

Preparation of a composition based on a finely divided active principle of low water solubility

- 1 This invention relates to a process for the preparation of a composition based on a finely divided active principle sparingly soluble in water and intended to be dispersed in water without forming a deposit.
- 5 The deposition or sedimentation of an active principle substantially insoluble in water during reconstitution in water is a well-known problem. It is also a particularly acute problem, above all in the case of medicaments. This is because the patient wishing to take a medicament has to
- 10 follow the posology of the doctor treating him or her. If, during reconstitution in water, part of the active principle remains at the bottom of the glass and if the operation is repeated several times a day, there is a considerable risk of ineffectuality of the treatment envisaged. Various
- 15 solutions have been proposed with a view to overcoming this problem. For example, emulsifiers or dispersants are added to pharmaceutical or nutritive compositions of the type in question to facilitate suspension of the active principle. However, the inclusion of additives such as these is not
- 20 always permitted by law so that the composition of the preparations differs according to the countries where they are to be marketed. On the other hand, such additions increase the price of the preparation in question.

The process according to the present invention enables

25 the disadvantage of incorporating an additional substance in a composition intended for dispersion in water to be eliminated whilst at the same time improving said dispersibility in water.

The present invention relates to a process for the

30 preparation of a composition based on a finely divided active principle sparingly soluble in water and intended to be dispersed in water without forming a deposit, in which from 0.4 to 10% by weight of the active principle is mixed with non-fat milk

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1 solids, preferably skimmed milk powder, the percentage being based on the weight of the mixture of active principle and non-fat milk solids, and in which the particles of the mixture of active principle and non-fat milk solids are subjected to movement at a temperature above 40°C.

5 According to the invention, concomitance between the movement of the particles of the mixture and the heat treatment is essential.

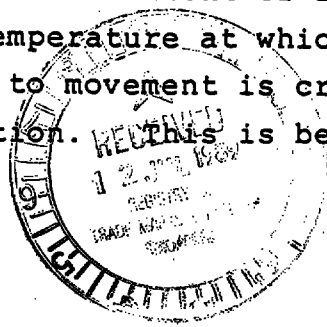
The water-insoluble active principle treated is not critical. It may be any powder-form substance substantially
10 insoluble in water and usable in the form of a dispersion in water. This may be a pharmaceutical active principle or a compound usable for nutritive purposes. Pharmaceutical active principles include, in particular, systemic anti-inflammatory, such as those according to German Patent
15 Application DE-OS 25 37 070 or their homologs, particularly the product known as Tenoxicam, or those according to US-PS 3 591 854 or their homologs, particularly Piroxicam.

The nutritive active principle used in accordance with the invention is preferably cocoa or carob bean.

20 In the context of the invention, finely divided is understood to mean particles ranging from about 0.2 to 40 microns in size.

The problem of sedimentation of sparingly water-soluble products is further aggravated if products of high specific
25 gravity are used. This is particularly the case with Tenoxicam. The active principle sediments to the bottom of the container more quickly, further increasing the risks of wrong posology. In addition, with a pharmaceutical active principle, it is known that this can cause gastric disorders in patients. Milk powder has already been proposed
30 to reduce this incompatibility, instant skimmed milk powder having a water content of from 2 to 4% preferably being used.

The temperature at which the particles of the mixture are subjected to movement is critical in the process according to
35 the invention. This is because, if the temperature is too



1 low, there is no "trapping" or "adsorption" of the active
principle by the milk powder. On the other hand, if the
temperature is too high, it promotes "burning" of the milk
powder. The treatment temperature is preferably in the
5 range of from 60 to 90°C.

When cocoa is the active principle, the entire quantity
of instant skimmed milk powder is preferably mixed directly
with the cocoa. In that case, from 5 to 10% by weight of
cocoa is mixed with the milk powder.

10 When the active principle is a pharmacologically active
substance, it is mixed in a quantity of from 0.4 to 10% by
weight with the milk powder and skimmed milk powder is then
added so as to obtain a concentration of active principle
of from 0.1 to 1% by weight.

15 This embodiment of the process according to the invention
is carried out in two steps. In the first step, the active
principle is mixed with part of the milk powder and the
resulting mixture is subjected to the heat treatment. In
the second step, the rest of the milk powder is added to
20 obtain the desired concentration of active principle.

It is obvious that the embodiment for the nutritive
active principle may be envisaged for the pharmaceutical
active principle and vice versa.

Besides the heat treatment, it is important according to
25 the invention to subject the particles of the mixture to
movement. The particles are subjected either to a sudden
and rapid treatment or a long and gentle treatment.

In the first embodiment, the particles of the mixture
are moved by mechanical means, preferably in the form of an
30 electrical blade mill, for example by an electrical mixer.
This treatment lasts for 15 to 120 seconds. In view of
the heating of the motor, the mixture simultaneously under-
goes a heat treatment at a temperature of from 60 to 90°C.

In the second embodiment, the mixture is moved by
35 agitation means, for example by a magnetic agitator. In

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1 this case, the mixture of particles is placed in a water bath at a temperature of from 50 to 80°C and the treatment lasts for 15 to 120 minutes.

When the process according to the invention is applied,
5 a powder is obtained in which the milk particles have at least partially encapsulated the active substance, thus making it possible during reconstitution in water to obtain a suspension which remains sufficiently stable for longer than the period of time envisaged for ingestion of said
10 suspension. It may also be added that the powder obtained may readily be stored for as long a period as the milk powder alone.

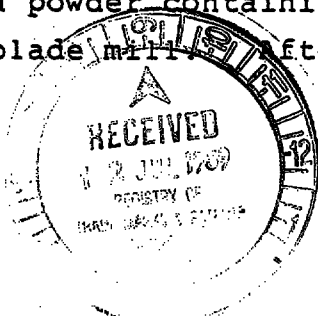
The present invention also relates to the product obtained by the process described above. This product is
15 in the form of a powder or tablets. In the case of a nutritive active principle, preference is attributed to the powder form whereas, in the case of the pharmaceutical active principle, the product is preferably in tablet form.

Irrespective of whether the product is in powder or
20 tablet form, it may also contain any additive known in the art, for example flavorings, sweeteners, such as sugars, aspartame and others or any of the known excipients usable in pharmaceutical compositions, such as those used for example in anti-inflammatory compositions. These additives
25 may be used in the quantities in which they are normally used in the art.

The process according to the invention is illustrated by the following Examples in conjunction with the accompanying drawings in which Figures 1 and 2 represent sedimentation
30 as a function of time as analyzed with a spectrophotometer and by the Imhof test.

EXAMPLE 1

27 g of instant skimmed milk powder are introduced with 3 g of cocoa powder containing 17% lipids into a high-speed
35 electrical blade mill. After 90 seconds operation, the



1 temperature of the powder is 82°C. The primary structure
of the milk powder, although greatly modified, provides for
rapid dissolution in water and imparts to the cocoa the
ability to remain suspended for a much longer time than
5 in the reference.

To demonstrate this, a sedimentation test is carried
out using a spectrophotometer. The principle of this test
is based on measurement of the light intensity of a re-
flected light beam after having passed through the sample
10 to be studied.

The factor L denotes this reflected light intensity.
The spectrophotometer used, namely a PYE-UNICAM Mod.
SP-8/100, is calibrated with whole milk which is given the
value L = 100%. The value L = 0 would be the total absence
15 of reflection, namely with a black body. The incident beam
has a wavelength of 546 nm.

Fig. 1 shows the variation of the factor L as a function
of time for the reference (curve a) and according to Example 1
(curve b). The reference comprises 10% cocoa cold-mixed
20 with instant skimmed milk powder. The mixture according to
the present Example contains the same amount of cocoa,
but treated in accordance with the invention. A low value L
means that the particles are in suspension whereas a high
L value indicates sedimentation.

25 A rapid increase in L can clearly be seen for the
reference whereas the factor L varies only very slightly
for the sample according to Example 1. In the first case,
therefore, there is rapid sedimentation of the cocoa whereas,
for the sample according to the invention, there is very
30 little sedimentation after two hours.

The Imhof test also enables the sedimentation of a
suspended product to be demonstrated. In this case, 100 g
of dry matter are mixed with 900 ml of water and the sedi-
mentation S in ml is studied in a drawn-out test tube.
35 Figure 2 shows the results of this test for the reference

1 (curve a) and for the sample according to the invention
(curve b). The difference is very clear: the reference
shows a sedimentation of 40% after 5 hours whereas the
sample according to the invention shows only 10% sedi-
5 mentation after the same period.

EXAMPLE 2

90 g of instant skimmed milk powder and 10 g of cocoa
powder are simultaneously introduced into a glass container
equipped with a magnetic agitator which is subjected to a
10 rotational speed of 180 r.p.m. The whole is thermostatically
controlled in a water bath at 60°C agitated under the
described conditions for 20 minutes.

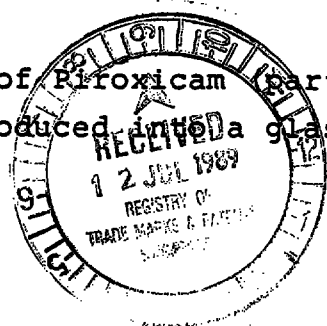
The product thus obtained has virtually retained its
structure although, during reconstitution in water, the
15 insoluble cocoa is kept in suspension as in Example 1.

EXAMPLE 3

3 g of Tenoxicam are treated with 27 g of instant skimmed
milk powder under the conditions described in Example 1.
After 90 seconds treatment, the temperature is 85°C and an
20 extremely homogeneous and fine powder is obtained. Dry
mixing of 4 g of this powder with 96 g of instant skimmed
milk powder gives a yellow/cream colored granular preparation
containing 20 mg of Tenoxicam per 5 g dose (therapeutic
dose) with the property of perfect stability of the
25 suspension during dispersion of the preparation in water.
The bitterness induced by the intense dispersion of the
bitter active principle may be reduced by using aspartame
(25 mg/dose), flavoring (vanillin 10 mg/dose) and approx.
1% of gelatinizing agent (Hercules Powders carboxymethyl-
30 cellulose). In the untreated reference, 45% of the
Tenoxicam has sedimented 15 mins. and 95% 20 mins. after
suspension in water.

EXAMPLE 4

8 g of Rifoxycam (particle size between 0.2 and 4 μ)
35 were introduced into a glass reactor with 92 g of instant



- 1 skimmed milk powder. After treatment for 20 minutes with gentle magnetic agitation (as in Example 2) in a water bath at 70°C, a heavily colored granular mixture is obtained and, after dilution by ordinary dry-mixing in 600 g of instant
- 5 skimmed milk powder and 300 g of casein condensed with formol (PLASVITA, a product of DYNAMIT NOBEL), is tabletted by the usual methods, one 2.5 g tablet containing 20 mg of finely dispersed active principle.

10 Contacting the tablet with water results in rapid dispersion and the colored active principle does not sediment, even after a prolonged period. A sweetener and a flavoring are used as in Example 3.

In all the above Examples, the water content of the instant skimmed milk powder was 3.5%.



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CLAIMS

1. A process for the preparation of a composition based on a finely divided active principle sparingly soluble in water and intended to be dispersed in water without forming a deposit, characterised in that from 0.4 to 10% by weight of the active principle is mixed with non-fat milk solids, preferably skimmed milk powder, the percentage being based on the weight of the mixture of active principle and non-fat milk solids, and in that the particles of the mixture of active principle and non-fat milk solids are subjected to movement at a temperature above 40°C.
2. A process as claimed in Claim 1, characterized in that the active principle is selected from cocoa and carob beans and a pharmacologically active principle, such as a systemic anti-inflammatory.
3. A process as claimed in Claim 2, characterized in that the systemic anti-inflammatory is selected from Tenoxicam, Piroxicam and their homologs.
4. A process as claimed in Claim 1 or 2, characterized in that the particles of the mixture are subjected to movement at a temperature of from 60 to 90°C.
5. A process as claimed in Claim 1 or 2, characterized in that instant skimmed milk powder having a water content of from 2 to 4% is used.
6. A process as claimed in Claim 2, characterized in that from 5 to 10% of cocoa is mixed with the skimmed milk powder.
7. A process as claimed in Claim 2 or 3, characterized in that from 0.4 to 10% by weight of pharmacologically active principle is mixed with skimmed milk powder and in that skimmed milk powder is then added so as to obtain a concentration of active principle of from 0.1 to 1% by weight.
8. A process as claimed in Claim 1 or 2, characterized in that the particles are subjected to movement by means of an electrical blade mill for between 15 and 120 seconds.
9. A process as claimed in Claim 1 or 2, characterized in that the particles of the mixture are subjected to movement by moderate agitation for between 15 and 120 minutes.





10. The product obtained by the process claimed in any of Claims 1 to 9, characterized in that it is in the form of powder or tablets.
