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**Datasheet for the decision
of 27 May 2008**

Case Number: T 0199/05 - 3.3.01

Application Number: 00108560.4

Publication Number: 1048668

IPC: C07D 475/14

Language of the proceedings: EN

Title of invention:

Process for preparing spray granules containing riboflavin

Patentee:

DSM IP Assets B.V.

Opponent:

BASF SE

Headword:

Riboflavin granulate/DSM

Relevant legal provisions:

EPC Art. 54, 56, 83

Keyword:

"Sufficiency of disclosure (yes)"
"Novelty and inventive step (yes)"

Decisions cited:

-

Catchword:

-



Case Number: T 0199/05 - 3.3.01

DECISION
of the Technical Board of Appeal 3.3.01
of 27 May 2008

Appellant: DSM IP Assets B.V.
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Respondent: BASF SE
(Opponent) D-67056 Ludwigshafen (DE)

Representative: Wolf, Christian
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 10 December 2004
revoking European patent No. 1048668 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: P. Ranguis
Members: J. Jonk
R. Menapace

Summary of Facts and Submissions

I. The Appellant (Proprietor of the patent) lodged an appeal against the decision of the Opposition Division revoking the European patent No. 1 048 668 (European patent application No. 00 108 560.4), Claims 1 and 6 as granted reading as follows:

"1. A process for the manufacture of flowable, non-dusty, binder-free riboflavin granulates, which process comprises subjecting an aqueous suspension of riboflavin crystals of crystal modification B/C to a fluidized bed spray drying process, a single fluid nozzle spray drying process or a disk-type spray drying process."

"6. A riboflavin granulate obtainable by a process in accordance with any one of claims 1-5."

II. The opposition was filed against the patent as a whole, and based on the grounds of lack of novelty and inventive step as indicated in Article 100(a) EPC and lack of sufficiency within the meaning of Article 100(b) EPC. It was supported by the following documents:

- (1) EP-B-0 457 075,
- (2) Riboflavin, Ed. Rivlin R.S., Plenum Press 1975, New York, p. 110, 111, 146, 147, 150 and 151,
- (3) US-A-2 603 633 and
- (4) EP-A-0 307 767.

III. The Opposition Division held that the subject-matter of Claim 1 of the main request and that of Claim 1 of the

first auxiliary request lacked clarity within the meaning of Article 84 EPC and that the subject-matter of Claim 1 of the second auxiliary request lacked an inventive step in view of documents (1) and (4). The closest prior art document (1) did not disclose the use of an aqueous suspension of riboflavin crystals of crystal modification B/C to a spray drying process as defined in Claim 1. However, the use of such a suspension was considered obvious to the skilled person in the light of document (4), since the spherulitic form of riboflavin obtained according to this document had already improved flow and compression properties.

IV. Oral proceedings before the Board were held on 27 Mai 2008.

V. The Appellant defended the patentability of the subject-matter of the patent in suit on the basis of a main request and two auxiliary requests all submitted during the oral proceedings before the Board on 27 May 2008.

Claim 1 of the present main request read as follows:

"A process for the manufacture of flowable, non-dusty, binder-free riboflavin granulates, which process comprises dissolving needle-shaped riboflavin of stable modification A in an aqueous mineral acid solution at 5 to 25°C with intensive intermixing, adding active charcoal to the resulting solution in order to absorb impurities present in the solution, subjecting the medium containing the active charcoal to a cross-flow filtration over a ceramic membrane having a pore size of 20 to 200 nm, mixing a five to ten-fold amount

(wt./wt.) of water with the resulting filtrate to allow crystallization at a temperature between 4 and 10°C, separating the precipitated, spherical riboflavin crystals by centrifugation or filtration, and subjecting an aqueous suspension of the thus-produced crystals of riboflavin of crystal modification B/C to a fluidized bed spray drying process, a single fluid nozzle spray drying process or a disk-type spray drying process."

and

Claim 6 corresponded to Claim 6 of the patent in suit as granted.

These Claims 1 and 6 of the present main request substantially corresponded to Claims 1 and 6 of the second auxiliary request before the Opposition Division.

VI. The Appellant argued that the subject-matter of Claim 6 of the main request was novel and involved an inventive step over the cited prior art.

In this context, the Appellant emphasised by referring to Picture 5 of the test report filed on 20 April 2005 that the treatment of riboflavin before spray drying as indicated in present Claim 1 involving a crystallisation step at 4 to 10°C provided a crystalline form B/C being substantially free of needle-shaped crystals and by referring to Picture 3 that the spray drying step of this particular crystalline form lead to a riboflavin granulate, in which the riboflavin substantially also had said crystalline form B/C without having been reverted to

the more thermostable needle-shaped crystalline form of type A. The so obtained granulate had improved solubility properties and by subjecting it to a direct tableting process tablets showing an improved hardness and also a better solubility were achieved.

The cited prior art documents (1) and (4) did not disclose the production of a riboflavin granulate or riboflavin particles being essentially free of needle-shaped crystals and even taught away from the claimed subject-matter of the patent in suit by teaching that the crystallisation step should preferably carried out at a temperature of preferably 20 to 30°C and 20 to 35°C, respectively. At these crystallisation temperatures riboflavin crystalline forms containing needle-shaped crystals would be obtained as had been shown in Pictures 6 and 7 of the test report.

Furthermore, document (3) disclosed a method of preparing riboflavin having the crystalline form C. The method for preparing this crystalline form totally differed from the process of present Claim 1, and also did not provide any indication that the riboflavin product having the crystalline form of type C could be subjected to a granulation process as indicated in present Claim 1 in order to obtain a riboflavin granulate having the desired solubility and compression properties.

The Appellant also considered that the subject-matter of Claim 1 of the present main request involved an inventive step for the same reasons.

VII. The Respondent (Opponent) argued that the subject-matter of present Claims 1 and 6 lacked sufficiency within the

meaning of Article 83 EPC, since in the test report submitted by the Appellant it had been explicitly stated that the desired spherical crystal modification could only be obtained at a temperature of 4 to 8°C.

The Respondent also argued that the subject-matter of Claim 6 of the present main request lacked novelty in view of document (1), since a suitable starting material for the process of this document was a suspension of a riboflavin crystalline form obtained by a fast crystallisation of riboflavin from an aqueous mineral acid solution at a temperature of preferably 20 to 30°C and because according to Example 3 of the patent in suit a crystallisation temperature of 20°C would lead to a crystalline form B/C being suitable to achieve the objects of the patent in suit. Concerning the test report submitted by the Appellant he submitted that the crystalline form of the particles of Picture 4 apparently had been obtained by granulating a riboflavin having the crystalline form of type A as shown in Picture 7 of the test report and that the granulation of riboflavin in the crystalline form as obtained according to documents (1), (3) and (4) would rather provide a granulate having a particle form shown in Picture 3. Moreover, the claimed subject-matter lacked also novelty in view documents (3) and (4), because document (3) disclosed riboflavin particles obtained by crystallising at a temperature of 10°C and document (4) disclosed the production of riboflavin in the form of spherical particles having good handling properties.

Concerning the required inventive step the Respondent considered that the subject-matter of Claims 6 and 1

was obvious to the skilled person having regard to document (1) as closest prior art in combination with documents (2), (3) and/or (4). In this context the Respondent submitted that the technical problem underlying the patent in suit, i.e. the provision of a riboflavin granulate having the alleged improved properties, would not be solved within the scope of Claim 1 of the present main request as a whole in view of the statement in the test report of the Appellant himself that the crystallisation temperature was critical and had to be 4 to 8°C. Moreover, having regard to the decision T 279/89 the claimed subject-matter would also not meet the requirements for acknowledging a selection invention.

VIII. The Appellant requested that the decision under appeal be set aside and the patent be maintained with the claims according to the main, first or second auxiliary request submitted during the oral proceedings.

The Respondent requested that the appeal be dismissed.

IX. At the conclusion of the oral proceedings the Board's decision was pronounced.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 *Amendments under Article 123(2) and (3) EPC*

2.1.1 The subject-matter of Claim 1 of the patent in suit as granted was restricted by indicating the preparation of the spherical riboflavin crystals, which in the form of an aqueous suspension are subjected to one of the specified spray drying processes. The corresponding amendments find their basis in the patent application as filed on:

- page 2, lines 10, 11 and 18 to 20, with respect to the dissolution step of the needle-shaped riboflavin of the modification A in an aqueous mineral acid solution,

- page 2, lines 25 to 27, concerning the purification step with active charcoal,

- page 3, lines 6 to 8, 12 and 13, with respect to the filtration step for removing the impurities,

- page 3, lines 20 to 22, and Examples 1 and 3, with respect to the mixing of the filtrate with a five- to ten-fold (wt./wt.) amount of water to allow crystallisation,

- page 3, lines 26 to 31, concerning the crystallisation temperature of between 4 and 10°C, and

- page 4, lines 28 and 29, with respect to the separation of the riboflavin crystals.

2.1.2 Furthermore, the subject-matters of present Claims 2 to 10 correspond to those of Claims 2 to 10 of the application as filed and are reflected by the subject-matters of the corresponding claims of the patent as granted.

2.1.3 Therefore, the amended subject-matter of the present claims does not contravene Article 123(2) and (3) EPC.

2.2 *Sufficiency within the meaning of Article 83 EPC*

2.2.1 The Respondent argued that the subject-matter of present Claims 1 and 6 lacked sufficiency within the meaning of Article 83 EPC, since in the test report submitted by the Appellant it had been explicitly stated that the desired spherical crystalline form could only be obtained at a temperature of 4 to 8°C.

2.2.2 However, having regard to Examples 1 and 2 of the patent in suit disclosing the crystallisation at 10°C and 9 to 10°C, respectively, a skilled person would not have any difficulties to perform the crystallisation at a temperature of 4 to 10°C.

2.2.3 Therefore, this submission of the Respondent fails and the requirements under Article 83 EPC are met.

2.3 *Novelty*

2.3.1 According to the consistent jurisprudence of the Boards of Appeal a product defined by a product-by-process as in present Claim 6 is only patentable if it is novel and involves an inventive step as such, i.e. independently from the process. Thus, novelty could be

established only if evidence has been provided that modification of process parameters resulted in other products, i.e. if it has been shown that differences existed in the properties of the products (see decisions cited in Case Law of the Boards of Appeal, 5th edition 2006, 11.13.6.2).

2.3.2 In the present case, the Appellant submitted, as indicated in the patent in suit (see paragraphs [0016] and [0017]), that the treatment of riboflavin before the spray drying step as indicated in present Claim 1 involving a crystallisation step at 4 to 10°C provided a crystal modification B/C being substantially free of the needle-shaped crystal modification A and that the spray drying step as specified in Claim 1 of this particular crystal modification lead to a riboflavin granulate, in which that crystal modification had been maintained, i.e. had not been reverted to the more thermostable needle-shaped crystal modification A.

In this context, the Appellant noted that, as indicated in the patent in suit (see paragraph [0019]), the term "crystal modification B/C" relates to the riboflavin crystalline form obtained according to the treatment of riboflavin as indicated in present Claim 1 and being used as starting material in the subsequent spray drying step. In the moist state of said crystalline form a mixture of crystals of modification B and C is present, whereas the dried crystals exhibit the crystal modification B.

In support of these submissions the Appellant referred to his test report showing:

- that crystallisation of riboflavin at a temperature of 25°C lead to a substantially needle-shaped crystalline form (Picture 7),
- that crystallisation of riboflavin at a temperature of 20°C gave a mixture of a spherical crystals of modification B/C with needle-shaped crystals (Picture 6),
- that riboflavin crystallisation at a temperature of 8°C resulted into a substantially needle-free spherical B/C-crystal modification (Picture 5),
- that spray drying of a suspension of needle-shaped riboflavin modification A provided granulate particles essentially consisting of needle-shaped crystal modification A (Picture 4), and
- that spray drying of a suspension of riboflavin of spherical crystal modification B/C gave granulate particles substantially free from needle-shaped crystals (see Picture 3).

Moreover, the Appellant submitted by referring to the examples in the patent in suit that granulates obtainable according to present Claim 1, compared to granulates obtained from riboflavin of crystal modification A, had improved solubility properties (see Table 2) and better compression properties leading to tablets showing an improved hardness and a high solubility (see Tables 4 and 6, and paragraph [0049], last sentence).

2.3.3 The Respondent contended that the fluid bed spray drying process of document (1) starting from an aqueous suspension of crystalline riboflavin obtained by a rapid crystallisation from an acidified aqueous riboflavin solution at 20°C (see column 4, lines 47 to 54) necessarily lead to the a riboflavin granulate corresponding to the product of Claim 6 of the patent in suit. In support, he referred to Example 3 of the patent in suit giving under the same conditions a riboflavin product having the crystal modification B. With respect to the improvements shown in the examples of the patent in suit, he submitted that they related to a comparison of granulates of the claimed invention with granulates having a crystal modification A instead of the crystal modification B as obtained according to document (1).

2.3.4 This novelty objection in view of document (1) is, in fact, based on the assumption that a crystallisation temperature of 20°C as applied according to document (1) would lead to a crystalline form being identical to a crystalline form obtained at 4 to 10°C according to Claim 1 of the patent in suit and that the crystalline form of document (1) would have the same thermo-stability as the crystalline form obtained at 4 to 10°C, i.e. would not reverse during separation and spray drying to the more stable crystal modification A.

However, having regard to the evidence submitted by the Appellant showing that the content of needle-shaped crystals decreases at lower crystallisation temperatures, that at a temperature of 8°C the crystal modification is substantially needle-free and that this crystal modification is maintained during a subsequent

spray drying, the validity of said assumption is questionable.

Therefore, in the absence of any evidence in support on this assumption, the Board does not accept the Respondents novelty objection based on document (1).

2.3.5 The novelty objections based on documents (3) and (4) cannot be accepted either, since none of these documents discloses a spray drying step and because such a step would provide riboflavin particles having different properties as follows from the Respondents own patent document (1).

2.3.6 Thus, the Board concludes from the above considerations that the subject-matter of the present claims is novel under Article 54(1) and (2) EPC.

2.4 *Inventive step*

2.4.1 Article 56 EPC states that an invention shall be considered as involving an inventive step if, having regard to the state of the art (in the sense of Article 54(2) EPC), it is not obvious to a person skilled in the art.

2.4.2 For deciding whether or not a claimed invention meets this criterion, the Boards of Appeal consistently apply the problem and solution approach, which essentially involves identifying the closest prior art, determining in the light thereof the technical problem which the invention addresses and successfully solves, and examining whether or not the claimed solution to this

problem is obvious for the skilled person in view of the state of the art.

- 2.4.3 The Board considers, in agreement with the parties to the proceedings, that the closest state of the art with respect to the claimed subject-matter of the patent in suit is the disclosure of document (1).

This document is concerned with a process for preparing binder-free riboflavin granulates having improved handling properties, in which an aqueous suspension of fine particulate pure riboflavin is subjected to a fluidised bed spray drying process (see column 1, lines 6 to 27, and column 2, lines 18 to 41). Suitable fine particulate pure riboflavin can be obtained by a rapid crystallisation from an acidified aqueous riboflavin solution, preferably at 20 to 25°C (see column 4, lines 47 to 54). As indicated under points 2.3.1 to 2.3.4 above, this riboflavin material differs from that obtainable according to present 1 by crystallising at a temperature of 4 to 10°C and also gives a granulate by applying a fluidised bed spray drying process, which differs from that of present Claim 6.

- 2.4.4 As to this closest prior art the Appellant submitted that the riboflavin granulates of present claim 6 had improved solubility and tableting properties.

- 2.4.5 Therefore, the technical problem underlying the patent in suit in the light of the closest prior art document (1) can be seen in the provision of a riboflavin granulate having improved solubility properties and being suitable for producing tablets showing an improved hardness and solubility.

2.4.6 The patent in suit suggests as the solution to this problem a granulate as defined in present Claim 6 being obtainable in accordance with the process of present Claim 1, which is essentially characterised in that the crystallisation is performed at a temperature of between 4 and 10°C.

Taking into account the test report submitted by the Appellant and the examples of the patent in suit, the Board is satisfied that the technical problem as defined above has been credibly solved. The test report shows that the content of needle-shaped crystals having the more insoluble crystal modification A decreases by varying the crystallisation temperature from 25°C to 20°C and further to 8°C, and that at a crystallisation temperature of 8°C as applied according to present Claim 1 the achieved crystalline form is substantially needle-free and that this crystalline form is maintained during the subsequent production of the spray dried granulates (see point 2.3.2 above). Furthermore, the examples of the patent in suit show that granulates obtainable according to present Claim 1 having the substantially needle-free crystalline form have improved solubility properties compared to granulates obtained from riboflavin material having a needle-shaped crystal modification A (see Table 2) and that tablets obtained by direct tableting of the granulates obtainable according to present Claim 1 have an improved hardness and also a better solubility (see Tables 4 and 6, and paragraph [0047], last sentence).

2.4.7 In this context, the Respondent objected that the improved properties shown in the examples of the patent in suit relate to a comparison with a riboflavin

granulate having the needle-shaped crystal modification A and that instead a comparison had to be made with a riboflavin granulate obtained by spray drying of a riboflavin material achieved at a crystallisation temperature of 20°C as disclosed in document (1), which corresponds to that of Example 3 of the patent in suit. However, in view of the fact, that according to the test report (Picture 6) such a riboflavin material has a crystal modification still containing a considerable amount of needle-shaped crystals of modification A, the Board finds it plausible that also in comparison with that "closer" riboflavin granulate a relevant improvement will be obtained. Therefore, the Respondent's objection put forward without any convincing evidence that no improvement with respect to that prior art embodiment would be obtained cannot be accepted by the Board.

- 2.4.8 Furthermore, the Respondent's unsupported allegation that the technical problem underlying the patent in suit as defined above would not be solved within the scope of present Claims 1 and 6 and, in particular, within the crystallisation temperature of between 4 and 10°C as a whole, cannot be accepted either. Although it is true that it has been stated in the test report that the desired spherical crystal modification could only be obtained at a temperature of 4 to 8°C, this statement must be seen in the context of the comparative tests being carried out at crystallisation temperatures of 25°C, 20°C and 8°C, respectively, whereby the desired substantially needle-free crystal modification shown in Picture 5 had been obtained at 8°C. Moreover, this allegation is refuted by the examples of the patent in suit showing the improved

solubility and compression properties of the riboflavin granulates obtained from riboflavin material having crystal modifications achieved at 10°C and 9°C (see Examples 1 and 2 in combination with Tables 2, 4 and 6).

- 2.4.9 In assessing inventive step, the next question to be answered is whether a skilled person starting from document (1) and by following the suggestions made in the cited prior art as a whole when trying to solve the technical problem as defined above, would arrive at a riboflavin granules falling within the scope of present Claims 1 and 6.
- 2.4.10 Document (1) discloses - as indicated above under point 2.4.3 - a process for preparing binder-free riboflavin granulates having improved handling properties, which is characterised by subjecting an aqueous suspension of fine particulate pure riboflavin to a fluidised bed spray drying process. However, it does not provide any incentive to the skilled person that the technical problem underlying the patent in suit could be solved by subjecting a pure riboflavin material obtainable by a process being essentially characterised by a crystallisation at a temperature between 4 and 10°C to the spray drying process. In fact, document (1) rather leads away from the claimed subject-matter of the patent in suit, since it indicates that the preparation of the fine particulate riboflavin material to be subjected to the subsequent spray drying step preferably involves a crystallisation step at 20 to 25°C.
- 2.4.11 Also a combination of the technical teaching of document (1) with that of document (4) does not lead to

the subject-matter of the patent in suit as claimed for the same reasons, since according to this last document a spherulitic riboflavin product having improved flowing and handling properties is obtained by a process involving a crystallisation step being preferably performed within a temperature from 20 to 35°C (see page 2, lines 23 to 32, page 4, lines 34 to 39, and page 5, lines 27 and 28). Document (4) further discloses that the drying step is preferably carried out with dryers which would not be destructive to the resulting spherulitic configurations (see page 6, lines 10 to 12). Therefore, this teaching leads away from subsequently preparing a suspension in water and subjecting the obtained suspension to a granulation step as applied according to document (1) as an essential technical feature.

2.4.12 Document (3) discloses that the riboflavin crystalline form of type A consisting of long, silky hair-like needles is only slightly soluble in water, that the crystalline form of type B consisting of short, thin needles in bunches of shelves has a solubility in water of about 200 mg/l and that the new crystalline form C existing as clusters of short wide needles or plates dissolves completely in water to an extent of 1200 ml/l at room temperatures (see column 2, lines 1 to 28). As indicated in column 8, lines 34 to 43, the crystalline form C can be prepared, by dissolving crude riboflavin in an aqueous alkaline solution to give a riboflavin concentration of between 10 and 30 g/l. The solution is filtered and acidified with an acid, whereby the riboflavin immediately crystallises in the form of bunches or rosettes of well defined, plate-like needles.

The crystals are then filtered, washed and dried in a vacuum oven.

It is true, that document (3) discloses an embodiment, in which the crystallisation step is performed at a temperature of about 10°C, but this low temperature must only be applied if the concentration of the riboflavin in the aqueous alkaline solution is below 10 g/l, whereas the crystallisation temperature can be 20 to 25°C if said concentration is between 10 and 30 g/l (see column 9, lines 3 to 14). Furthermore, examples 1 and 2 of document (3) show that said crystallisation temperatures have no influence on the solubility properties of the obtained crystalline form C.

From the technical teaching of this document, the Board concludes that on its own it does not give a pointer to the skilled person to the claimed solution of the patent in suit, since it does not suggest a granulation step.

Moreover, the skilled person would not combine the teaching of document (3) with that of document (1), since according to document (1) the granulation step is preferably carried out with a suspension having a fine particulate riboflavin content of 15 to 30 wt.% (see column 3, lines 22 to 25, column 5, lines 40 to 42, and the examples), whereas the crystalline form C of riboflavin obtained according to document (3) is apparently not suitable for this purpose in view of its complete solubility up to about 1200 g/l.

2.4.13 Substantially in conformity with document (3), document (2) only discloses that there are three crystalline

forms of riboflavin, namely A, B and C having the appearance of long hair-like fibres, short thin needles and short wide needles, respectively, and a solubility (mg/ml at 25°C) of 0.05 to 0.1, 0.15 to 0.25 and 0.50 to 1.40, respectively. Therefore, this technical information does not lead the skilled person to the solution of the present technical problem either.

2.4.14 The Respondent also submitted, by referring to the decision of a Board of Appeal T 279/89, that the subject-matter of present Claim 1 did not meet the requirements for acknowledging a selection invention. However, this submission made in relation to the question of inventive step fails, since said decision only concerns the question of novelty of a selection invention.

2.4.15 It results from these considerations that the solution of the existing technical problem, as claimed in present Claim 6, was not obvious in the light of the cited documents. Moreover, the subject-matter of Claim 1 involves an inventive step for the same reasons as given for the subject-matter of Claim 6.

The further claims of the present main request relate to particular embodiments of the subject-matter of Claims 6 and 1. They are therefore also allowable.

Consequently, the claimed subject-matter of the main request involves an inventive step within the meaning of Article 56 EPC.

3. *Auxiliary requests*

- 3.1 Since the subject-matter of the claims of the main request meets the requirements of the EPC, there is no need to decide on the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to maintain the patent with the Claims 1 to 10 submitted as main request during the oral proceedings before the Board and a description yet to be adapted.

The Registrar:

The Chairman:

M. Schalow

P. Ranguis