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(54) COMPOSITIONS PHARMACEUTIQUES COMPRENANT DES LACTOBACILLES POUVANT ETRE ADMINISTREES A TRAVERS LES MUQUEUSES

(54) PHARMACEUTICAL COMPOSITIONS COMPRISING LACTOBACILLI SUITABLE FOR TRANS-MUCOSAL ADMINISTRATION

(57) Description de capsules vaginales de gélatine molle qui contiennent une quantité efficace sur le plan thérapeutique d'un lyophilisat de Lactobacillus fermentum I-789, mis en suspension dans un excipient approprié. Les capsules se caractérisent par le fait qu'elles contiennent de 2 à 5 %, en poids, de gel de silice ou de silice précipitée, par rapport au poids du lyophilisat.

(57) Soft gelatin vaginal capsules are described, which contain a therapeutically effective amount of Lyophilized Lactobacillus fermentum I-789, suspended in a suitable vehicle, characterized in that they contain from 2 to 5%, by weight of silica gel or precipitated silica, with respect to the weight of the lyophilizate.

Abstract

PHARMACEUTICAL COMPOSITIONS COMPRISING LACTOBACILLI SUITABLE FOR TRANS-MUCOSAL ADMINISTRATION

Soft gelatin vaginal capsules are described, which contain a therapeutically effective amount of Lyophilized Lactobacillus fermentum I-789, suspended in a suitable vehicle, characterized in that they contain from 2 to 5%, by weight of silica gel or precipitated silica, with respect to the weight of the lyophilizate.

PHARMACEUTICAL COMPOSITIONS COMPRISING LACTOBACILLI SUITABLE FOR TRANS-MUCOSAL ADMINISTRATION

The present invention concerns pharmaceutical compositions comprising lactobacilli suitable for trans-mucosal administration.

The therapeutic use, in particular the use of lactobacilli, has been known for long time.

In particular, the use of lactobacilli in gynaecology for the treatment of the vaginal bacterial flora's disorders, has been described for example in FR M6836 and US 4 592 748.

The patent EP-B-353851 discloses a strain of Lactobacillus fermentum, deposited by the Institut Pasteur on 21.07.1988 at the number C.N.C.M. I-789, which is characterized by direct inhibitory activity towards patogen fungi, particularly against Candida albicans.

Said patent describes also pharmaceutical compositions in form of cream, vaginal ovules or capsules containing the Lactobacillus fermentum strain C.N.C.M. I-789 optionally associated to other Lactobacillus strains and to conventional excipients.

Among the vaginal administration forms, the soft gelatin capsules wherein the lyophilized microrganisms are suspended in an excipient like a medium-chain triglyceride mixture or other oleous excipient (Migliol$^{(R)}$) are generally preferred for their use practicity.

However an unsatisfying stability has been noted for the compositions described in EP-B-353 381, which

are subjected to a two order of magnitude reduction in the bacterial charge just after few months at room temperature.

The clinical experiences carried out on the Lactobacillus fermentum I-789 have evidenced an optimal dose of at least one billion (10^9) of living cells.

The study of a pharmaceutical form which allows the minimum number of the required cells to survive in the validity interval of the same preparation is thus necessary for the commercialization.

Now, it has been found that the use of the silica gel in particular ratios with respect to the weight of the lyophilized microorganism increases in a completely unexpected way the cell viability also for long periods, ranging up to 2-3 years. Such a stabilizing effect of the silica on the lactobacillus cell viability was not predictable on the basis of the state of the art which provides mostly the use of the silica in solid oral pharmaceutical formulations like tablets or granulates as an anti-adhesive agent.

The known de-humidifying and water-absorbent activities of the silica gel are not sufficient to explain the surprising stability improvement also in view of the fact that the lyophilized microrganisms should be already sufficiently protected from the water absorption by the gelatin envelopes and by the lipophylic excipient in which they are suspended.

Thus the invention refers to soft gelatin-vaginal capsules containing a therapeutically active amount of lyophilized Lactobacillus fermentum I-789, suspended in an appropriate vehicle, characterized in that it

contains from 2 to 5% by weight of silica gel or precipitated silica, with respect to the weight of the lyophilizate.

The compositions of the invention optionally contain other known eubiotic bacterial strains, in particular those described in EP-B-353 581.

The percentage of silica gel is preferably comprised between 3 and 4% by weight and more preferably it is about 3,6% by weight with respect to the weight of lyophilized I-789.

Suitable suspending vehicles are represented by medium-chain semisynthetic triglycerides like Migliol(R). The gelatin envelopes, generally consisting of gelatin mixtures, dimethylpolysiloxane, glycerol and titanium dioxide, are commercially available. The capsules sold by Scherer under the trademark "Softigel(R)" are particulary preferred.

The preparation procedure for the capsules of the invention is substantially of the conventional type and it is preferably carried out by performing all the operations under inert gas atmosphere, for example under nitrogen.

Thus the obtained capsules can be packaged into blisters or other packages, impermeable to the humidity, optionally comprising suitable drying materials.

In the following table the stabilities of the capsules which are the object of the invention are reported, compared to the stabilities known from EP-B-353 581.

TABLE

Stability at 22°C

Capsules containing 1 g of the lyophilizate	Start	2 months	4 months	6 months	12 months
	1.7×10^{11}	0.7×10^{11}	0.28×10^{11}	0.1113×10^{11}	$0.15^{5} \times 10^{11}$
Compositions according to the invention	1.7×10^{11}	0.6×10^{11}	0.2×10^{9}	1×10^{8}	--

The data clearly demonstrate that the compositions of the invention mantain an high bacterial charge at least up to 12 months, while the known compositions show a non-acceptable bacterial charge decrease just after only 4 months at 22°C. After 6 months, the count value is already under the prescribed therapeutic amount.

The following example illustrates the invention in more details.

EXAMPLE

Soft vaginal capsules

Capsule composition

Lactobacillus fermentum	NLT 10^{10} (equal to about 1 g of lyophil)
Medium-chain triglicerides	1964 mg
Silica (Aerosil 300)	36 mg

Preparation:

The substance, obtained as described in EP-B-353 581, is mixed with Aerosil 300 under nitrogen current. The mixture is disperded in Migliol(R) with slow stirring and always under nitrogen current, till an oily homogeneous suspension is obtained.

The obtained suspension is refined by colloidal mill to assure the homogeneous fragmentation of the particles in the mass, carefully controlling that the temperature thereof does not exceed 30°C.

The suspension is then subjected to vacuum activity by means of a proper equipment so that the air which eventually has been incorporated during the previous operations can be eliminated, in order to exclude any possible oxidation of the active ingredient and in order to guarantee a perfect volumetric dosage of the mixtures

in the capsules.

The suspension is then incapsulated in glycogelatin envelopes (Softigel(R), Scherer) extruded by a proper encapsulator. The capsules, after drying for 60 hours at 20°C and with relative humidity lower than 45%, are distributed in glass flasks with cap-reservoir containing the silica gel.

CLAIMS

1. Soft gelatin vaginal capsules containing a therapeutically active dose of lyophilized Lactobacillus fermentum I-789 suspended in a suitable vehicle, characterized in that they contain from 2 to 5% by weight of silica gel or precipitated silica, with respect to the weight of the lyophilizate.

2. Capsules according to claim 1, wherein the vehicle is constituted by medium-chain triglycerides.

3. Capsules according to claim 1 or 2 wherein the silica is comprised between 3 and 4% by weight, with respect to the weight of the lyophilizate.

4. Capsules according to any of claims 1-3 wherein the gelatin-capsules are constituted by a mixture of gelatin, glycerol, dimethylpolysiloxane and titanium dioxide.

5. Capsules according to any of the previous claims containing other eubiotic bacteric strains in combination with Lactobacillus fermentum I-789.