PHARMACEUTICAL COMPOSITION IN THE FORM OF AN ORAL SUSPENSION COMPRISING A FLAVONOID FRACTION AND XANTHAN GUM

The present invention relates to a high-dose oral suspension comprising diosmin, and optionally other flavonoid compounds, and as excipient xanthan gum, and also to use thereof in the treatment of venous insufficiency.

Preferably, the present invention relates to a high-dose suspension of a flavonoid fraction and xanthan gum for oral administration, and also to use thereof in the treatment of venous insufficiency.

The flavonoid fraction is obtained from a Rutaceae extract. The purified and micronised flavonoid fraction used in the invention contains from 87% to 93% diosmin and other flavonoids concomitantly. Those other flavonoids, constituting about 10% of the content, 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 particle size of the micronised flavonoid fraction is strictly less than 5 µm, preferably less than 4 µm, 3 µm, 2 µm and more preferably less than 1.6 µm.

The flavonoid fraction according to the invention is administered at daily doses ranging from 1000 mg to 3000 mg in order to treat the manifestations of chronic venous insufficiency of the lower limbs. In view of the high degree of metabolisation of the flavonoid fraction in the gastrointestinal tract, a high dose of this active ingredient must be given on each administration. Furthermore, treatments based on a flavonoid fraction are long-term treatments which necessitate simple administration in order to encourage patients' compliance with the treatment. Consequently, preference is given to developing formulations which, in the case of the elderly, are easy to take and, in the case of patients taking the medication outside the home, do not require water to be added.

Therapeutic use, in accordance with the invention, of the flavonoid fraction extracted from Rutaceae has been described in the patent specification EP 0 711 560. That patent specification describes a high-dose effervescent granulate composition containing 1000 mg of flavonoid fraction. However, those effervescent granulates have to be dispersed in water before being taken.

Drinkable solutions comprising flavonoids and xanthan gum have been described in the patent specification US 5,240,732. That patent specification discloses a solution in which the flavonoids have been dissolved in an alcohol, unlike the present invention which relates to an aqueous suspension in which the flavonoid fraction is homogeneously dispersed.

Drinkable suspensions comprising polyphenols and dispersion stabilisers have been described in the patent application US 2012/0070475. The suspensions according to the application US 2012/0070475 contain low doses of quercetin and exclusively use gellan gum as dispersion stabiliser.

The subject-matter of the present invention is a pharmaceutical composition in the form of a high-dose oral suspension comprising as active ingredient diosmin, and optionally other flavonoid compounds, and as excipient xanthan gum.

Preferably, the subject-matter of the present invention is a pharmaceutical composition in the form of a high-dose oral suspension comprising as active ingredient a flavonoid fraction and as excipient xanthan gum.

The percentage of flavonoid fraction in the pharmaceutical composition is between 7% w/w and 20% w/w.
The amount of flavonoid fraction in the pharmaceutical composition is between 1000 mg and 3000 mg, inclusive, for example 2000 mg, 1500 mg and 2500 mg.

The oral suspension having a high dose of active ingredient in accordance with the present invention must have a viscosity that is suitable, on the one hand, for allowing the suspension to flow in the production machines and, on administration, to flow out of the sachet and, on the other hand, for preventing the flavonoid fraction from undergoing sedimentation in the sachet and for allowing it to remain stable over time.

In order to satisfy all those functional properties, the oral suspension must satisfy specific rheological properties.

The viscosity of the suspension must not be dependent on the time for which it is subjected to shearing forces. It is necessary for the suspension to regain its initial viscosity after application of a stress, whatever the duration of its application. The viscosity of the suspension must therefore be reversible over the shear range of 0.01 to 1000 s^{-1}. This rheological property, i.e. that of the suspension entirely regaining its viscosity during periods at rest, is essential in the steps of pumping and pre-packaging, through transportation and storage, and up to the oral suspension in a sachet being used by the ultimate consumer.

Furthermore it appears to be necessary for the viscosity of the suspension to be independent of temperature over the range 15°C-60°C, the range of ad hoc temperatures at the end of production and during the steps of transportation, processing and packaging of the final product.

The viscosity measurements are carried out using the Anton Paar rheometer or the Brookfield rheometer. The results obtained with those two types of rheometer are entirely comparable.

The rheological properties and stability required by the oral suspension according to the invention are obtained with the aid of thickening of the pharmaceutical composition. Thickening of the pharmaceutical composition is obtained by virtue of use of a thickening agent.

The thickening agent according to the invention is xanthan gum. Xanthan gum is a high-molecular-weight anionic polysaccharide comprising as

predominant hexoses D-glucoses and D-mannoses. In solution, the molecules of xanthan gum enter into association with one another to form a network of tangled molecules.

The concentration of xanthan gum in the pharmaceutical composition according to the invention is between 0.45% w/v and 0.55% w/v, inclusive. The concentration of the xanthan gum may be, for example, 0.50% w/v, 0.47% w/v, 0.53% w/v.

The amount of xanthan gum in the pharmaceutical composition is between 0.30% w/w and 0.60% w/w.

The pharmaceutical composition in the form of an oral suspension having a high content of flavonoid fraction in accordance with the invention is free of surfactants. Surfactants are generally used in oral suspensions in order to improve the dispersion and wettability of the particles in suspension.

Besides the flavonoid fraction and the xanthan gum, the pharmaceutical composition according to the invention comprises one or more pharmaceutically acceptable excipients such as preservatives, aromas, sweeteners or pH-adjusters.

By way of examples of excipients there may be mentioned:

as preservatives: sodium benzoate, benzalkonium chloride, methyl parahydroxybenzoate, propyl parahydroxybenzoate;
as aromas: orange aroma, lemon aroma, soft caramel aroma, vanilla/lemon aroma;
as sweeteners: maltitol, sorbitol, aspartame, xylitol, potassium acesulfame, sodium saccharin;
as pH-adjusters: citric acid, ascorbic acid, tartaric acid.

The pharmaceutical composition according to the invention is in the form of a drinkable suspension in a sachet. The sachet or stick-pack preferably has

a unit volume of 10 ml containing the daily dose of flavonoid fraction. For better patient compliance, the unit volume of the sachet should not be too large, for example 10 ml, 12 ml, 15 ml, 17 ml or, at most, 20 ml.

The present invention relates also to use of the pharmaceutical compositions according to the invention in the treatment of venous disease, more especially venous insufficiency. These pharmaceutical compositions are used as venotonics and vasculoprotectives.

The Examples hereinbelow illustrate the invention in non-limiting manner.

Example 1: Pharmaceutical composition for a sachet containing a suspension of 1 g of flavonoids

Sodium benzoate	0.015 g/10 ml
Citric acid	0.0125 g/10 ml
Orange aroma	0.015 g/10 ml
Maltitol	1.8 g/10 ml
Flavonoid fraction	1.0 g/10 ml
Xanthan gum	0.05 g/10 ml
Purified water	q.s.p. 10 ml

Preparation of the suspension of Example 1:

For about 100 000 sachets:

700 litres of purified water and 1.5 kg of sodium benzoate are carefully mixed at 20°C until dissolution is complete. 1.25 kg of citric acid and 1.5 kg of orange aroma are added to the solution. 180 kg of powdered maltitol are added to the solution and carefully mixed. 100 kg of the flavonoid fraction are added to the mixture very slowly until a homogenous suspension is formed. 5 kg of xanthan gum are very slowly introduced directly into the

suspension. Purified water is added q.s.p. to obtain a final volume of 1100 litres.

Example 2: Stability of the oral suspension of Example 1 (Batch LP02)

The stability of the pharmaceutical composition of Example 1 according to the invention in sachets was tested under various temperature and humidity conditions.

The sachets are composed of a multilayer composite (polyethylene PET12/aluminium AL12 /extruded polyethylene composite PE50).

	Sachet			
T	Density (Eur. Ph.)			
	25°C / 60% RH	30°C / 65% RH	30°C / 75% RH	40°C / 75% RH
T0	1.11			
T0 + 1 month	1.10	1.10	1.10	1.10
T0 + 3 months	1.10	1.10	1.10	1.10

The Table above relating to the course of the density of the suspension in the sachet over time shows that the density is completely stable even under conditions of elevated temperature and humidity (40°C/75% RH). This stability of density shows that the suspension does not separate over time under conditions of elevated temperature and humidity.

	Sachet			
T	Particle size of the flavonoid fraction			
	25°C / 60% RH	30°C / 65% RH	30°C / 75% RH	40°C / 75% RH
T0	d10 0.658 d50 2.581 d90 6.642			
T0 + 1 month	d10 0.723 d50 2.679 d90 6.969	d10 0.741 d50 2.692 d90 6.675	d10 0.739 d50 2.694 d90 6.698	d10 0.760 d50 2.726 d90 6.685

T0 + 3 months	d10	0.726	d10	0.746	d10	0.751	d10	0.798
	d50	2.663	d50	2.779	d50	2.708	d50	2.818
	d90	6.670	d90	6.862	d90	6.690	d90	6.739

The particle size distribution of the flavonoid fraction is expressed in terms of the diameters d10, d50 and d90 wherein

d10 = d(v,0.1) corresponds to the value at 10% on the cumulative curve of particle size distribution in terms of volume;

d50 = d(v,0.5) corresponds to the value at 50% on the cumulative curve of particle size distribution in terms of volume;

d90 = d(v,0.9) corresponds to the value at 90% on the cumulative curve of particle size distribution in terms of volume.

The Table above shows that the size of the particles in the flavonoid fraction according to the invention does not increase over time under conditions of elevated temperature and humidity. The particles of the micronised flavonoid fraction neither agglomerate nor undergo sedimentation in the oral suspension according to the invention.

	Sachet			
T	Viscosity in cP			
	25°C / 60% RH	30°C / 65% RH	30°C / 75% RH	40°C / 75% RH
T0	321			
T0 + 1 month	293	298	294	296
T0 + 3 months	293	293	294	298

The Table above relating to the viscosity of the suspension in the sachet shows that the viscosity is extremely stable over time under conditions of elevated temperature and humidity.

Finally, a visual inspection of the suspension under the various conditions of temperature and humidity after 1 month and 3 months of assessment shows an absence of lumps and bubbles in the sachets.

Example 3: Uniformity of content of the pharmaceutical composition according to Example 1

The test is carried out on 10 sachets. The contents of each sachet are assayed; a diosmin reference solution is used as control.

The mean content X_m is expressed as follows:

$$X_m = (\Sigma X_i)/10$$

The acceptance value (AV), expressed as a percentage of the theoretical value, is given by the following formula:

$$AV = (M-X_m) + k \times s$$

wherein:

X_m is the mean content expressed as a percentage of the theoretical value;

M is the reference value expressed as a percentage of the theoretical value: M=98.5 if $X_m < 98.5$; M=X_m if $98.5 \leq X_m \leq 101.5$; M=101.5 if $X_m > 101.5$;

k is the acceptability constant (k = 2.4 for 10 sachets);

s is the standard deviation of the contents X_i.

Content uniformity parameters (diosmin)	Batch LP02 1000 litres (sachet) according to Example 1	
	Start of sachet filling	End of sachet filling
Mean content	100.5	102.1
Standard deviation	0.9	0.7
Acceptance value (AV)	2.2	2.3

According to the European Pharmacopoeia, Article 2.9.40, an acceptance value of less than 15 means that the content uniformity complies (level L1). The Table above therefore shows that the content uniformity of the diosmin contained in the formulation according to the invention meets regulatory requirements.

CLAIMS

1. Pharmaceutical composition in the form of an oral suspension comprising as active ingredient diosmin, and optionally flavonoid compounds, and as excipient xanthan gum.

2. Pharmaceutical composition according to claim 1, wherein the active ingredient is a purified and micronised flavonoid fraction.

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

4. Pharmaceutical composition according to claim 2, wherein the amount of the flavonoid fraction is between 7% w/w and 20% w/w, inclusive.

5. Pharmaceutical composition according to claim 1, wherein the concentration of xanthan gum is 0.5% w/v.

6. Pharmaceutical composition according to claim 1, wherein the amount of xanthan gum is between 0.30% w/w and 0.60% w/w, inclusive.

7. Pharmaceutical composition according to claim 1, comprising one or more pharmaceutically acceptable excipients selected from sweeteners, aromas, preservatives and pH-adjusters.

8. Pharmaceutical composition according to any one of claims 1 to 7, in the form of a drinkable suspension in a sachet.

9. Pharmaceutical composition according to any one of claims 1 to 8, for use in the treatment of venous insufficiency.