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D E C I S I O N
of 2 June 2004

Case Number: T 0998/00 - 3.2.2

Application Number: 92907654.5

Publication Number: 0580860

IPC: A61K 9/14

Language of the proceedings: EN

Title of invention:
Method of manufacturing solid dispersion

Patentee:
NIPPON SHINYAKU COMPANY, LIMITED

Opponent:
Ladenburg B.V.

Headword:
-

Relevant legal provisions:
EPC Art. 52(1), 54, 56, 84, 123(2)

Keyword:
"Novelty (yes, after amendment)"
"Clarity (yes)"
"Inventive step (yes, after amentments)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0998/00 - 3.2.2

D E C I S I O N
of the Technical Board of Appeal 3.2.2
of 2 June 2004

Appellant: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 18 July 2000 revoking European patent No. 0580860 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: W. D. Weiß
Members: S. S. Chowdhury
E. J. Dufrasne

Summary of Facts and Submissions

I. The decision of the opposition division revoking European patent No. 0 580 860 was dispatched on 18 July 2000. The patent had been opposed on the grounds that its subject-matter lacked novelty, or at least did not involve an inventive step.

II. On 27 September 2000 the appellant Nippon Shinyaku Co., Japan filed an appeal against this decision and paid the appeal fee on the same day. The statement of grounds of appeal was received on 28 November 2000.

III. The following documents were primarily relied upon during the appeal proceedings:

D5: US-A-4 957 681
D6: Brochure: "Zweiwelliger Schneckenkneter" ZSK 30, Dec 1986
D7: Food Extrusion News, "Twin Screw Extruders", vol. 1, no. 1, 1987
D8: Drawings ZSK 30 dated October 1981
D9: Brochure: "Zweiwelliger Schneckenkneter ZSK, July 1996
D12: US-A-4 880 585
D13: US-A-4 801 460
D16: Letter from Werner & Pfleiderer dated July 30, 1999
D17: Opinion of Professor Steffens dated May 23, 2000
D18: Exhibits A, B, C, D appended to D17
D22: Statement by the inventor, Mr. Kouichi Makamichi dated 28 November 2000
D36: Expert opinion of Prof. Kawashima dated 15 April 2004

D37: Expert opinion of Dr. Terashita dated 14 April 2004

D40: Follow-up example of D5 by different scientists of Nippon Shinyaku co. Ltd. dated 12-30 March 2004.

Oral proceedings (Article 116 EPC) took place on 2 June 2004.

IV. Requests

The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or, alternatively, on the basis of the first auxiliary request filed with letter of 30 April 2004, or the second auxiliary request as filed at the oral proceedings.

The respondent (opponent) requested that the appeal be dismissed.

V. Independent claim 1 of the main request reads as follows:

"A process for producing a solid dispersion of a drug dissolved or dispersed in a polymer, characterized by employing a twin-screw extruder equipped with paddle means.".

Independent claim 1 of the first auxiliary request reads as follows:

"A process for producing a solid dispersion of a drug dissolved or dispersed in a polymer, characterized by employing a twin-screw extruder equipped with paddle

means, wherein said polymer is selected from the group consisting of hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, methacrylic acid copolymer LD, methacrylic acid copolymer S, aminoalkyl methacrylate copolymer E, poly (vinylacetal) diethylaminoacetate, ethylcellulose, methacrylic acid copolymer RS, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium, dextrin, pullulan, acacia, tragacanth, sodium alginate, propylene glycol alginate, agar powder, gelatin, and glucomannan.".

Independent claim 1 of the second auxiliary request reads as follows:

"A process for producing a solid dispersion of a drug dissolved in a polymer, characterized by employing a twin-screw extruder equipped with paddle means, wherein said polymer is selected from the group consisting of hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, methacrylic acid copolymer LD, methacrylic acid copolymer S, aminoalkyl methacrylate copolymer E, poly (vinylacetal) diethylaminoacetate, ethylcellulose, methacrylic acid copolymer RS, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium, dextrin, pullulan, acacia, tragacanth, sodium alginate, propylene glycol alginate, agar powder, gelatin, and glucomannan.".

Claims 2 to 6 are appended to the main request and claims 2 to 4 are appended to each of the first and second auxiliary requests.

VI. The parties submitted the following arguments:

(i) Appellant

Main request

The problem underlying D5 was to develop a continuous metering method for the preparation of pharmaceutical mixtures which bore no relationship to the preparation of solid dispersions and for which it was immaterial whether a single-screw extruder, a twin-screw extruder with paddle means, a twin-screw extruder without paddle means, or even an injection molding machine was used. It was very likely, however, that a twin-screw extruder without paddle means was used. Since D5 was concerned only with processing mixtures, there was no need to supply additional energy using paddle means. In any case D5 did not directly and unambiguously disclose the use of a twin-screw extruder with paddle means.

The ZSK-30 extruder was provided as a modular kit of assembly blocks enabling many different combinations depending on the specific purpose of its use, and was fully functional without the paddle means, whose presence was not inevitable, accordingly. D5 only disclosed mixing and shaping a continuously metered mixture and consequently did not provide motivation to use the paddle means, which was the reason why the ZSK-30 extruder was mentioned in passing only. D12 and D13

related to subject-matter very close to that of D5 and none of these documents mentioned paddle means.

The patentee had attempted to reproduce Example 1 of D5 using a twin-screw extruder with paddle means but the attempt failed since the extruder squeaked and stopped functioning owing to the high viscosity of the mass. D36 and D37 showed that the mixture at the temperatures given in the Examples of D5 would be substantially non-fluidic and would cause any paddles to get stuck. Therefore, Example 1 of D5 could not have been performed using a twin-screw extruder with paddle means, and the same applied to Examples 53 and 58. If the idea was to heat the mixture it would be more sensible to increase the cylinder temperature rather than to supply the extra energy via paddle means. D40 was the report of a follow-up experiment of Example 1 of D5 but using a KEX-30 twin-screw extruder with paddle means, and showed that the formulation of Example 1 could not be processed. The counter-statement of Prof. Steffens was wrong, accordingly.

Moreover, D5 did not provide any disclosure that a solid dispersion of a drug in a polymer matrix was obtained, and according to the case law, even if the process of D5 inherently resulted in a solid dispersion of a drug in a polymer matrix, this teaching was still not made available to the public by D5.

Auxiliary requests

The polymers disclosed in D5 were excised from the polymers listed in granted claim 4, which was now combined with claim 1, so the claimed process was

novel. The patent in suit overcame the disadvantages of the prior art solvent and the fusion processes. The closest prior art, D13, disclosed the process of making a solid pharmaceutical preparation using a very specific polymer only and the patent provided an alternative method which was applicable to a wide range of different polymers.

(ii) Respondent

Main request

The person skilled in the art would recognise that the ZSK-30 twin-screw extruder had paddle means disposed on its screw shafts, and the documents D6 to D9 proved that the paddle means were the core feature of such an extruder. D18 was the report of tests conducted to duplicate Examples 53 and 58 of D5 using a ZSK-30 twin-screw extruder with the setup described in D5, and they proved that solid dispersions and solid solutions were produced. Further experiments proved that a solid dispersion was also produced using a ZSK-30 twin-screw extruder without paddle means, and even with a single-screw extruder. That the processes of D5 would always produce a solid dispersion was also supported by the statement of Prof. Steffens. Had the ZSK-30 twin-screw extruder of D5 been used without the paddle means then this was material information whose omission in the US patent would be fatal in view of the "best mode" requirement of US law. The experimental evidence in D40 was flawed and not credible since it did not reproduce the setup of Example 1 of D5 faithfully, for example a KEX-30 extruder with 5 shots was used instead of a ZSK-

30 extruder with 6 shots, and the first barrel temperatures were different.

D5 explicitly stated that an extrudate was obtained, this was also stated in D12 and D13. The barrel temperatures in D5 were too low to plastify the mixture, so some other energy source must have been present and this could only be the kinetic energy supplied by paddle means. The person skilled in the art could not have overlooked the fact that the end product coming out of the extruder in the process of D5 was a solid dispersion since this property could not remain hidden.

Auxiliary requests

Claim 1 lacked clarity since there was no test described in the patent as to how to distinguish between a dispersion of particles and a molecular solution.

D5 referred to polymers in general so that the remaining polymers listed in claim 1 were also disclosed in D5 and the subject-matter of the claim lacked novelty. Starting from D13 as the closest prior art document, D5, whose Example 3 was identical with Example 3 of D13, taught the use of a ZSK-30 extruder as an alternative extruder to a single-screw extruder or an injection molding machine, in fact everything about the processes were interchangeable. This was a straighforward teaching of how to make a solid solution and the process of claim 1 lacked inventive step.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Novelty*

2.1 D5 describes a process for manufacturing pharmaceutical compositions in the form of tablets comprising a drug and a polymer by extruding the ingredients at elevated temperatures. There are two main points of contention between the parties as follows: Does the ZSK-30 extruder used in D5 inherently include kneading elements (which term, the parties agree, is synonymous with the "paddle means" of the patent in suit), and does the process of D5 produce a solid dispersion of a drug dissolved or dispersed in a polymer within the meaning of the patent? These questions are investigated in turn below.

2.2 Example 1 of D5 describes a process for manufacturing pharmaceutical compositions in the form of tablets using an extruder of the type ZSK-30, wherein the temperatures of the extruder cylinder consisting of six shots were 30°, 60°, 60°, 60°, 60°, and 60°C, and the extrudate obtained was pressed directly into tablets. The same Example, using the same apparatus with the same setup as well as the same ingredients, is also described as Example 1 of D12. According to claim 1 and column 1, lines 18 to 23 of D12 the extruder forms a melt which can be pressed between two rollers. Thus, these Examples show that the end product of the

extruder was an extrudate, ie a plastified melted product.

The six barrels of the extruder were set at a maximum temperature of 60°C which, however, would not be sufficient to produce such a plastified melted product, so another energy supply would be needed. Since no such source is mentioned, it must be the kinetic energy supplied internally by paddle means. The appellant, on page 5 of its letter dated 30 April 2004, stated that the heat generated by the paddle means could raise the temperature in the cylinder by several tens of degrees Celcius so as the melt the sample, so it is plausible that this was the source of the additional energy in the apparatus of D5. Therefore, the ZSK 30 extruder in Example 1 of D5 must have included the paddle elements, and these are, therefore, implicit for the person skilled in the art.

2.3 Regarding the expression "solid dispersion", this is defined in the patent at page 2, lines 8 and 9 thus: "The term 'solid dispersion' is used herein to mean a drug-containing pharmaceutical bulk substance comprising the drug dissolved or dispersed in a polymer". This is a broad definition and would include anything dispersed within a solid matrix, including crystalline microparticles embedded in a matrix which show Debye-Scherrer X-ray diffraction peaks. In fact this definition includes everything but the unmodified starting mixture of polymer particles and drug substance particles and is not restricted to a drug substantially dissolved in the polymer or at least being present in an amorphous state.

In as much as the polymer in D5 plastifies to extrude the mass smoothly out of the extruder and the pharmaceutically active ingredient is incorporated into the matrix polymer to form a solid mass, the product of D5 may be termed a solid dispersion within the meaning of the patent.

2.4 Since the ZSK 30 extruder of D5 must have included paddle elements to supply the energy necessary to produce the extrudate, and since the extrudate is a solid dispersion, the other process steps of claim 1 being disclosed in Example 1 of D5, this Example anticipates the process of claim 1, which process lacks novelty, accordingly.

2.5 The appellant's argument, that the fact that D5 does not disclose paddle means explicitly nor does it attach any importance thereto means that there was no direct and unambiguous disclosure of the use of a twin-screw extruder with paddle means in D5, lacks force since, as regards how a document is to be construed, the same standard must be applied to the patent as to D5. In the patent the paddle means are mentioned only once, on page 2, line 48, and that too amongst several other features such as a metering feeder unit, barrel heater-cooler means, exit dies, etc, none of which other features is essential to the invention. However, the paddle means have been picked out of this list and are now raised in importance to the central feature of the invention, despite the trifling reference to this feature in the patent and the fact that this feature is not mentioned in any of the Examples described and does not feature in the original claims.

If the patent can be read such that paddle means were implicitly disclosed in the Examples of the application as originally filed such as to support the invention as now claimed, then the skilled person is indeed justified in reading D5 such that the paddle means are an implicit feature thereof.

2.6 The appellant also argued that experiments performed on its behalf proved that the process of Example 1 of D5 could not have produced an extrudate. As the respondent has pointed out, the experiments described in D40 are flawed in that they do not reproduce Example 1 of D5 faithfully. The ZSK-30 and KEX-30 extruders can be configured in hundreds of different ways and there is a very large number of parameters, apart from the barrel temperatures, barrel diameter, number of barrels etc, which must be set, and it is unlikely that the experimental setup of D40 faithfully represented that of D5. Just to take one variable, the screw speed was set at 50 rpm in the experiments, which appears to be very low when compared with screw speeds which are normally used, for example 200 rpm in Example 1 of the patent, and 100-500 rpm in D18. The low screw speed in D40 alone could account for the apparatus stopping. Moreover, owing to the late submission of the test results, the respondent had not had the opportunity of countering the results of the test by its own tests, so the document D40 must be set aside.

First auxiliary request

3. Claim 1 of the first auxiliary request defines a process for producing a solid dispersion of a drug dissolved or dispersed in a polymer, using the same

extruder as in claim 1 of the main request, but being limited to the use of certain polymers not specifically disclosed in D5. However, those polymers remaining in claim 1 are typically used in the art of manufacturing pharmaceutical preparations and their use in the context does not affect the technical effect to be achieved since the invention of this document does not depend on the nature of the polymers used (see claim 1 of D5, which does not depend on the polymer used). The person skilled in the art would, in the normal course of experimentation, extend the teaching of D5 to at least some of the polymers listed in claim 1. The process of this claim does not involve an inventive step, accordingly.

Second auxiliary request

4. *Amendments*

Claim 1 of the patent as granted includes two alternatives, ie a process for producing a solid dispersion of a drug dissolved in a polymer, and a process for producing a solid dispersion of a drug dispersed in a polymer. Claim 1 of the second auxiliary request is restricted to only one of these alternatives, the first one. If there is any unclarity in the claim, it does not arise out of the amendment whose sole effect is to excise one alternative from the granted claim, and the claim may not now be improved in this respect, assuming such improvement is necessary.

The new claim is narrower in scope as compared with the granted claim since it now covers only the one alternative, and is also limited to the use of some of

the polymers listed in claim 4 of the patent as granted. There are no objections to the claim under Article 123(2) or (3) EPC accordingly.

5. *Article 52(1) EPC*

5.1 Claim 1 of the second auxiliary request is limited to the production of a solid dispersion of a drug dissolved in a polymer, which is understood to be a solid solution, whereby only those polymers are used which are not used in D5, for which reason the process is novel over the processes disclosed in D5. D5 does not explicitly name or make reference to any other polymers, contrary to the respondent's assertion in this respect.

The claimed process is novel over D5 for the additional reason that the processes used in D5 do not necessarily result in a solid solution. The patent makes clear that a solid solution is one in which the drug is substantially dissolved (ie in an amorphous state) in the polymer matrix so as not to produce any Debye-Scherrer X-ray diffraction peaks, and although the polymer in D5 plastifies and the pharmaceutically active ingredient is incorporated into the matrix polymer to form a solid dispersion, this is not necessarily a solid solution.

Prof. Steffens (D17) states that a solid dispersion or even a solid solution would be produced by the process of D5, and D18 would appear to support this. However, although D18 describes the setup of the ZSK-30 extruder used in the tests in great detail and also includes XRPD analyses, the same considerations as set out with

respect to the novelty of the main request in point 2.6 above also apply here. This is, the detailed setup in D5 is unknown and it is not clear that the tests of D18 also reproduce the setup of D5 faithfully.

All that the tests of D18 do prove is that the apparatus described in D5 could be used to make solid solutions if the person skilled in the art put his mind to it, and if this result is intended, in which case the extruder configuration and parameters could be set accordingly. However, the tests of D18 were produced with hindsight and with the benefit of already knowing the disclosure of the patent in suit. Since D5 is completely silent on the physicochemical properties of the product thereof, in particular the formation of a solid solution, there is no evidence that the configuration and parameters selected in D5 would have produced a solid solution, so that the respondent's arguments that D5 inevitably produces a solid solution are not persuasive.

5.2 Closest prior art

D13 describes a process for the preparation of solid pharmaceutical forms by using NVP polymers as binder, by injection molding or extrusion and shaping. The plastic extrudate is pressed into tablets using the apparatus described in D12 (see Example 3). Moreover, this is the only document cited which mentions solid solutions, for which reason all the parties acknowledged D13 as being the closest prior art document.

5.3 D13 discloses the process of making a solid pharmaceutical preparation using very specific polymers only, ie specific NVP polymers. The use of specific polymers also limits the range of pharmaceutical products which may be manufactured by the method.

The technical problem of the patent may, therefore, be seen as: how to extend the range of pharmaceutical products which may be prepared?

5.4 The solution is to use a twin-screw extruder equipped with paddle means. D13 implies that, for the purposes of that invention, any extruder or injection molding machine may be used. The passages beginning in column 1 at line 60 onwards, which describe the invention, do not lay any emphasis on the type of extruder to be used, but simply say that the mixture is subjected to injection molding or extrusion (column 2, lines 2 and 3). The Examples mention the use of an injection molding machine, a twin-screw extruder, or a single-screw extruder, and claim 1 leaves open which type of machine is used for the step of subjecting the mixture to injection molding or extrusion defined therein. Nowhere does D13 suggest that the use of a twin-screw extruder equipped with paddle means would enable a greater variety of products to be produced.

The selection of a twin-screw extruder equipped with paddle means in the patent in suit from amongst the types of extruders available enables a wide range of polymers, enumerated in claim 1, to be used. The solid dispersion can be produced without being limited by the polymer matrix that can be used, and a correspondingly

wide range of pharmaceutical products can be manufactured.

5.5 This solution was not suggested in the prior art, for which reason the subject-matter of claim 1 involves an inventive step.

5.6 The respondent argued that the person skilled in the art would realise that the end product of the process of D5 would be a solid solution, and since this document states that the different types of extruders are completely equivalent and interchangeable, the use of one of the alternatives is not inventive. However, the nexus thus established between D5 and D13 is unallowable since it is not clear that the process D5 inevitably produces a solid solution (see point 5.1 above).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent in amended form on the basis of the following documents:

– Claims 1 to 4 according to the second auxiliary request as filed at the oral proceedings;

– description pages 2 and 3 as filed at the oral proceedings, pages 4 to 13 as granted;

– figures as granted.

The Registrar The Chairman

V. Commare W. D. Weiß