

Substances that are particularly suitable are magnesium stearate as well as other stearates, highly disperse silicon dioxide, stearic acid, talcum and polyglycols (for example with molecular weights of 4000 to 6000).

Flow regulating agents that may preferably be used are 0.002 to 0.02 parts by weight, in particular 0.005 to 0.008 parts by weight per 1 part by weight of ifosfamide and, as antiadhesion agents, 0.004 to 0.08 parts by weight, in particular 0.016 to 0.032 parts by weight of ifosfamide.

Moreover the capsules may optionally also contain fillers such as starch, cellulose, lactose, fructose, saccharose, mannitol, sorbitol, calcium phosphate, binding agents such as gelatine, cellulose, pectins, alginates, polyvinylpyrrolidone, disintegrants such as alginates, carboxymethyl celluloses, polyvinylpyrrolidones, ultraamylopectin.

Flow regulating agents that may in particular be used are highly disperse silicon dioxide (for example Aerosil^{R} such as Aerosil^{R} V 200) as well as magnesium stearate.

The amount of microcrystalline cellulose in the capsule of the invention generally amounts to 0.2 to 4 parts by weight, preferably 0.25 to 1 part by weight, in particular 0.3 to 0.35 parts by weight, related to 1 part by weight of ifosfamide.

The crystallinity of the microceystalline cellulose used should display a crystallinity index* between 0.5 to 0.9, for example 0.7.

The degree of polymerization of the microcrystalline cellulose is for example in the range of 200 to 300. In addition, the microcrystalline cellulose used in accordance with the invention should for example have a mean grain size of ca. 50 µm or under 50 µm. This has for example under 40 µm, in particular at 20 µm. Avicel^{R} is preferably used as microcrystalline cellulose, for example Avicel^{R} with a grain size spectrum of less than 38 µm (Avicel^{R} PH 105) (that is at least 90% of the microcrystalline celluloses have a mean particle size smaller than 38 µm, in particular 20 µm).

In addition it was also surprisingly possible to manufacture tablets with the active substance ifosfamide, the combination of tricalcium phosphate and polyethylene glycol being of special importance. By means of this measure it is now possible for the first time to effect pressing on a conventional tablet press.

Because of its physical properties, the substance ifosfamide cannot be pressed into tablets in a conventional manner using a tabletting machine. All attempts to press the active substance using known auxiliary substances such as for example microcrystalline cellulose, lactose, starch,

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* Crystallinity index is understood to be the quotient of the crystalline portion and the sum of crystalline and amorphous portion. For crystalline cellulose of a grain size of ca. 50 µm the index value is for example 0.71.

talcum, highly disperse silicon dioxide and calcium hydrogen phosphate have failed. All attempts using granulations in a conventional manner or in a fluidized air bed did not lead to tablet masses which could be processed in a perfect manner. In each case the mass adhered to very greatly to the die or mould during the pressing process.

Related to one part by weight of ifosfamide, the tablets of the invention contain

0.1 - 1.0 parts by weight of tricalcium phosphate and

0.04 to 0.4 parts by weight of polyethylene glycol (for example molecular weight 4000 to 6000)

as well as, related to the tablet weight

5 - 60 % by weight of a filling and flow regulating agent

1 - 10 % by weight of a disintegrant

0.1 - 10 % by weight of an antiadhesion agent and

0.1 - 80 % by weight of a binding agent.

In accordance with the invention use is for example made per 1 part by weight of ifosfamide of:

0.1 - 1.0 parts by weight, preferably 0.2 - 0.5, in particular 0.25 - 0.30 parts by weight of tricalcium phosphate. Related to the tablet mixture, the amount of tricalcium phosphate is for example 3.5 to 35 % by weight, preferably 7 to 17.8 % by weight, in particular 9 to 11 % by weight.

The amount of polyethylene glycol is for example 0.04 to 0.4 parts by weight, preferably 0.1 - 0.2, in particular 0.13 to 0.15 parts by weight per 1 part by weight of ifosfamide. It is in particular possible to consider

polyethylene glycol with molecular weights of 4000 to 6000, preferably polyethylene glycol 6000. Related to the tablet mixture, the amount of polyethylene glycol is for example 1 to 14.0 % by weight, preferably 3.5 to 7.5 % by weight, in particular 4.5 to 7 or also 4.5 to 6 % by weight. The weight ratio of tricalcium phosphate to polyethylene glycol is for example 1 : 0.5.

The following are in addition also contained in the tablet of the invention:

Fillers and flow regulating agents in an amount of 5 to 60 % by weight, related to the tablet weight. Fillers that may for example be considered are starches, celluloses, lactose, saccharose, fructose, sorbitol, mannitol, calcium phosphate, calcium carbonate, calcium sulphate, magnesium carbonate or magnesium oxide. 5 - 50 % by weight are used, related to the tablet weight.

Flow regulating agents that may for example be considered are microcrystalline cellulose, lactose, polyglycols, starches, celluloses, talcum, talcum siliconisatum, calcium arachinate or calcium stearate, cetyl alcohol, stearyl alcohol, myristyl alcohol, stearic acid, lauric acid. Should the flow regulating agent not also serve as a filler, 0.5 - 10 % by weight are used hereof, related to the tablet weight.

Disintegrants: use is for example made of alginates, starches (corn starch), pectins, carboxymethyl celluloses, polyvinylpolypyrrolidone, ultraamylopectin, betonite. 1 - 10 % by weight are used, related to the tablet weight.

Antiadhesion agents: use is for example made of glycols, talcum, talcum siliconisatum, talcum stearinicum, calcium stearate, aluminium stearate, stearic acid. 0.1 - 10

% by weight are used, related to the tablet weight.

Binding agents: for example gelatine, cellulose ethers, amyloses, pectins, cellulose,dextrose, polyglycols, tragacanth. Use is made of 0.1 - 80 % by weight, related to the tablet weight.

In particular the tablet of the invention contains the following substances, apart from ifosfamide, tricalcium phosphate and polyethylene glycol: microcrystalline cellulose 0.2 - 1.2 parts by weight, preferably 0.4 - 1.0, in particular 0.70 - 0.90 parts by weight, related to one part by weight of ifosfamide or related to the tablet weight 7 to 43, preferably 15 to 35 % by weight;

lactose 0.15 - 1.0 parts by weight, preferably 0.24 - 0.68, in particular 0.30 - 0.40 parts by weight, related to one part by weight of ifosfamide or related to the tablet weight 5.0 to 36, preferably 8.5 to 25 % by weight;

corn starch 0.02 - 0.24 parts by weight, preferably 0.05 - 0.20, in particular 0.1 - 0.15 parts by weight, related to one part by weight of ifosfamide or related to the tablet weight 0.7 to 8.5, preferably 2.0 to 6.5 % by weight;

talcum 0.02 - 0.30 parts by weight, preferably 0.06 - 0.20, in particular 0.07 - 0.09 parts by weight, related to one part by weight of ifosfamide or related to the tablet weight 0.70 to 10, preferably 2 to 6.5 % by weight;

magnesium stearate 0.004 - 0.2 parts by weight, preferably 0.02 - 0.12, in particular 0.035 - 0.05 parts by weight, related to one part by weight of ifosfamide or related to the tablet weight 0.1 to 7.2, preferably 0.7 to 4.5 % by weight.

Tablets as well as capsules may be provided with a coating in known manner. It is possible to apply water soluble, swellable, water insoluble or gastric juice resistant coatings which may be applied to the tablets or capsules from aqueous dispersion or solution or also from solution or dispersion in organic solvents such as for example ethanol, isopropanol, acetone, ether, dichloromethane, methanol.

The manufacture of the capsules and tablets occurs for example between 15°C and 26°C, preferably between 18°C and 22°C. The relative humidity in the production rooms should not exceed 40%.

The process for the production of the inventive solid oral ifosfamide formulations is characterized in that between 15°C and 30°C either 1 part by weight of the active substance ifosfamide and 0.1 - 4, preferably 0.2 - 4, particularly 0.25 -1 parts by weight of microcrystalline cellulose and optionally small amounts of conventional flow regulating and antiadhesion agents are homogeneously mixed and filled into capsules or one part by weight of ifosfamide and

0.1 - 1.0 parts by weight of tricalcium phosphate and
0.04 - 0.4parts by weight of polyethylene glycol as well as in addition
0.15 - 2, preferably 0.5 - 1.5, particularly 1 - 1.3 parts by weight of a filling and flow regulating agent
0.03 - 0.5 preferably 0.05 - 0.4, particularly 0.08 - 0.2 parts by weight of a disintegrant
0.003 - 0.5, preferably 0.01 - 0.4, particularly 0.05 - 0.2 parts by weight of an antiadhesion agent and
0.003 - 3 preferably 0.01 - 2, particularly 0.1 - 1 parts by weight of a binding agent

are homogeneously mixed and then pressed into tablets

and optionally the so obtained capsules and tablets respectively are provided with an usual coating.

Example 1:

Ifosfamide capsule mass

In accordance with the invention, the capsule mass is for example manufactured according to the following method:

For 12,000 capsules of 250 mg each, 3.0 kg ifosfamide, 1.002 mg microcrystalline cellulose and 0.018 kg highly disperse silicon dioxide are for example passed through a 0.8 mm sieve and then mixed in a suitable mixer for 4 minutes. 0.06 kg of magnesium stearate are then added to this mixture (sieved through a 0.8 mm sieve) and mixing repeated for 1 minute. The finished capsule mass is then filled in a capsule machine fitted with size 1 moulds into size 1 hard gelatine capsules so that each capsule contains ca. 340 mg of the capsule mass.

For 20,000 capsules of 500 mg each, 10.0 kg ifosfamide, 3.34 kg microcrystalline cellulose and 0.06 kg highly disperse silicon dioxide are for example passed through a 0.8 mm sieve and then mixed in a suitable mixer for 4 minutes. 0.2 kg of magnesium stearate are then added to this mixture (sieved through a 0.8 mm sieve) and mixing repeated for 1 minute. The finished capsule mass is then filled in a capsule machine fitted with size 00 moulds into size 00 hard gelatine capsules so that each capsule contains ca. 680 mg of the capsule mass. The microcrystalline cellulose is used for example in the form of Avicel PH 105. Avicel PH 105 has a special grain size spectrum and is a filling substance with good binding and flowing properties.

To manufacture gastric juice resistant capsules, a

coating suspension in organic solvent (ifosfamide) is for example applied to 2500 size 1 capsules containing 250 mg ifosfamide. The 3000 g of suspension contain:

1440 g anionic polymerisate of methacrylic acid and methacrylic acid esters with a mean molecular weight of for example 150,000, to which a conventional softener has been added, 18 g of 1,2-propandiol, 36 g of magnesium stearate and 1506 g of isopropanol.

The copolymerisate of methacrylic acid and methylmethacrylate that may for example be considered is Eudragit L^R, in particular in the form of a 12.5 % solution in ifosfamide (Eudragit L^R/12.5 %). Copolymerisates for this type are soluble in neutral to weakly alkaline medium through salt formation with alkalis.

Example 2:

Ifosfamide tablets

The composition of a tablet containing 250 mg of active substance is for example:

One 700 g tablet contains:

ifosfamide	250 mg
tricalciumphosphate, fine	70 mg
microcrystalline cellulose	200 mg
lactose	85 mg
polyglycol 6000	35 mg
corn starch	30 mg
talcum	20 mg
magnesium stearate	10 mg

To manufacture the tablet mass for 1500 tablets, 375 g

ifosfamide, 105 g tricalcium phosphate (fine), 300 g microcrystalline cellulose, 127.5 g lactose, 52.5 g polyglycol 6000, 45 g corn starch and 30 g talcum are passed through a sieve of mesh size 0.8 mm and mixed for 15 minutes in a suitable mixer. 15 g of magnesium stearate (also sieved) are added and mixing continued for 2 minutes. The tablet mass is then pressed into tablets on a suitable tablet press.

To manufacture tablets with a gastric juice resistant coating, 500 g of an aqueous dispersion as described below are for example applied to 1050 g of tablets:

100 g of the aqueous dispersion contain:	
polyglycol 6000	1,600 g
titanium dioxide	1,100 g
iron oxide, yellow	0.156 g
talcum	4,000 g
dimethylpolysiloxan	0.100 g
Eudragit L^{R} 30 D*	55,000 g
water	38,044 g
	100,000 g

Conventionally used apparatus, in which the solution or dispersion agent is continuously removed through drying, is for example used to spray on the film solution.

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*Eudragit L^{R} 30 D is the aqueous dispersion of a copolymerisate of an anionic nature based on methacrylic acid and ethyl acrylate. The ratio of the free carboxyl groups to the ester groups is about 1 : 1. The mean molecular weight is 250,000.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Solid oral ifosfamide formulations in the form of ifosfamide capsules and tablets; the capsules having a capsule mass comprising the active substance ifosfamide and, in relation to one part by weight of ifosfamide, 0.2 to 4 parts microcrystalline cellulose; and the ifosfamide tablets containing, for each part by weight of ifosfamide:

0.2 - 1.2 parts by weight of microcrystalline cellulose,

0.1 - 1.0 parts by weight of tribasic calcium phosphate,

0.04 - 0.4 parts by weight of polyethylene glycol,

as well as, related to the weight of the tablet:

5 - 60% by weight of a filling and flow-regulation agent,

1 - 10% by weight of a disintegrant,

0.1 - 10% by weight of an antiadhesion agent, and

0.1 - 80% by weight of a binding agent.

2. A solid oral ifosfamide formulation according to claim 1, in the form of a capsule.

3. An ifosfamide-containing capsule according to claim 2, including small amounts of conventional flow-regulation and antiadhesion agents.

4. An ifosfamide-containing capsule according to claim 2 or 3, wherein the microcrystalline cellulose has a degree of crystallinity of 0.5 to 0.9.

5. A solid oral ifosfamide formulation according to claim 1, in the form of a tablet.

6. A process for the production of solid oral ifosfamide formulations, which comprises: homogeneously mixing, at 15°C. - 30°C., 1 part by weight of the active substance ifosfamide and 0.2 - 4 parts by weight of microcrystalline cellulose, and optionally small amounts of conventional flow-regulating and antiadhesion agents, and dispensing the resulting mixture into capsules; or homogeneously mixing one part of ifosfamide and 0.2 - 1.2 parts by weight microcrystalline cellulose, 0.1 - 1.0 parts by weight of tribasic calcium phosphate, 0.04 - 0.4 parts by weight of polyethylene glycol, 0.15 - 2 parts by weight of a filling and flow regulating agent, 0.03 - 0.5 parts by weight of a disintegrant, 0.003 - 0.5 parts by weight of an antiadhesion agent and 0.003 - 3 parts by weight of a binding agent, and pressing the resulting mixture into tablets; and optionally providing the so-obtained capsules or tablets with a conventional coating.

7. A process as defined in claim 6, wherein the microcrystalline cellulose has a degree of crystallinity of 0.5 to 0.9.