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[54] **PHARMACEUTICAL PREPARATION CONTAINING METFORMIN AND A PROCESS FOR PRODUCING IT**

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[58] **Field of Search** 424/464, 482, 424/466, 480, 489

[56] **References Cited**

U.S. PATENT DOCUMENTS

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[57] **ABSTRACT**

The present invention concerns pharmaceutical compositions containing metformin as an active substance and a hydrocolloid-forming agent as a retardant and optionally standard pharmaceutical auxiliary substances, the residual moisture content in the pharmaceutical composition being 0.5–3% by weight. The invention also concerns a process for producing pharmaceutical compositions containing metformin as an active substance and a hydrocolloid-forming agent as a retardant and optionally standard pharmaceutical auxiliary substances characterized in that the active substance and retarding agent or a portion thereof are granulated with an aqueous solvent which can optionally contain a binder and where appropriate the other portion of the retardant or other standard pharmaceutical auxiliaries are admixed with the granulate which is then dried until the residual moisture content is reduced to 0.5–3% by weight.

19 Claims, No Drawings

PHARMACEUTICAL PREPARATION CONTAINING METFORMIN AND A PROCESS FOR PRODUCING IT

The invention concerns pharmaceutical preparations containing metformin hydrochloride (also called metformin in the following) as an active substance and a hydrocolloid-forming agent as a retardant and a process for their production.

It is known that metformin hydrochloride is a biguanide derivative (1,1-dimethylbiguanide monohydrochloride) which has an oral antidiabetic action. Metformin delayed release tablets containing 850 mg metformin hydrochloride per film tablet (Glucophage® retard) are on the market. Since metformin in contrast to other active substances cannot be pressed in its pure form (the mass disintegrates in an unchanged form after the compression) framework-forming auxiliary substances such as polyvinylacetate were used in these high-dose delayed release tablets as a retarding agent (Lipha, technical information Glucophage® August 1991, "Bundesverband der Pharmazeutischen Industrie e.V.", publ. Rote Liste 1993, Edition Cantor, Aulendorf 1993). The mechanism of action of such framework tablets is based on the fact that the readily water-soluble metformin diffuses out of the tablet independently of pH in the gastrointestinal tract whereas the tablet framework with the coating is excreted largely unchanged.

The disadvantage of using such framework-forming auxiliary substances such as polyvinylacetate is, however, that they have to be processed with organic solvents in particular during the granulation process, the organic solvent having to be removed again as completely as possible before the granulate is processed further to compressed pharmaceutical forms of administration and for example pressed into tablets.

The object of the invention was to provide an improved pharmaceutical composition for the active substance metformin. In particular the form of administration should contain the active substance metformin with a highest possible content of active substance and a retardant, the retardant causing a controlled release of the active substance. In particular the new pharmaceutical composition should not contain framework formers which have to be processed with organic solvents but should be composed on the basis of substances that can be processed aqueously. These pharmaceutical compositions should be readily or easily compressible so that they are suitable for the manufacture of solid pharmaceutical forms of administration such as e.g. tablets, dragées or comprimates for filling into capsules. In the case of the manufacture of tablets or other comprimates the maximum total weight should be about 1200–1300 mg in order not to jeopardize the therapeutic safety (patient compliance) since larger oral forms of administration are often not taken in the prescribed regularity.

Another object in the processing of the granulate for these high-dose forms of administration especially in the manufacture of tablets was to solve the problem of capping caused by the active substance which is particularly pronounced in the case of metformin in order to avoid losses of yield during the production and impairment of the pharmaceutical quality. Capping denotes the detachment of compressed mass in layers from the manufactured compact during the pressing or shortly afterwards (Schepky G. in: Bruchhausen, F. von et al.; publ. Hagers Handbuch der pharmazeutischen Praxis, Volume 2, Methoden, 5th ed. "Springer Verlag", Berlin 1991). In the case of metformin and especially when high doses of active substance are present in the granulate it has turned out that the tendency for capping is particularly high during the production of tablets.

The causes for these tabletting problems can be diverse and complex. Capping can be caused by an inadequate binding agent action, an inadequate or excessive moisture content of the granulate, unsuitable crystal forms, strongly aerophilic substances, excessive porosity, excessive proportion of powder, excessive interparticulate binding between the granulate particles and by unsuitable granulate forms. Machine factors which can lead to capping are an excessive pressing force, badly applied or worn tools, excessive pressing rates and poor deaeration of the matrix (fixed pressure). However, in the case of the active substance metformin it has turned out that the usual measures are not adequate to satisfactorily control the capping of the tabletting mass. A relatively high proportion of defective tablets was found during tablet production and the tabletting had to be discontinued due to high reject rates.

In the present case the object of the invention is achieved by providing high-dose pharmaceutical compositions containing metformin which contain a hydrocolloid-forming agent as a retardant and have a residual moisture content in the pharmaceutical composition of 0.5–3% by weight. These pharmaceutical compositions can be advantageously manufactured using aqueous solvents so that organic solvents are no longer required. In addition these compositions are surprisingly easy to compress. They are therefore particularly suitable for the manufacture of solid pharmaceutical forms of administration such as e.g. tablets, dragées or capsules and these can be manufactured with the aid of standard processing machines on a technical scale and in a good quality as well as in a high yield without large losses due to the undesired capping. Accordingly a subject matter of the invention is also a corresponding process for the production of these solid forms of administration in which the appropriate pharmaceutical compositions according to the invention are used in the form of granulates with a residual moisture content of 0.5–3% by weight. The residual moisture content is preferably 1–2.5% by weight in particular 1.5–2% by weight.

Surprisingly it was also found that in the case of the granulate according to the invention it was possible to omit the addition of humectants which are otherwise often necessary to set a constant residual moisture content until the granulate is compressed. This is particularly advantageous because it minimizes the addition of auxiliary substances and pharmaceutical compositions are obtained with a relatively high content of active substance. In addition these compositions have the advantage that they are stable on storage for a period of two days or more (starting from the production up to the use of the granulate for tabletting) with regard to the moisture content before they are compressed without there being a detectable disadvantageous change in the composition. This is particularly advantageous since it enables several partial batches of production lots of the pharmaceutical composition to be produced and these can then be mixed as a mass ready to be pressed at a later time in a common last process step and can be processed to solid pharmaceutical forms of administration.

In addition it surprisingly turned out that the use of a hydrocolloid-forming agent enabled for the first time the known poor compressibility of metformin to be brought under control in a technically satisfactory manner. In addition the solution according to the invention enables the desired retardation and compressibility to be ensured by the selection of the hydrocolloid-forming agent as the retardant and with a suitable control of the production process (adhering to the critical residual moisture content of 0.5–3% by weight in particular of 1–2.5% by weight and 1.5–2% by

weight) although the proportion of the hydrocolloid-forming agent in the formulation composition is unusually low. This is even more surprising since the active substance whose water absorbing capacity is very small (the pure active substances only binds 0.04% by weight water at a relative moisture content of 90%) forms the major proportion of the formulation (about 70–95% by weight).

The proportion by weight of the active substance in the high-dose pharmaceutical composition is in the range of at least 70% by weight, preferably 80–95% by weight relative to the pharmaceutical composition. The active substance can be used in the form of acid addition salts of inorganic or organic acids such as e.g. hydrochloric acid, formic acid, acetic acid, malic acid, tartaric acid or furmaric acid. The hydrochloride salt is preferably used.

The proportion of hydrocolloid-forming agent in the pharmaceutical composition is up to 15% by weight preferably 4–10% by weight and especially about 6–8% by weight.

Within the sense of the invention the standard hydrophilic gel forming agents are suitable as hydrocolloid-forming agents or as hydrophilic swelling substances such as for example cellulose derivatives, dextrins, starch, carbohydrate-based polymers, natural or hydrophilic gums, xanthanes, alginates, gelatin, polyacrylic acid, polyvinyl alcohol or polyvinylpyrrolidone. In the case of the cellulose derivatives the alkyl or hydroxyalkyl cellulose derivatives preferably come into consideration such as e.g. methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose or sodium carboxymethyl cellulose. In a preferred procedural variant of the invention methylhydroxypropyl cellulose (MHPC) is used. The hydrocolloid-forming agents can be used individually as well as in mixtures of two or several colloid-forming agents. The standard polymers suitable for pharmaceutical purposes with various degrees of substitution and/or different molecular weights corresponding to a different degree of viscosity of the aqueous solution can be used as suitable cellulose-based polymeric colloid-forming agents.

The use of hydrocolloid-forming agents as retardants is based on the property of the hydrocolloid-forming agents to swell and form a gel matrix when they are contacted with a release medium or digestive juices which erodes to release the active substance. The interaction between the amount of hydrocolloid-forming agent and the degree of viscosity determines the time course of the release. Thus for example a high proportion (70–95% relative to the core weight of the tablet) of polyvinyl alcohol of a lower or average viscosity level can for example retard riboflavin for several hours (M öckel J. E., Lippold B. C., Pharm. Research, 1993, 10, 1066–1070).

The compressed forms of administration that are produced using the pharmaceutical composition according to the invention such as for example metformin delayed-release tablet cores can be additionally provided with a film envelope. The film envelope can on the one hand cause an additional retardation by using those film materials which represent a film-forming agent which is usually suitable for these purposes. On the other hand the film envelope used can be a taste-neutralizing film-forming agent to which dyes can optionally be added. In addition it is also possible to for example use films that are resistant to gastric juice. The proportion by weight of the film envelope relative to the final tablet is in the usual range of 0.3–3.0% by weight preferably of 0.8–1.2% by weight. Film formers such as for example ethyl cellulose, poly(methylmethacrylate) derivatives (Eudragit®) and also soluble cellulose derivatives such as methylhydroxypropyl cellulose and cellulose derivatives for forming films resistant to gastric juice such as cellulose acetate phthalate or methylhydroxypropyl cellulose phthalate come into consideration as film formers. Ethyl cellulose is preferably used. The dissolution of the active substance can be delayed by the film that is formed. Softeners, pore formers and pigments may be present in the film envelope as standard auxiliary substances.

The pharmaceutical composition according to the invention can also be used to produce compressed capsule filling materials. These comprimates or compacted granulates can then be filled into commercial capsules by means of suitable devices. In comparison to the other standard capsule filling materials containing metformin these compacted granulates have the advantage with the same content of active substance and the same dosage that smaller capsules can be used due to their smaller volume which can be more easily swallowed by the patient.

The pharmaceutical forms of administration according to the invention such as e.g. tablets contain—apart from the active substance whose proportion in the form of administration can be in the range of 70–95% by weight (for example 850 mg of the active substance is preferably used in the case of retarded tablets) and the retardant—preferably 2–10% by weight binder, up to 2% by weight preferably 0.1–0.3% by weight flow regulating agent and up to 2% by weight preferably 0.4–1.1% by weight lubricant each in relation to the total weight of the material ready to be tabletted or of the tablet core. The weight of a tablet core is usually between 200 and 1300 mg preferably in the range of less than 1200 mg especially of about 500–1000 mg. Flow regulating agents which come into consideration for the tablet according to the invention are standard agents such as for example colloidal silicon dioxide. Talcum or stearic acid or alkali or alkaline earth salts thereof in particular magnesium stearate are for example suitable as lubricants. Examples of binding agents that can be used are cellulose derivatives especially alkyl and hydroxyalkyl celluloses in particular methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, sodium carboxymethyl cellulose etc., dextrins, starches, especially soluble starches, other polymers based on carbohydrates such as e.g. galactomannans, natural gums such as gum arabic, Traganth, Sterculia, Acacia and others, xanthane, alginates, polyacrylic acid, polyvinyl alcohol and polyvinylpyrrolidone. Polyvinylpyrrolidone is preferably used.

The pharmaceutical forms of administration according to the invention such as e.g. tablets are produced by dry mixing the active substance, the retardant or a portion of the retardant and optionally further auxiliary substances, wet-granulating with water or an aqueous solution of a binder, drying the material ready for tabletting to a desired residual moisture content and subsequently where appropriate the remaining portion of the retardant or other pharmaceutical auxiliary substances are admixed with the granulate so that in the last process step a residual moisture content of 0.5–3% by weight is achieved in the pharmaceutical composition. The determination of the residual moisture content is carried out by known analytical methods of aquametry for example by determining the water content with the aid of the Karl-Fischer reagent or other alternative methods of determination. In the wet granulation a portion of the active substance, the auxiliary substances used as well as the retardant may also be present dissolved or suspended completely or par-

tially in water. Optionally it is also possible to add organic solvents that are miscible with water such as for example acetone or lower alcohols such as methanol or ethanol.

It is expedient to adjust the residual moisture content while drying in a fluid bed process in which the moist granulate is dried until the measured moisture content in the outlet air has reached the value previously determined when the residual moisture content in the drying material was calibrated. The composition produced in this manner is subsequently processed in the usual manner to form pharmaceutical forms of administration and for example pressed into tablets. The tablets can be coated with a film using the standard coating processes. It was found that the residual moisture content of 0.5–3% by weight that was set with the aid of the hydrocolloid-forming agent ensures that the material ready for tabletting can be compressed over the entire range of pressing force required to produce large tablets without capping.

The active substance can be processed completely or partially with the hydrocolloid-forming agent used for the retardation to form a granulate or the hydrocolloid-forming agent is mixed completely with a granulate free of hydrocolloid-forming agent after its production. However, an additional improvement in the tablet-forming properties is achieved when the hydrocolloid-forming agent or a portion thereof is granulated with the active substance.

The tablet is coated by standard methods such as e.g. the coating pan or fluid bed process.

The retarded tablets according to the invention release metformin in a controlled manner over a time period of 0.5–10 hours preferably over 4 hours (FIG. **1**). Since due to the use of a hydrocolloid-forming agent large amounts of additional auxiliary substances and in particular no humectants such as for example glycerol or sorbitol are necessary, the maximum weight of the tablets is 1200 mg preferably below 1000 mg.

It is intended to elucidate the invention in the following by the procedural examples without limiting it thereto.

In the following examples 1–6 the residual moisture content was adjusted to the range according to the invention before the pharmaceutical composition in the form of a mass ready for pressing was pressed into tablets. In examples 7 and 8 the residual moisture content was set to a value of less than 0.5% by weight. In these two cases the tabletting had to be terminated due to high losses caused by capping.

EXAMPLE 1

Hydrocolloid-forming agent: methylhydroxypropyl cellulose (MHPC). The MHPC content can be varied e.g. from 40–95 mg.

residual moisture: 2.1%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 mio. pieces]
Core:		
metformin hydrochloride	850.00	850.00
methylhydroxypropyl cellulose	60.00	60.00
polyvidone	38.00	38.00
magnesium stearate	5.00	5.00
core total:	953.00	953.00
Film envelope:		
methylhydroxypropyl cellulose	20.00	20.00
ethyl cellulose	12.00	12.00
Macrogol	4.00	4.00
titanium dioxide	4.00	4.00
envelope total:	40.00	40.00
film tablet total:	993.00	993.00

Production

The production of granulate for an amount of about 1 million tablets is carried out in five partial batches. For each of the five partial batches 170 kg metformin hydrochloride and 12 kg methylhydroxypropyl cellulose were dry mixed together and wet-granulated in a mixer with a 10% aqueous binder solution of polyvidone. Subsequently the granulate is dried in a fluid bed granulator until it has an adequate residual moisture content. The five partial batches are combined and admixed with 5 kg magnesium stearate. The mass ready for pressing is tabletted. The tablet cores are coated in a coating pan with the film of the described composition.

In the stated formulation the residual moisture content is adjusted to 2.1%. The tabletting proceeds correspondingly without problems i.e. a capping of the manufactured tablet mass cannot be detected.

EXAMPLE 2

Hydrocolloid-forming agent: hydroxyethyl cellulose

Residual moisture: 2.0%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 mio. pieces]
Core:		
metformin hydrochloride	850.00	850.00
hydroxyethyl cellulose	70.00	70.00
polyvidone	40.00	40.00
magnesium stearate	5.00	5.00
core total:	965.00	965.00
Film envelope:		
methylhydroxypropyl cellulose	5.00	5.00
lactose	5.00	5.00
ethyl cellulose	10.00	10.00
Macrogol	3.00	3.00
titanium dioxide	3.00	3.00
envelope total:	26.00	26.00
film tablet total:	991.00	991.00

The granulate is produced and processed analogously to example 1; the tabletting proceeds correspondingly without problems.

EXAMPLE 3

Hydrocolloid-forming agent: sodium carboxymethyl cellulose

Residual moisture: 2.1%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 mio. pieces]
Core:		
metformin hydrochloride	850.00	850.00
sodium carboxy methyl cellulose	80.00	80.00
polyvidone	35.00	35.00
magnesium stearate	5.00	5.00
core total:	970.00	970.00
Film envelope:		
methylhydroxypropyl cellulose	5.00	5.00
ethyl cellulose	10.00	10.00
Macrogol	4.00	4.00
titanium dioxide	3.00	3.00
envelope total:	22.00	22.00
film tablet total:	992.00	992.00

The granulate is produced and processed analogously to example 1; the tabletting proceeds correspondingly without problems.

EXAMPLE 4

Hydrocolloid-forming agent: polyacrylic acid

Residual moisture: 2.8%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 mio. pieces]
Core:		
metformin hydrochloride	850.00	850.00
polyacrylic acid	60.00	60.00
methylhydroxypropyl cellulose	30.00	30.00
magnesium stearate	5.00	5.00
core total:	945.00	945.00
Film envelope:		
methylhydroxypropyl cellulose	10.00	10.00
ethyl cellulose	10.00	10.00
Macrogol	3.00	3.00
titanium dioxide	3.00	3.00
envelope total:	26.00	26.00
film tablet total:	971.00	971.00

The granulate is produced and processed analogously to example 1. As a variant methylhydroxypropyl cellulose in this case serves as a binder. The tabletting proceeds correspondingly without problems.

EXAMPLE 5

Hydrocolloid-forming agent: hydroxypropyl cellulose

Residual moisture: 1.95%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 mio. pieces]
Core:		
metformin hydrochloride	850.00	850.00
hydroxypropyl cellulose	60.00	60.00
polyvidone	40.00	40.00
magnesium stearate	5.00	5.00
core total:	955.00	955.00
Film envelope:		
poly(ethylacrylate-methyl methacrylate) dispersion 30%	6.00*	6.00*
talcum	1.20	1.20
anti-foaming agent	0.07	0.07
envelope total:	7.27	7.27
film tablet total:	962.270	962.270

*Stated quantity refers to the dry substance.

The granulate is produced and processed analogously to example 1. As a variant the hydrocolloid-forming agent hydroxypropyl cellulose is in this case not granulated simultaneously but admixed dry with the completed granulate.

EXAMPLE 6

Hydrocolloid-forming agent: methylhydroxypropyl cellulose

Residual moisture: 2.0%

In the following example an additional binder is completely omitted, the methylhydroxypropyl cellulose used adopts the function of both binder and retardant.

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 mio. pieces]
Core:		
metformin hydrochloride	850.00	850.00
methylhydroxypropyl cellulose	100.00	100.00
magnesium stearate	5.00	5.00
core total:	955.00	955.00
Film envelope:		
methylhydroxypropyl cellulose	20.00	20.00
ethyl cellulose	12.00	12.00
Macrogol	4.00	4.00
titanium dioxide	4.00	4.00
envelope total:	40.00	40.00
film tablet total:	995.00	995.00

Production

The production of granulate is carried out in five partial batches. For each of the five partial batches 170 kg metformin hydrochloride and 18 kg methylhydroxypropyl cellulose are placed in a fluid bed granulator. 2 kg methylhydroxypropyl cellulose is dissolved in 50 l water. The dry mixture is granulated with the binder solution in a fluid bed granulator and subsequently dried. The five partial batches are combined and admixed with 5 kg magnesium stearate.

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