(19) ORGANISATION AFRICAINE DE LA PROPRIETE INTELLECTUELLE

ORGANISATION AFRICAINE DE LA PROPRIETE INTELLECTUELLE

(51) Inter. Cl.[8] A61K 31/7048 (2018.01)
A61K 9/00 (2018.01)
A61K 9/14 (2018.01)
A61P 9/14 (2018.01)

(11) N° 20008

FASCICULE DE BREVET D'INVENTION

(21) Numéro de dépôt : 1202100022
PCT/EP2019/069498

(22) Date de dépôt : 19/07/2019

(30) Priorité(s) :

FR n° 18/56769 du 20/07/2018

(24) Délivré le : 07/06/2021

(45) Publié le : 31/08/2021

(73) Titulaire(s) :

LES LABORATOIRES SERVIER,
35 rue de Verdun,
92284 SURESNES (FR)

(72) Inventeur(s) :

MARSAS, Stéphanie (FR)
PEAN, Jean-Manuel (FR)

(74) Mandataire : S.C.P AKKUM, AKKUM & Associates,
Quartier Mballa II, Dragages,
B.P. 4966, YAOUNDE (CM).

(54) Titre : Pharmaceutical composition in the form of a chewable tablet of Diosmin or of a flavonoid moiety.

(57) Abrégé :

A pharmaceutical composition in the form of a chewable tablet containing a high dose of micronised diosmin. This pharmaceutical composition comprises a percentage of micronised diosmin of from 20% to 80% of the total mass of the pharmaceutical composition. This pharmaceutical composition is used in the treatment of venous insufficiency and haemorrhoidal attack.

PHARMACEUTICAL COMPOSITION IN THE FORM OF A CHEWABLE TABLET OF DIOSMIN OR OF A FLAVONOID MOIETY

The present invention relates to a pharmaceutical composition in the form of a chewable tablet containing a high dose of micronised diosmin.

The present invention relates also to a pharmaceutical composition in the form of a chewable tablet containing a high dose of micronised purified flavonoid fraction (MPFF).

The flavonoid fraction is derived from a Rutaceae extract. The micronised purified flavonoid fraction used in the invention contains from 87% to 93% of diosmin and other flavonoids concomitantly. These other flavonoids in an amount of approximately 10% comprise from 2.5% to 5.0% hesperidin, from 0.9% to 2.8% isorhoifolin, from 0.9% to 2.8% linarin and less than 1% diosmetin.

The diosmin and the flavonoid fraction according to the invention are micronised. Micronisation of the active ingredient significantly increases its bioavailability. The micronisation of flavonoids, including diosmin, is particularly valuable for enhancing the digestive absorption of these substances, which are poorly soluble in water and therefore poorly absorbed by the digestive mucosa. Consequently, it is preferable to develop galenic forms comprising micronised diosmin or a micronised flavonoid fraction in order to improve the bioavailability.

Moreover, the flavonoid fraction according to the invention is administered in daily doses ranging from 1000 mg to 3000 mg in order to treat the symptoms of chronic venous insufficiency of the lower limbs. Owing to an increase in the daily dosages in the treatment of the main therapeutic indications of the flavonoid fraction and diosmin, these active ingredients must be given in high doses each time they are administered. Moreover, treatments based on flavonoid fraction are long-term treatments which must be easy to take in order to encourage compliance with the treatment on the part of patients. Consequently, it is preferable to develop galenic forms which can be taken

easily by elderly persons and without the addition of water for patients who consume them out of the home.

The therapeutic use of the flavonoid fraction extracted from Rutaceae according to the invention has been described in patent specification EP 0 711 560. That patent specification describes a composition of effervescent granules containing a high dose of 1000 mg of flavonoid fraction. The effervescent granules are to be dispersed in water prior to consumption.

Pharmaceutical forms of a chewable tablet, suckable tablet or tablet for chewing containing diosmin have been described in international patent application WO 2004/032942. The pharmaceutical forms according to application WO 2004/032842 do not contain a high dose of diosmin and do not employ the active ingredient in micronised form.

Accordingly, the present invention relates to pharmaceutical compositions in the form of a chewable tablet containing a high dose of micronised diosmin or micronised purified flavonoid fraction (MPFF).

The pharmaceutical composition of the chewable tablet according to the invention must have specific functional properties in order to address the technological difficulties relating to chewable tablets containing a high dose of micronised active ingredient.

Indeed, it is necessary that the pharmaceutical composition is sufficiently compressible while avoiding phenomena of splitting and friability. The very high proportion of active ingredient and the small proportion of excipients, so as not to increase the final mass of the chewable tablet, have a negative impact on the desired mechanical properties of the chewable tablet.

Moreover, the effect of micronising the active ingredient powders is to reduce the flowability of said powders given the increase in the forces between the particles. The size of the particles is an essential factor in the pourability of the powders, which can likewise be influenced by the shape of the particles and/or humidity.

The present invention provides a pharmaceutical composition in the form of a chewable tablet containing a high dose of micronised purified flavonoid fraction comprising diosmin, hesperidin, isorhoifolin, linarin and diosmetin.

The French term "comprimé à croquer" is understood according to the invention as meaning a pharmaceutical form known in English by the term "chewable tablet". A "chewable" tablet or a tablet "for chewing" here denote equivalent pharmaceutical forms.

Chewable pharmaceutical forms are very well accepted by patients and improve their compliance despite the fact that these chewable forms are large tablets with a unit mass of at least 3000 mg.

The diosmin and the flavonoid fraction are micronised in the pharmaceutical compositions according to the invention. Micronisation is a process by which the size of the particles of a powder can be reduced. Micronisation of the active ingredient such as diosmin or a flavonoid fraction can be carried out by means of different micronisation systems. These micronisation systems may be a grinder, an air jet mill or a bead milling microniser, in which the pressure of the air jets or the rate of supply of powder vary according to the expected particle size of the micronised active ingredient.

The grain size is a particularly important characteristic of pulverulent materials such as powders. Characterisation of the size of a particle is made according to its diameter or the diameter of the equivalent spheres if the particle is of irregular shape. The grain diameters determined by a laser

diffraction granulometer allow a particle size distribution or granulometry d_{50}, d_{90} (distribution of the size of the particles) to be characterised.
In the present invention, a "d_{50} below X µm" means that at least 50% of the particles of the micronised product have a size below X µm. In the present invention, a "d_{90} below X µm" means that at least 90% of the particles of the micronised product have a size below X µm.

In one embodiment, the d_{90} of the micronised active ingredient is below 5 µm. A d_{90} below 5 µm includes a d_{50} below 4 µm, 3 µm, 2 µm, 1.8 µm, 1.6 µm, 1.5 µm.
In one embodiment, the d_{50} of the micronised active ingredient is below 5 µm. A d_{50} below 5 µm includes a d_{50} below 4 µm, 3 µm, 2 µm, 1.8 µm, 1.6 µm, 1.5 µm.
In some embodiments, the micronised diosmin or the micronised purified flavonoid fraction are characterised by the following granulometry:

- a d_{50} below 2 µm, preferably below 1.6 µm, and/or
- a d_{90} below 5 µm, preferably below 2 µm, yet more preferably below 1.6 µm.

The mean diameter of the particles of micronised active ingredient in the pharmaceutical composition according to the invention is strictly below 5 µm, preferably strictly below 1.6 µm.

The percentage of micronised diosmin or micronised purified flavonoid fraction in the pharmaceutical composition is from 20% to 80% of the total mass of the composition. Preferably, the percentage of micronised active ingredient is from 30% to 60% of the total mass of the composition. The pharmaceutical compositions according to the invention make it possible to administer a large quantity of flavonoids by the oral route for each unit dose. "High dose" pharmaceutical compositions are understood as meaning formulations containing at least 20% active ingredient. The quantity of

diosmin or flavonoid fraction in the pharmaceutical composition is from 1000 mg to 3000 mg, including 2000 mg, 1500 mg, 2500 mg.

The pharmaceutical compositions in the form of high dose chewable tablets comprise from 30% to 60% by weight of micronised diosmin or micronised purified flavonoid fraction, based on the total mass of the composition, and from 40% to 70% by weight of polyols, based on the total mass of the composition.

In order to address the industrial constraints inherent in the manufacture of the chewable tablet containing a micronised active ingredient in a high dose, it is necessary to select excipients which assist in overcoming said industrial constraints. An excipient must be understood as being any compound forming part of the formulation which is intended to act simply as a support, that is to say which is not intended to have biological activity.

The pharmaceutical compositions according to the invention comprise at least one polyol serving as diluent.

A diluent serves to obtain a volume of powder sufficient to manufacture a tablet of the desired size and the physical characteristics of which are compatible with processes of manufacture by direct compression, for example. One or more polyols are used as diluent. The polyol used is preferably sorbitol. There can advantageously be used two different polyols, and preferably a mixture of mannitol and sorbitol. Polyols as diluent have the advantage of providing a sweet taste and have excellent properties of binding and compressibility. It is possible to replace the mannitol or the sorbitol with a different polyol, especially xylitol or maltitol.

In the pharmaceutical composition according to the invention, the ratio of the mass of the polyol or polyols to the mass of active ingredient is strictly less than 2, preferably the ratio is less than 1.6.

In addition to the micronised active ingredient and the polyol or polyols, the pharmaceutical composition according to the invention contains one or more pharmaceutically acceptable excipients. For example, the invention can provide a pharmaceutical composition comprising the micronised active ingredient, (a) polyol(s) and a binder, or a pharmaceutical composition comprising the micronised active ingredient, (a) polyol(s), a binder and a lubricant.

Binders or agglutinants are agents whose role is to bind the different particles of the pharmaceutical composition together. Among the binders there may be mentioned maltodextrin and povidone. The purpose of the lubricants is to avoid phenomena of jamming, adhesion and cohesion during the different industrial processes. The lubricant is chosen *inter alia* from stearic acid, magnesium stearate or talc.

Other pharmaceutically acceptable excipients may be added to the pharmaceutical composition according to the invention, such as flavours or sweeteners.

There may be mentioned as examples of excipients:

flavouring agents or flavours, the purpose of which is to mask unpleasant tastes and reduce earthy consistencies: orange flavour, lemon flavour, soft caramel flavour, vanilla/lemon flavour;

sweeteners enhance the sweet taste of the composition: aspartame, acesulfame potassium, saccharin sodium, potassium cyclamate; and

flow agents such as anhydrous colloidal silica.

The composition according to the invention can be an immediate-release, prolonged-release or delayed-release pharmaceutical composition. The composition according to the invention is preferably an immediate-release composition.

The invention relates also to a process for the preparation by wet granulation of a chewable tablet as described above, which process comprises at least the following steps:

a) mixing of micronised diosmin or micronised purified flavonoid fraction, polyols, binders, flavours and sweeteners;

b) after mixing, carry out wetting. The wet mass so obtained subsequently being granulated, dried and then graded;

c) lubrication of the granules obtained in step b) by means of colloidal silica and magnesium stearate;

d) compression of the lubricated mixture.

In a preferred embodiment, the chewable tablet according to the invention is prepared by a direct compression process comprising at least the following steps:

a) mixing of micronised diosmin or micronised purified flavonoid fraction, polyols, binders, flavours and sweeteners;

b) lubrication of the mixture obtained in step a) by means of colloidal silica and magnesium stearate;

c) direct compression of the lubricated mixture.

In an embodiment which is likewise preferred, the chewable tablet according to the invention is prepared by a process of compaction granulation or dry granulation comprising at least the following steps:

a) mixing of micronised diosmin or micronised purified flavonoid fraction, polyols, binders, flavours and sweeteners;

b) after mixing, carry out compaction to form granules;

c) lubrication of the granules obtained in step b) by means of colloidal silica and magnesium stearate;

d) compression of the lubricated mixture.

Preferably, there are obtained at the end of the process chewable tablets whose hardness, measured by diametral crushing, is from 180 N to 220 N (N = newtons). Preferably, the chewable tablets have a hardness of from 180 N to 200 N.

The present invention relates also to the use of the pharmaceutical compositions according to the invention in the treatment of venous disease, more particularly of venous insufficiency such as heavy legs, pain, restless legs syndrome, capillary fragility, and the treatment of haemorrhoidal attack. These pharmaceutical compositions are used as a venotonic and vascular protector.

The examples below illustrate the invention without limiting it.

Example 1: Pharmaceutical compositions of chewable tablets

Ingredients	Quantity (mg)	Content (%)
MPFF - Diosmin 90% - Flavonoids 10%	1000.0 900.0 100.0	33.3 30 3.3
Mannitol	409.13	13.6
Sorbitol	1227.37	40.9
Maltodextrin	300	10
Orange flavour	33	1.1
Acesulfame potassium	2	0.06
Magnesium stearate	22.5	0.75
Anhydrous colloidal silica	6	0.2
Final mass	3000.0	

Ingredients	Quantity (mg)	Content (%)
Micronised diosmin	1000.0	33.3
Mannitol	409.13	13.6
Sorbitol	1227.37	40.9
Maltodextrin	300	10
Orange flavour	33	1.1
Acesulfame potassium	2	0.06
Magnesium stearate	22.5	0.75
Anhydrous colloidal silica	6	0.2
Final mass	3000.0	

Manufacture of the chewable tablets of Example 1:

The micronised diosmin or the micronised purified flavonoid fraction is carefully mixed with the excipients of the internal phase, i.e. mannitol, sorbitol, maltodextrin, orange flavour, acesulfame potassium. The mixture is wetted with purified water by means of a pressurised vessel and then granulated.

The granules are dried to obtain a residual humidity which complies with specifications, that is to say approximately 2% residual humidity. The granules are subsequently graded, homogenised and then lubricated with the magnesium stearate. The granules are finally sieved through a sieve of mesh size 0.8 mm and then compressed by means of punches.

The chewable tablets of micronised diosmin and micronised purified flavonoid fraction according to Example 1 have a hardness of 196 N and 192 N (N = newtons), respectively.

Example 2: Flow properties of the pharmaceutical compositions according to the invention

The pourability of a powder is its ability to flow freely in a regular and constant manner in the form of individual particles. The flowability of powders therefore determines the performance and correct operation of the production processes and plays a role in the quality of the final product. Thus, a powder having good pourability flows without assistance. By contrast, a cohesive powder has poor pourability and a mechanical (agitation, vibration) or chemical (coating) device must be provided in order to facilitate its movement.

The pourability of the powders and granules containing a high dose of micronised diosmin and a high dose of micronised purified flavonoid fraction according to the invention measured by different methods (Carr index, Hausner ratio and Schultze flow function) shows that the pharmaceutical compositions according to the invention are very effective in the processes for manufacturing the chewable tablets. Despite factors which are very detrimental to the yield of the manufacturing processes, such as micronisation of the active ingredient and/or a high dose of an active ingredient, the pourability of the pharmaceutical compositions according to the invention meets the industrial and regulatory requirements.

The Carr index (Ic) describes the flow of a powder bed as a function of the density. It is determined by the equation below:

$$Ic = (\rho_{tapped} - \rho_{bulk}) / \rho_{tapped}$$

where ρ is the density and Ic is a dimensionless physical quantity.

The Carr index values are interpreted as follows:

Ic < 0.15 good pourability

0.15 < Ic < 0.25 moderate pourability

Ic > 0.25 poor pourability

The Hausner ratio (Hr) describes the compressibility and the flow of a power on the basis of density (ρ) measurements. It is calculated by the ratio of the tapped density (ρ_{tapped}) to the bulk density (ρ_{bulk}) according to the equation:

$$Hr = \rho_{tapped} / \rho_{bulk}$$

Hr is a dimensionless physical quantity. If Hr is between 1.0 and 1.2, the powder has little compressibility, is loosely cohesive and has good flowability; if Hr is between 1.2 and 1.4, the powder is compressible, cohesive and has poor flowability.

Finally, the Schultze apparatus is a shear cell for measuring the flow function (FFC). Good flow is characterised by an FFC between 4 and 10 and free flow is characterised by an FFC above 10.

Methods	Powders or granules	
	micronised diosmin	micronised purified flavonoid fraction
Ic	0.12-0.25 (moderate to good pourability)	
Hr	1.1-1.3 (good to fairly good pourability)	
FFC	7-13 (easy to free flow)	

Claims

1. Pharmaceutical composition in the form of a chewable tablet comprising 1000 mg micronised diosmin as active ingredient, characterised in that:

- the d_{50} of the micronised diosmin is below 5 µm,
- the composition comprises at least one polyol,
- the composition comprises from 30% to 60% by weight of micronised diosmin, based on the total mass of the composition.

2. Pharmaceutical composition in the form of a chewable tablet comprising 1000 mg micronised purified flavonoid fraction as active ingredient, characterized in that:

- the d_{50} of the micronised purified flavonoid fraction is below 5 µm,
- the composition comprises at least one polyol,
- the composition comprises from 30% to 60% by weight of micronised purified flavonoid fraction, based on the total mass of the composition.

3. Pharmaceutical composition according to claim 2, characterised in that the flavonoid fraction comprises diosmin, hesperidin, isorhoifolin, linarin and diosmetin.

4. Pharmaceutical composition according to any one of claims 1 to 3, characterised in that it comprises from 40% to 70% by weight of polyols, based on the total mass of the composition.

5. Pharmaceutical composition according to any one of claims 1 to 4, characterised in that the ratio of the mass of the polyol or polyols to the mass of active ingredient is strictly less than 2.

6. Pharmaceutical composition according to any one of claims 1 to 5, wherein a polyol is sorbitol.

7. Pharmaceutical composition according to any one of claims 1 to 6, comprising a polyol and a binder.

8. Pharmaceutical composition according to any one of claims 1 to 7, comprising a polyol, a binder and a lubricant.

9. Process for the manufacture of a pharmaceutical composition according to any one of claims 1 to 8, characterised in that it is a process of wet granulation, dry granulation or direct compression.

10. Pharmaceutical composition according to any one of claims 1 to 8 for use in the treatment of venous insufficiency and haemorrhoidal attack.

11. Use of micronised diosmin or micronised purified flavonoid fraction in the manufacture of a pharmaceutical composition in the form of a chewable tablet for the treatment of venous insufficiency and haemorrhoidal attack, wherein the micronised diosmin or micronised purified flavonoid fraction is the active ingredient in the pharmaceutical composition, wherein the pharmaceutical composition comprises 1000 mg of active ingredient, the d_{50} of the active ingredient is below 5 µm, the percentage of active ingredient is from 30% to 60% of the total mass of the pharmaceutical composition, and the composition comprises at least one polyol.

Abstract

A pharmaceutical composition in the form of a chewable tablet containing a high dose of micronised diosmin. This pharmaceutical composition comprises a percentage of micronised diosmin of from 20% to 80% of the total mass of the pharmaceutical composition. This pharmaceutical composition is used in the treatment of venous insufficiency and haemorrhoidal attack.