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(54) Title: PHARMACEUTICAL METFORMIN HYDROCHLORIDE FORMULATION AND TABLET COMPRISING SAID FORMULATION

(57) Abstract: A formulation is described comprising micronized metformin HCl useful for the preparation of pharmaceutical tablets by simple compression.

PHARMACEUTICAL METFORMIN HYDROCHLORIDE FORMULATION AND TABLET COMPRISING SAID FORMULATION

Field of the invention

The present invention relates to the field of pharmaceutical formulations for tablets.

State of the art

The intrinsic properties of the product, its dosage form, the biopharmaceutical target and the economic aspects of the operations involved will determine selection of the best production process for use in the preparation of a pharmaceutical form.

The three main processes for producing tablets can be described thus:

wet granulation, direct compression and dry granulation.

Dry granulation can be used when one of the constituents, primarily the drug or the diluent, has sufficient cohesive properties to form tablets. This method consists of pre-compressing the single ingredients or a mixture of two or more ingredients to obtain aggregates with good flowability, able to form tablets on addition of external excipients. This type of process is suitable for water-sensitive active ingredients, for example.

The wet granulation method is used for converting a powder mixture into granules with cohesive and flow properties suitable for compression into tablets. The procedure consists of agglomerating an ingredient or a powder mixture with a granulating solvent or a solution. The wet granulate, once dried and sized, is combined with external excipients and compressed.

Direct compression is regarded as a relatively quick method in which the powdered material is compressed directly without changing the chemical and physical properties of the drug.

The advantages of direct compression include: elimination of heat and moisture, restoration of primary particles during dissolution, physical stability, ease of process transfer operations, fewer manufacturing steps with cost and time advantages.

High dose drugs can be compressed directly only if the drug itself has suitable

physical characteristics (e.g. flowability and cohesiveness) for this process.

Unfortunately, without excipients, most drugs particularly at high doses cannot be directly compressed into tablet form. This is mainly due to the poor flow and cohesive properties of these drugs. Generally, therefore, the applicability of direct compression is linked to medium or high dilution with excipients having a particle size greater than those of the active principle, or to the use of specific highly functional excipients.

Metformin hydrochloride is a hypoglycemic agent used in the treatment of non-insulin dependent diabetes. Metformin HCl is considered a high dose drug (normally from 400 to 1000 mg/dose), being relatively hygroscopic and not inherently compressible, hence presenting formulation problems. Consequently most tablet formulations, which comprise a quantity of 70 to 85% of the drug, adopt the wet granulation method.

For direct compression formulations, the most used method is a medium or high dilution with excipients; with this method the active principle does not normally exceed 20-30% of the total. This dilution allows the poor functional properties of the drug to be overcome without the weight and size of the tablet produced being excessive.

To avoid the drawbacks associated with swallowing tablets, dispersible or soluble tablets have been formulated.

WO 2004/082664 claimed soluble tablets based on a soluble salt of metformin and a soluble alcohol in high weight tablets (more than 900 mg for 500 mg of active principle). Although formulations containing up to 95% metformin are said to have been prepared, it is understandably likely that in this case the wet granulation method was used. Despite this, the characteristics of the tablets are limited (their hardness is stated as being not greater than 8 kP).

The objective of modifying the original characteristics of the powder can be achieved for example by pre-compression and compaction of the drug. This is commonly applied to drugs such as paracetamol, ranitidine HCl, amoxicillin. However this procedure must doubtless be regarded as a procedure additional to the direct compression process.

In order to increase flowability, larger sized particles can be used with the purpose

of limiting inter-particle friction. This is precisely the case described in US 6,117,451 in which the formulation to be directly compressed is strictly confined to the use of metformin HCl of particle size from 400 to 600 micrometres. The use of components of said particle size is helpful in terms of flowability but most certainly reduces compaction properties, known to be correlated with the external surface area of the solid involved in the compaction process (no data is given on tablet performance). Moreover, segregation problems can occur as a result of the different particle sizes of the other excipients utilized in the formula. Frequently, functional excipients, able to confer appropriate characteristics on the tablets, can also be employed. These excipients should be characterized by a high compressibility at low usage percentage. These materials include cellulose derivatives in general (ethyl, hydroxyethyl, hydroxypropyl, hydroxypropylmethyl cellulose etc.), this being one of the most widely used classes though more often specified for controlled release applications (US 6,524,618).

This is the case reported in US 6,117,451 where hydroxypropyl methylcellulose and hydroxypropyl cellulose are used to form a dynamic hydrophilic matrix which induces formation of a gel layer, delaying disintegration time and consequently active principle release. This effect is dependent to a greater or lesser extent on the content and viscosity of the polymer used. However, this should not be a characteristic of immediate release tablets (data on the behaviour of metformin HCl at release are not supplied).

Besides the active or therapeutic ingredients, the tablets can contain a number of inert materials called excipients. These can be classified according to their function. The basic components normally include: binders, diluents, lubricants, disintegrants and anti-adherents (glidants).

In direct compression particular attention must be given to the binder; it is an agent which provides the following desirable qualities to the powdered material: high compactibility, good flowability, cohesiveness.

Diluents or fillers are added to increase mixture mass up to the required level for compression, but also to increase or modulate tablet properties.

Lubricants are generally added to prevent adhesion of the material to the punches and to minimize friction during compression and ejection. Said excipients are

generally included in the final mixture in small amounts, but can be increased in relation to the surface area characteristics of the powders.

Disintegrants are often added to ensure an acceptable degree of disintegration.

Glidants or anti-adherents are other excipients commonly added to increase flowability from the discharge hopper to the punch die.

Description of the invention

The present invention relates to a metformin HCl formulation in the form of a cohesive and free-flowing powder, suitable for the preparation of tablets by means of direct compression, utilizing the least possible quantity of excipients in order to reduce the final weight of the finished product, by a simple and economical manufacturing process.

According to the invention, metformin HCl tablets can be obtained in dosage units which have a good dissolution profile, an acceptable degree of hardness and resistance to chipping as well as a short disintegration time.

This is possible by using smaller active principle particles, i.e. within the range from 10 to 200 micrometres, which result in an increase in surface interactions without reducing flow characteristics. This ensures the two-fold advantage of having an effective formula with a very low quantity of excipients so as to reduce tablet size. The present invention also includes the use of a polymer, namely vinylpyrrolidone-vinyl acetate copolymer, in the form of particles also within the size range of 10-200 micrometres, presenting very high flow and compactness properties and without affecting tablet disintegration (within 15 minutes) and consequent active principle release (more than 80% within 15 minutes).

In general a formulation according to the present invention comprises:

a) from 70 to 85% by weight of metformin HCl having a particle size range from 10 and 200 micrometres;

b) from 10 to 25% by weight of a suitable pharmaceutically acceptable binder, preferably vinylpyrrolidone-vinyl acetate copolymer with a particle size range from 10 to 200 microns;

c) from 1 to 10% by weight of a suitable pharmaceutically acceptable diluent, selected from: hydroxypropyl cellulose or dibasic calcium phosphate or microcrystalline cellulose or pregelatinized starch;

d) from 1 to 5% by weight of a suitable pharmaceutically acceptable disintegrant selected from: croscarmellose sodium or sodium starch glycolate or crospovidone;

e) from 0.1 to 2% of a suitable pharmaceutically acceptable glidant, preferably colloidal silica;

f) from 0.1% to 4% by weight of a pharmaceutically acceptable lubricant selected from: magnesium stearate, sodium stearyl fumarate, glyceryl docosanoate or glyceryl palmitostearate.

N,N-dimethylimidodicarbonimidic diamide hydrochloride (metformin HCl), is freely soluble in water and intrinsically non-compressible. For the purposes of the present invention, it is considered pure at 98.5-100% by weight, preferably in the form of a white crystalline powder with a particle size range from 10 to 200 microns.

The use of vinylpyrrolidone-vinyl acetate copolymer 60/40, with a particle size range from 10 to 200 microns, ensures good distribution, good compaction characteristics, slow disintegration time and a high percentage of dissolution. The very plastic behaviour of this excipient combines perfectly with the chipping characteristics of metformin HCl and, related to this, the high dilution capacity exhibited (the amount of excipient required for acceptable mixing and tablet properties). The spherical particles contribute significantly to the flowability of the metformin HCl mixture. Moreover, the binder particle sizes are so well related to those of the active principle, as to avoid all possible segregation problems.

The composition can also include one or more diluents/binders preferably selected from: hydroxypropyl cellulose, dibasic calcium phosphate, microcrystalline cellulose or pregelatinized starch. These excipients can be regarded as adjuvants for flow or compaction characteristics. In general, for our formulation a quantity from 1 to 10% by weight was considered, in relation to the characteristics of the particular excipient selected,

Hydroxypropyl cellulose is chemically substituted with 50-70% hydroxypropyl groups. This chemical substitution allows for a low viscosity, i.e. within the range from 300 to 600 cps. This renders the polymer suitable for use as an auxiliary binder in standard rather than extended release matrix formulations (US 6,524,618). The particle sizes, 100% being less than 100µm, confer a good

distribution despite the low quantity used in the formula. The type and quantity of this cellulose does not alter disintegration time, a property which is strictly related to the dissolution profile.

Dibasic calcium phosphate is typically used in direct compression formulations in its non-ground or otherwise crude form. It appears as a high density material, a property which reduces tablet volume. Having a nominal mean particle size of 100-200 microns, it improves flow properties. It is virtually insoluble in water, such as to help improve tablet disintegration.

Microcrystalline cellulose is another excipient that may be used in these formulations. It is highly compressible and produces strong tablets even with low pressures. It can certainly help to prevent chipping and capping of metformin HCl tablets. Microcrystalline cellulose improves flow characteristics if used at a particle size range from 100-200 microns; if used as a finer material, with a nominal mean particle size of less than 70 microns, it improves compressibility. Because of this characteristic, it is also self-lubricating and so helps reduce ejection force during the tablet compression process.

Pregelatinized starch is a modified starch which has undergone chemical or mechanical treatment. This process imparts good compaction and flow properties to the starch. Having a nominal mean particle size range from 30 to 150 microns, it is perfectly suited to the particle sizes of the active principle.

In the composition of the invention, a disintegrant selected from the following can also be introduced in order to improve tablet disintegration: sodium croscarmellose, sodium starch glycolate or crospovidone. By virtue of their capillary and swelling capabilities, a quantity of 1 to 5% by weight on the final tablet can be considered adequate, depending on the formula selected.

In the present invention, colloidal silica is ideal as a glidant. It improves the flow of the powder blend from the discharge hopper to the punch die. Colloidal silica has very small particles (generally less than 20 µm), a large surface area (generally 200 m^2/g) and is used in percentages of 0.1-2% by weight.

Lubricants can be divided into water-soluble and non-water-soluble types; the second type is particularly preferred for their better lubricating properties. Of these latter lubricants, the best example is magnesium stearate. It is very effective in

reducing friction between the die wall and the powder blend during compression, thus facilitating tablet ejection. Moreover it improves the flow properties of the powder blend and helps prevent adhesion to the punches and die. A level of 0.1-2.0% by weight of magnesium stearate can be used in these formulations. It is considered best to avoid a long mixing time, as this can lead to a reduced final tablet hardness and an increased disintegration time. For this reason other less hydrophobic lubricants can be considered, selecting them from the following group: glyceryl docosanoate, glyceryl palmitostearate (at levels of 1-4% by weight). Formulations in accordance with the present invention are obtained by direct compression which consists only in the steps of mixing and compression. The process does not involve any preliminary procedure such as granulation or pre-compaction.

Metformin HCl and the colloidal silica are sifted and blended for a few minutes. The binder, diluent and disintegrant are added and mixed with the aforesaid. Finally the lubricant is added and mixed for the minimum time necessary. The resulting blend is compressed into final units using a rotary tablet press equipped with suitable punches, such as to provide tablets of the required shape and size.

A general formula based on the aforedescribed components is given below. Using this formula, the final product obtained by means of direct compression, has the desired technological characteristics, namely: good resistance to breakage (not less than 10 kP), short disintegration time (no longer than 15 minutes), low friability (not greater than 0.5%) and no chipping, capping or lamination effect. Moreover the tablets have a good dissolution profile (more than 80% in 15 minutes) and the final product, contained within suitable packaging material, is stable over time.

COMPONENTS	QUANTITY (%)
Metformin HCl	70-85
Vinylpyrrolidone-vinyl acetate copolymer	10-25
Diluents	1-10
Disintegrants	1-5
Colloidal silica	0.1-2
Lubricants	0.1-4

EXAMPLES

Some examples of reproducible formulas are given below. These formulas are based on a quantity of metformin HCl equal to 500 mg, though similar formulas can also be obtained with different doses, the invention being applicable with metformin HCl doses from 400 mg to 1000 mg. The following examples are however merely illustrative and in no way limit the present invention.

Example 1

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	100.00
Crospovidone	10.00
Colloidal silica	5.00
Sodium stearyl fumarate	5.00
Total	620.00

Example 2

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	120.00
Crospovidone	20.00
Colloidal silica	5.00
Magnesium stearate	5.00
Total	655.00

Example 3

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	130.00
Crospovidone	30.00
Colloidal silica	5.00
Sodium stearyl fumarate	5.00
Total	670.00

Example 4

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	120.00
Starch glycolate	25.00
Colloidal silica	5.00
Sodium stearyl fumarate	5.00
Total	655.00

Example 5

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	100.00
Hydroxypropyl cellulose	25.00
Crospovidone	10.00
Colloidal silica	5.00
Glyceryl docosanoate	2.00
Total	650.00

Example 6

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	96.00
Microcrystalline cellulose	20.00
Crospovidone	7.00
Colloidal silica	1.00
Sodium stearyl fumarate	1.00
Total	625.00

Example 7

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	90.00
Hydroxypropyl cellulose	10.00
Microcrystalline cellulose	50.00
Crospovidone	20.00

Colloidal silica	5.00
Sodium stearyl fumarate	2.00
Total	680.00

Example 8

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	95.00
Croscarmellose	25.00
Colloidal silicon dioxide	5.00
Magnesium stearate	5.00
Total weight	630.00

Example 9

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	40.00
Hydroxypropyl cellulose	35.00
Calcium phosphate	10.00
Starch glycolate	25.00
Colloidal silica	5.00
Sodium stearyl fumarate	5.00
Total	620.00

Example 10

Ingredients	Weight (mg) per tablet
Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	100.00
Pregelatinized starch	15.00
Croscarmellose	20.00
Colloidal silica	5.00
Glyceryl docosanoate	20.00
Total	685.00

Example 11

Ingredients	Weight (mg) per tablet

Metformin HCl	500.00
Vinylpyrrolidone-vinyl acetate copolymer	110.00
Hydroxypropyl cellulose	10.00
Calcium phosphate	20.00
Crospovidone	10.00
Colloidal silica	5.00
Glyceryl monostearate	25.00
Total	680.00

Claims

1. Pharmaceutical formulation comprising metformin hydrochloride and at least one binder, both being in the form of particles having sizes from 10 to 200 micrometres.

2. Formulation according to claim 1 wherein said metformin HCl is 98.5-100% pure metformin HCl by weight, said binder being vinylpyrrolidone-vinyl acetate copolymer.

3. Pharmaceutical formulation based on metformin hydrochloride comprising:

a) from 70 to 85% by weight of metformin HCl having a particle size range from 10 to 200 micrometres;

b) from 10 to 25% by weight of a pharmaceutical grade binder, namely vinylpyrrolidone-vinyl acetate copolymer 60/40, with a particle size range from 10 to 200 micrometres together with pharmaceutically acceptable excipients.

4. Pharmaceutical formulation according to claim 3 wherein said pharmaceutically acceptable excipients comprise at least from 1 to 10% by weight of a diluent selected from the group: hydroxypropyl cellulose, dibasic calcium phosphate, microcrystalline cellulose or pregelatinized starch.

5. Pharmaceutical formulation according to claim 3 wherein said pharmaceutically acceptable excipients comprise at least from 1 to 5% by weight of a disintegrant selected from: croscarmellose sodium or sodium starch glycolate or crospovidone.

6. Pharmaceutical formulation according to claim 3 wherein said pharmaceutically acceptable excipients comprise at least from 0.1 to 2% by weight of colloidal silica as glidant.

7. Pharmaceutical formulation according to claim 3 wherein said pharmaceutically acceptable excipients comprise at least from 0.1 to 4% by weight of a lubricant selected from: magnesium stearate, sodium stearyl fumarate, glyceryl docosanoate or glyceryl palmitostearate.

8. Pharmaceutical formulation according to claims 1-5 having the following relative weight percentage composition of its basic constituents: metformin HCl 70-85%, vinylpyrrolidone-vinyl acetate copolymer 10-25%, diluent 1-10%, disintegrant 1-5%, colloidal silica 0.1-2%, lubricant 0.1-4%.

9. Pharmaceutical tablets consisting of a formulation according to claims 1-8.

10. Process for producing the tablets of claim 9 wherein a formulation according to claims 1-8 is subjected to compression.

11. 98.5-100% pure metformin HCl by weight, in the form of particles of size from 1 to 200 micrometres.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/052036

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/155 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/038226 A (RUBICON RES PVT LTD [IN]; PILGAONKAR PRATIBHA SUDHIR [IN]; RUSTOMJEE M) 13 April 2006 (2006-04-13) page 8, line 16 - line 26; examples page 31, line 5 - line 10 page 11, line 20 - line 29 page 27; example 7	1-11
X	US 6 524 618 B1 (KUMAR VIJAI [US] ET AL) 25 February 2003 (2003-02-25) column 5, line 21 - line 67	11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/052036

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006038226 A	13-04-2006	EP 1814528 A2	08-08-2007
US 6524618 B1	25-02-2003	NONE	