and unfreeze the capsules. This, however, can lead to a lack of treatment compliance, leading to patient unadherence.

Several attempts have been performed in order to reduce the aqueous component of the stool. Dewatering of the microbial community through techniques such as lyophilisation is one of the main routes. However, the dewatering process is physically demanding and reduces the viability of the microbes significantly. In addition, sometimes the dewatering of the microbial community is not enough to achieve the appropriate stability, and special containers have to be developed with that aim. As an example, KR20080059605 discloses the packaging of lyophilized bacteria in a container with a particular design to reduce the environment humidity in contact with the capsule. This Korean patent document provides, among others, stability data with the lyophilized bacteria with (Example 6) or without (Example 5) excipients. Example 6 provides data with capsules comprising lyophilized bacteria together with microcrystalline cellulose and magnesium stearate. It is remarkably that the capsule without excipients was more stable within the particular container than when the capsules were formulated with the excipients.

In spite of the efforts made until now, there is still the need of stable home-based FMT based on live bacterial cells.

SUMMARY

In a first aspect, the present disclosure refers to a solid oral pharmaceutical composition comprising a pharmaceutically effective amount of living microorganisms and one or more pharmaceutically acceptable water absorbing excipient(s), wherein the composition has a water content, determined according to European Pharmacopoeia 9.4, section 2.5.12., from 0.5 to 30% with respect the total weight of the composition.

In another aspect, the present disclosure refers to a process for preparing an oral pharmaceutical composition disclosed herein, wherein the process comprises mixing living microorganisms with one or more water absorbing excipient(s).

In yet another aspect, the present disclosure refers to a solid oral pharmaceutical composition disclosed herein, for use in therapy.

In a further aspect, the present disclosure refers to a use of a water absorbing excipient for stabilizing living microorganisms in a pharmaceutical composition.

The present inventors have developed live microbiota capsules stable enough to be stored at about 4°C rather than at -65°C or at -80°C, meaning that the capsules can be stored in a conventional freezer in the home of the recipient.

As it is shown below, the present inventors firstly prepared a mix of fecal microbiota pellet (obtained from an aqueous solution of the stool in glycerol) with microcrystalline cellulose (hereinafter also referred as “MCC”) and a lubricant (magnesium stearate). When capsules were prepared with that mixture, it was found that they had a humidity content, following European Pharmacopoeia 9.4, section 2.5.12., of about 30% with respect the total weight of the composition (see Table 1 below).

Surprisingly, the inventors have found that said capsules, comprising live microbiota in an environment with a water content up to about 30%, were stable during 3 months at 4ºC (temperature which is equivalent to fridge temperature) even at such high humidity content. In this regard, Table 1 shows that the inclusion of the water absorbing excipient confers to the encapsulated live microbiota a stability which is of the same order as the one achieved with lyophilized microbiota. Therefore, the inclusion of the water absorbing

excipient is an effective alternative to the lyophilisation technique (which is more “aggressive” with the bacteria viability).

This is something unpredictable in view of the prior art. As discussed above, the state of the art has taught two options to achieve stable encapsulated fecal microbiota: reducing the temperature to about -80ºC, thus getting freezed fecal microbiota; or reducing as much as possible the water content by lyophilizing the fecal microbiota. Even recent publications have disclosed the encapsulation of lyophilized bacteria and the packaging of the resulting lyophilized bacteria in a special container which reduces even more the humidity content within the container (such as the Korean patent KR20080059605). Therefore, the present disclosure provided herein, i.e. stable live fecal microbiota (which require a high humidity content when compared with lyophilization) at milder temperature is surprising in view of the state of the art.

The stability of the capsules was not only in terms of bacterial viability but also in terms of capsules’ morphology. As provided below, no changes in terms of length, width or odor were found when the capsules formulated with the fecal microbiota and the water absorbing excipient (MCC) were stored at 4ºC for three months.

Altogether the composition of the present disclosure, therefore, means a great advance in the field of FMT because the treatment can be done by the recipient at home, avoiding transportation to a medical clinic. In addition, it is advantageous because it can improve treatment compliance by offering an improved convenience to patients, therefore leading to an increased patient adherence.

Thus, in a first example the present disclosure provides a solid oral pharmaceutical composition comprising a pharmaceutically effective amount of living microorganisms and one or more pharmaceutically acceptable water absorbing excipient(s), wherein the mixture has a water content, determined according to European Pharmacopoeia 9.4, section 2.5.12., from 0.5 to 30% with respect the total weight of the composition.

In a second example the present disclosure provides a process for preparing an oral pharmaceutical composition as defined in the first example of the invention, the process comprising mixing living microorganisms with the one or more water absorbing excipient(s).

An advantage of the present disclosure compared to the prior art is that the process for obtaining the composition of the present disclosure requires few steps under mild conditions (room temperature and humidity) which minimizes the risk of loss of viable bacteria.

In a third example, the present disclosure provides an oral pharmaceutical composition obtainable by the process as defined in the second example of the present disclosure.

In a fourth example, the present disclosure provides the oral pharmaceutical composition as defined in the first or third example of the present disclosure for use in therapy.

It is the first time that it is reported the ability of a water absorbing excipient in stabilizing encapsulated living microorganisms. In fact, from the data provided by the Korean patent KR20080059605, the skilled person would have expected that water absorbing excipients negatively affected the stability of the microbiota when the data provided in Examples 5 and 6 of the prior art were compared.

Without being bound to the theory, the present inventors believe that such surprising effect is due to the fact that the water absorbing excipient (such as MCC, as illustrated below) interacts with the water present in the fecal microbiota pellet, such as part of the water remains “free” and a minor amount is absorbed as “structured water”, the latter giving rise to the formation of a molecular sponge. In this way, the solid pharmaceutical composition would comprise a content of water up to about 30% (which would correspond to the water content of the starting fecal microbiota pellet used in the preparation of the capsule), but a great part of that water would be within a kind of “sponge” (the physical formed taken by the absorbing excipient) formed. Such “sponge” could act as a water reservoir or protection barrier: the live microbiota within the capsule, under the particular environment conditions, could gradually use the water available in the capsule. Therefore, the water absorbing excipient is able to exert the stabilizing effect thanks to the water content in the mixture.

The above would explain why in the Korean patent 20080059605 the same water absorbing excipient (MCC) cannot provide such stabilizing effect: the excipient is not able to stabilize the microorganism because it cannot absorb enough water because (a) the bacteria are lyophilized (i.e., do not comprise a significant amount of water), and (b) the environment humidity content is low due to the particular design of the container.

Thus, in a fifth example, the present disclosure provides the use of a water absorbing excipient for stabilizing living microorganisms in a solid oral pharmaceutical composition.

Finally, the present disclosure further provides the solid oral composition as defined in the first or third example of the present disclosure for use in the treatment of a disease associated with dysbiosis. This example can alternatively be formulated as the use of the solid oral

composition as defined in the first or third example of the present disclosure in the manufacture of a medicament for the treatment of a disease associated with dysbiosis. This example can alternatively be formulated as a method of treating or preventing a disease associated with dysbiosis, the method comprising administering a therapeutically effective amount of the composition as defined in the first or third example of the present disclosure to a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

All terms as used herein in this application, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. Other more specific definitions for certain terms as used in the present application are as set forth below and are intended to apply uniformly through-out the specification and claims unless an otherwise expressly set out definition provides a broader definition. In addition, for the purposes of the present invention, any ranges given include both the lower and the upper end-points of the range. Ranges given, such as temperatures, times, weights, and the like, should be considered approximate, unless specifically stated.

As provided above, in a first aspect the present invention refers to an oral solid pharmaceutical composition comprising living microorganisms and one or more water absorbing excipient(s).

The expression "therapeutically effective amount" as used herein, refers to the amount of living microorganisms that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease which is addressed. The particular dose of living microorganisms administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and the similar considerations.

The expression “pharmaceutical composition” refers to those compositions with a beneficial effect in humans and non-humans.

In one embodiment of the first aspect of the invention, optionally in combination with any of the embodiments provided below, the living microorganism is a probiotic microorganism or fecal microbiota. In another embodiment, optionally in combination with any of the embodiments provided above or below, the living microorganisms is fecal microbiota.

In the present context, the term "microbiota" refers to the community of microorganisms