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D E C I S I O N
of 10 December 1998

Case Number: T 0251/95 - 3.3.2

Application Number: 89810376.7

Publication Number: 0351353

IPC: A61K 31/19

Language of the proceedings: EN

Title of invention:
Anti-inflammatory pharmaceutical composition with an ibuprofen base, with elimination, in solution, of the bitter taste, burning in the throat and intestinal toxicity

Patentee:
Elan Corporation PLC

Opponent:
Zambon Group S.p.A.
The Boots Company PLC

Headword:
Effervescent composition/ELAN

Relevant legal provisions:
EPC Art. 52(1), 54, 56, 83, 123(2)

Keyword:
"Sufficiency (yes): Invention reproducible on the basis of the disclosure and the general specialist knowledge"
"Novelty (yes)"
"Inventive step (no): Effervescent compositions of ibuprofen obvious on the basis of the prior art in combination with the general specialist knowledge"

Decisions cited:
T 0060/89

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0251/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 10 December 1998

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 27 January 1995 revoking European patent No. 0 351 353 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent application No. 89 810 376.7 comprising 8 claims was filed by the appellants (proprietors). European patent No. 0 351 353 with 7 claims was granted to the appellants in response to the above-identified European patent application. The claims as granted are worded as follows:

"1. An anti-inflammatory pharmaceutical composition, with elimination, in solution, of the bitter taste, burning of the throat and intestinal toxicity, comprising the following ingredients in intimate admixture:
200 to 800 mg ibuprofen or 221.3 to 885.2 mg ibuprofen sodium salt, 2.100 to 8.402 g sodium bicarbonate, and 0.450 to 1.800 g citric acid.

2. The composition according to claim 1, containing 200 to 800 mg ibuprofen.

3. The composition according to claim 1, containing 221.3 to 885.2 mg ibuprofen sodium salt.

4. An effervescent solution containing the composition according to claim 2 dissolved in water.

5. An effervescent solution containing the composition according to claim 3 dissolved in water.

6. A tablet comprising the composition according to claim 1 in compressed form.

7. The composition according to claim 1, wherein said ibuprofen or ibuprofen sodium salt is free of water-insoluble coating materials."

II. Notices of opposition to the grant of the patent were filed:

(i) by respondents (opponents) 01 under Article 100(a) and (b) EPC requesting revocation of the patent as a whole on the grounds of lack of inventive step (Articles 52(1) and 56 EPC), lack of industrial applicability (Articles 52(1) and 57 EPC), and insufficiency of disclosure (Article 83 EPC); and

(ii) by respondents (opponents) 02 under Article 100(a) and (c) EPC requesting revocation of the patent as a whole on the grounds of lack of novelty (Articles 52(1) and 54 EPC), lack of inventive step (Articles 52(1) and 56 EPC), and added subject-matter (Article 123(2) EPC).

By letter dated 8 April 1994, respondents 02 withdrew their objections on the grounds of lack of novelty (Articles 52(1) and 54 EPC) and added subject-matter (Article 123(2) EPC). They maintained, however, lack of inventive step (Articles 52(1) and 56 EPC) as ground for opposition and concurred with the opinion of respondents 01 that insufficiency of disclosure (Article 83 EPC) was a further ground for

opposition.

III. Out of the 12 citations relied on by the respondents in their statements of opposition in support of the above grounds, the following are referred to in this decision:

(A1) Labo-Pharma -Problèmes et Techniques, No. 271, December 1977, pp. 987-995:
Boymond, "Les comprimés effervescents"

(A4) British Pharmacopoeia, Volume II, 1988, page 893

(1) GB-A-971 700

(2) EP-A-0 228 164

(3) EP-A-0 203 768

(6) Martindale, The Extra Pharmacopoeia, The Pharmaceutical Press, London 1982, page 256.

IV. In the proceedings before the opposition division, the appellants (proprietors) requested maintenance of the patent as granted (main request) or, alternatively, maintenance in amended form on the basis of claims 1 to 4 filed during the oral proceedings on 24 October 1994 (auxiliary request). Claim 1 of the auxiliary request reads as follows:

"An anti-inflammatory pharmaceutical composition, with elimination, in solution, of the bitter taste, burning of the throat and intestinal toxicity, comprising the

following ingredients in intimate admixture:
200 mg ibuprofen or 221.3 mg ibuprofen sodium salt,
2.100 g sodium bicarbonate, and
0.450 g citric acid, or multiple amounts thereof in the same proportions up to 800 mg ibuprofen or 885.2 mg ibuprofen sodium salt, 8.402 g sodium bicarbonate, and 1.800 g citric acid."

Claim 1 is followed by dependent claims 2 to 4 corresponding to claims 5 to 7 of the patent as granted.

V. In support of their allegation of insufficiency respondents (opponents) 01 submitted some experimental test results set out as "Reference D" in their statement of opposition. The process of preparing the compositions described in Examples 1 to 8 of the contested patent and likewise the method of dissolving these in water were said by respondents 01 in “Reference D” to have been repeated **exactly following the wording of the examples and the relevant parts of the description (see especially page 3, lines 5 to 17)** of the contested patent. Nevertheless, according to the results, which were reported by respondents 01 for the compositions corresponding to those described in **Examples 1 to 4** of the contested patent, the amount of ibuprofen solubilised in water was only **about 10%**, whereas the amount of ibuprofen remaining undissolved in the form of solid particles in suspension was about 90%.

For compositions corresponding to those described in **Examples 5 to 8** of the contested patent the following

figures were reported: amount of ibuprofen solubilised in water **about 60%**; amount of ibuprofen remaining in suspension about 40%.

In reply, the appellants (proprietors) expressed doubts about whether the above-mentioned experiments had been carried out by a person with sufficient skill in the art and maintained that the skilled person would not proceed in the manner adopted by respondents 01 in "Reference D", where all the ingredients were simply mixed, placed in a fluidised bed and granulated with demineralised water, in spite of the clear instruction in line 5 on page 3 of the specification in suit that "suitable mixing" should be adopted. The technical relevance of the latter term in the context of the claimed invention was, in the appellants' opinion, well known to those skilled in the art, as evidenced by the enclosed declarations of the experts Dr Price and Professor Testa.

The appellants also criticised the fact that respondents 01 had, in their tests, apparently filtered off the solid material from the solution prior to complete dissolution of the claimed composition. Whereas disintegration occurred rapidly, complete dissolution would normally take 5 minutes from contact by the effervescent tablet with water.

The appellants filed their own test results, set out as "Exhibit A", in their reply to the oppositions. For the preparation of the composition of Example 2 of the contested patent the appellants used the following manufacturing process set out in "Exhibit A":

In a first phase, ibuprofen and sodium bicarbonate were mixed together and separately granulated, followed by a second phase involving the steps of first mixing and then separately granulating citric acid optionally with other ingredients used in the claimed composition. In this procedure each phase was separately granulated under identical conditions and then mixed together with the subsequent addition of selected flavourings, if desired, and compression of the granulate to form tablets.

Three different tablets obtained by the method described above were subsequently analysed by an independent laboratory (Laboratorio Analisi Speciali, 6853 Ligornetto, Switzerland). The solutions were prepared by dissolving the tablet in water within 5 minutes under temporary stirring. According to these analyses the amounts of ibuprofen solubilised in water amounted in all three charges to **92.6%**, **92.3%** and **93.3%** respectively, and were thus significantly greater than that reported for Example 2 in the test report of respondents 01.

VI. The opposition division considered in its decision that the claimed invention aimed at the provision of effervescent compositions comprising ibuprofen as the active ingredient which, placed in water, developed carbon dioxide and yielded aqueous solutions of ibuprofen containing only a small proportion of undissolved ibuprofen in the form of solid particles suspended in the solution.

It concurred with the allegations of both respondents that the conclusion to be derived from the tests submitted by respondents 01 was that neither the description nor the examples of the specification in suit disclosed the method and means of carrying out the invention in such a way that the results claimed in the contested patent were reproducible.

In the opposition division's view, the appellants (proprietors) themselves had admitted by the submission of their own experiments that application of the above-mentioned specific technical measures and methods, in particular the rather unusual separate granulation of the **acidic** drug (ibuprofen) with the **basic** component of the effervescent couple (sodium bicarbonate) adopted by the appellants in their test report, was necessary in order to obtain effervescent compositions which, when placed in water, provided a satisfactory (clear) solution of ibuprofen satisfying the requirements set forth above. Since the above-mentioned method of preparing a so-called "pre-mix" by separately mixing and granulating the individual ingredients of the claimed composition was, in the opposition division's view, neither derivable from the description of the invention in the originally filed application documents, nor part of the common specialist knowledge, it concluded that the disclosure of the invention was insufficient to enable the person skilled in the art to carry it out properly and to achieve the desired results on the basis of the instructions given in the application as filed.

Consequently, the opposition division decided to revoke

the patent under Article 102(1) EPC on the ground that neither the appellants' main nor the auxiliary request met the requirements laid down in Article 83 EPC.

Furthermore it expressed in its decision the opinion that the feature "in intimate admixture" in claim 1 of both requests was not adequately supported by the original disclosure contrary to the requirements of Article 123(2) EPC, although this objection had never been pleaded by the respondents in the course of the first-instance opposition proceedings, but was merely raised by the opposition division in the form of an *obiter dictum* in the discussion during the oral proceedings and was said to be not relevant to the decision in the circumstances of the present case.

As far as the requirements for patentability under Article 52(1) EPC were concerned, the opposition division was of the opinion that the claimed subject-matter was novel but did not involve an inventive step. It considered citation (2) to be the closest state of the art and saw the technical problem as that of providing a formulation of ibuprofen in solution which exhibits, in contrast to certain formulations disclosed in the state of the art, no bitter taste and overcomes the disadvantage of causing an unbearable burning in the throat and intestinal toxicity. The finding of insufficiency led the opposition division to the further conclusion that the invention as originally disclosed did not solve the problem mentioned above and, accordingly, did not involve an inventive step either.

VII. The appellants lodged an appeal against the above decision and filed a statement of grounds within the time limit and in the form provided in Article 108 EPC. They submitted in support of their appeal both in the written procedure and at the oral proceedings essentially the following arguments:

The opposition division's finding recorded in paragraph 5 of the impugned decision that the feature "in intimate admixture" was not supported by the originally filed documents was speculative and had no place in this opposition since it was not pleaded and should therefore not be regarded. The opposition division itself recognised in the minutes of the oral proceedings that it was *obiter*. In any event, the originally disclosed method for preparing the claimed compositions involved the step of suitably mixing the ingredients specified in present claim 1 in a fluidised bed to obtain a **close mixture** of these ingredients. This was more than an adequate support for the feature "in intimate admixture" in claim 1.

The conclusion of the opposition division that the method adopted by the appellants in "Exhibit A" for the preparation and analysis of the claimed compositions did not form part of the common general knowledge, was in the appellants' opinion entirely unfounded and wrong, since the pharmaceutical formulator at the priority date of the patent in suit would have been aware of a variety of methods for preparing effervescent compositions, including the method of forming a pre-mix of ibuprofen and the basic component of the effervescent couple followed by separate granulation and admixing granulated citric acid to the pre-mix.

The appellants contended further that their method and analytical technique used to determine the amount of ibuprofen in the aqueous phase was entirely correct and the respondents' criticism in this respect was based on an incorrect interpretation of the analytical methods used and described in the appellants' test report.

At the appeal stage, the appellant submitted additional experimental evidence in order to demonstrate that a nearly complete dissolution of ibuprofen could equally be obtained, even if all the components were mixed and granulated together. By using this technique the amount of ibuprofen dissolved in water was found to be **not less than 96%**, compared to 98% when the above-mentioned technique of premixing ibuprofen with the **basic** component of the effervescent couple (sodium bicarbonate) was employed. This evidence contradicted the assumption of the respondents adopted by the opposition division that a separate granulation of

ibuprofen with sodium bicarbonate was necessary to achieve the desired result and to solve the technical problem. Thus, based on this erroneous finding of fact the opposition division came to the wrong conclusion in revoking the patent under Article 83 EPC and, accordingly, to a wrong conclusion in finding lack of inventive step under Article 56 EPC.

Citation (2) contained no suggestion of solubilising ibuprofen for a therapeutic pharmaceutical preparation. Likewise, in (2) there was no recognition of the practical drawbacks inherent in preparations containing solid ibuprofen and there was certainly no suggestion of how to achieve a good degree of solubility in liquid pharmaceutical preparations of ibuprofen so as to avoid these problems.

Citation (3) disclosed effervescent compositions in the form of tablets or granules which dissolved in water to yield effervescent solutions containing a completely dissolved therapeutic agent. The only analgesic agent actually evaluated in (3) was acetaminophen. The solubility of the therapeutic agents appeared to be controlled by maintaining the particle size within a specific range. No reference was made to the problem addressed by the patent in suit. The skilled person would therefore not be prompted to combine the teachings of citations (2) and (3).

VIII. The respondents submissions in the proceedings can essentially be summarised as follows:

They fully concurred with the opinion of the opposition

division that the feature "in intimate admixture" could not be derived from the originally filed documents and, accordingly, contravened Article 123(2) EPC.

The opposition division concluded rightly that the disclosure was insufficient to enable the skilled person properly to carry out the alleged invention and rightly revoked the patent under Article 83 EPC. The processing information given in the specification as filed was exceedingly sparse. In any case, the disclosure of the invention was clearly insufficient to achieve the required results indicated on page 3, lines 5 to 12, of the contested patent, that is to say to provide an effervescent pharmaceutical composition which, placed in water, provides a clear solution having an ibuprofen content in the aqueous phase greater than 98% of the theoretically possible amount within the period of from 30 to 90 seconds. This was clearly derivable from the experimental evidence submitted by the respondents. The board should not attach any weight to the evidence submitted for the first time by the appellants with the grounds of appeal, since it was evident that it could have been filed much earlier.

The claimed formulation for ibuprofen was obvious since (A1) already disclosed, in the context of effervescent drug formulations, that an excess of bicarbonate produced a basic solution which might facilitate the dissolving of an acid active ingredient.

Citation (1) proposed an effervescent formulation of a series of compounds including ibuprofen. The choice of

the particular amounts of sodium bicarbonate and citric acid in the contested patent to provide a solution of ibuprofen did not involve an inventive step. In order to stand the best chance of producing a solution, it would have been obvious to the skilled person, that he would need to generate a basic environment with an excess of sodium bicarbonate at the end of effervescence so as to have the ibuprofen present as its soluble sodium salt.

Citation (2) disclosed a deliberate attempt to produce an effervescent suspension. This product was palatable and was specifically designed to minimise the material left in the glass. This was achieved by the addition of the insoluble hydrophilic polymer and the surfactant to give an optimised suspension. A suspension which has not been optimised would not be palatable. Since it was known that ibuprofen was soluble in alkaline solutions, it was obvious to a person skilled in the art, who wished, starting from (2), to obtain a solution of ibuprofen, to increase the amount of sodium bicarbonate to render the pH alkaline above a value of 7.
Citation (3) described effervescent compositions which dissolved rapidly in water to yield an effervescent solution containing a completely dissolved therapeutic agent. Ibuprofen was mentioned on page 6, line 27, and claimed in claim 21. Citric acid and sodium bicarbonate formed the preferred effervescent couple. Although the specific example of (3) related to acetaminophen, there was a clear and unambiguous instruction to those skilled in the art that ibuprofen could be used in the overall teaching of (3) and not just in the specific example. Citation (3) clearly suggested that what had

been observed for acetaminophen would also apply to ibuprofen and, consequently, rendered the claimed invention similarly obvious.

IX. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims as granted, or alternatively on the basis of claims 1 to 4 submitted as auxiliary request during the oral proceedings before the opposition division.

X. Both respondents 01 and respondents 02 requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments (Article 100(c) in conjunction with Article 123(2) EPC)*

2.1 Claim 1 of both the main request (see paragraph I above) and the auxiliary request (see paragraph IV above) relates to an anti-inflammatory composition comprising the particular ingredients ibuprofen, sodium bicarbonate and citric acid **"in intimate admixture"**. The opposition division considered in paragraph 5 of its decision that the feature "in intimate admixture" had no adequate basis in the application documents as filed and, consequently, that both requests on file contravened the provisions of Article 123(2) EPC.

2.2 As has been admitted by the appellants during oral proceedings before the board, the term "in intimate admixture" cannot be found word-for-word in the application as filed. Nevertheless, the description as originally filed contains in lines 1 to 6 of the second full paragraph on page 3 an explicit reference to the need for **suitably mixing** and then granulating the individual ingredients (*viz* ibuprofen, sodium bicarbonate and citric acid) of the claimed pharmaceutical composition using a suitable equipment and environment, more specifically a **fluidised bed**, in order to obtain the desired product capable of dissolving quickly and completely in water at ambient temperature.

Likewise, in all the Examples 1 to 8 contained in the application as filed the skilled person is given the clear instruction to transfer the ingredients of the respective pharmaceutical compositions to be prepared according to these examples in a fluidised bed granulator and then to proceed with the granulation. It was not contested by the respondents that fluidised beds are commonly used in the art to accomplish an effective mixing of solid particles (see in this respect e.g. Perry's Chemical Engineers' Handbook, sixth edition, McGraw-Hill Book Company, 1984, especially page 20 to 70).

Hence, the person skilled in the art who reads in the originally filed documents the method and means used for preparing the claimed pharmaceutical composition would, in the board's view, necessarily understand and conclude that the ingredients of such a composition are indeed closely mixed. In other words, when adhering to the originally disclosed method for preparing the claimed composition and mixing the ingredients specified in present claim 1 in a fluidised bed to obtain a **close mixture** of these ingredients, the result achieved apparently corresponds to what the skilled reader would reasonably understand by a composition comprising the ingredients in "**intimate admixture**".

In view of the above considerations, both requests are acceptable under the terms of Article 123(2) EPC.

3. *Sufficiency of disclosure (Article 100(b) in conjunction with Article 83 EPC)*

3.1 Even after a lot of discussion during oral proceedings as to the relevance of the experimental evidence submitted in the written procedure in response to the question of sufficiency and reproducibility, neither of the parties was able unequivocally and conclusively to elucidate the reasons for the remarkable difference in the results achieved by either party concerning the actual content of ibuprofen in the aqueous phase when the claimed compositions are dissolved in water. Attempts to explain this discrepancy essentially related to the fact that both parties had apparently used a **different granulation practice** and a **different lapse** between the first contact of the effervescent

composition with water and determination of the actual amount of ibuprofen dissolved in water.

The evidence and arguments submitted in support of insufficiency on the part of the respondents are, in the board's opinion, primarily directed towards criticising the feasibility of the claimed invention in connection with its scope. In this respect the respondents relied essentially on the disclosure at lines 5 to 12 on page 3 of the specification in suit stating that a claimed effervescent composition, placed in water, provides a clear solution having an ibuprofen content in the aqueous phase greater than 98% the theoretically possible amount (see lines 7 to 11) and that the solution obtained after total decomposition of the tablets - necessary time from 30 to 90 seconds - is tolerable (see lines 11 to 12).

3.2 Article 83 EPC requires that the disclosure of the **invention** be clear and complete so as to be sufficient to enable a person skilled in the art to carry it out. In the present case, the **invention** as claimed in present claims 1 to 7 consists of certain products, more specifically:

(i) anti-inflammatory pharmaceutical effervescent compositions in solid form, eg granules or tablets (see claims 1 to 3, 6 and 7) comprising some well-known, commercially available components, more specifically ibuprofen or ibuprofen sodium salt, sodium bicarbonate and citric acid in certain exactly defined proportions; claim 1 and similarly claims 2, 3, 6 and 7 (the latter claims by

reference to claim 1) further require that a solution, obtained by dissolving the claimed solid composition in water by any suitable method, has a good palatability (cf. "with elimination, in solution, of the bitter taste, burning of the throat and intestinal toxicity"); and

(ii) effervescent solutions containing the composition according to claim 2 or 3, dissolved in water (claims 4 and 5).

3.3 However, the respondents' objection of insufficiency goes wider than this and is based on the allegation that the appellants were unable to demonstrate that a person skilled in the art was indeed in a position to produce compositions exhibiting the particular properties mentioned in the description and referred to in point 3.1 (above). In this respect it is to be noted that neither the degree of solubility of the claimed composition of 98% minimum nor the period of 30 to 90 seconds maximum required to obtain a solution are features which form part of the definition of the **claimed invention**.

Hence, contrary to the respondents' assertion, the question whether or not compositions falling within the scope of the present claims indeed exhibit the above-mentioned particular properties and capabilities is immaterial to the question of sufficiency, as long as the person skilled in the art (ie the person at whom the disclosure of the contested patent is aimed) was able - on the basis of the original disclosure and possibly by using his common general knowledge to

supplement the information contained in the application as filed - to carry out the **invention,** that is to say to prepare effervescent pharmaceutical preparations containing ibuprofen, e.g. granules or tablets, which, when placed in a suitable amount of water, develop carbon dioxide and provide a palatable solution of the medicament (see point 3.2 above).

3.4 When considering whether or not the skilled person would have been able to carry out the claimed invention, it should be emphasised that the products according to the claims of the patent in suit may be prepared **by any method within the common general knowledge of the art** at the priority date of the contested patent. The board concurs with the appellant's submissions during oral proceedings that the addressee of the patent is the formulator in the pharmaceutical industry who is a specialist or a team of specialists of that skill being familiar, *inter alia*, with all kinds of materials and methods used for the preparation of effervescent pharmaceutical compositions, the particular chemical and physical properties of ibuprofen and its salts, specifically in context of their solubility in water, and the standard methods used for testing effervescent pharmaceutical preparations.

Hence, in addition to the particular instructions provided in the contested patent the specialist endowed with the high level of skill mentioned above would have known, for example, from citation (A1), which was acknowledged by both parties to represent the common general specialist knowledge at the priority date, that

the most **widely-used granulation method** for preparing effervescent compositions involves the step of blending and granulating the bicarbonate of the effervescent couple **separate** from the citric acid so as to form a pre-mix (see page 993, right-hand column, paragraph 6) and that it is necessary to determine in advance **the component** of the effervescent couple which is suitably blended and granulated with **the active agent** (see page 993, right-hand column, paragraph 8).

Moreover, the skilled person would have known from citation (A4) that an effervescent tablet complies with the well-recognised standards in pharmacy, if it dissolves under the conditions used in the parties' test reports **within 5 minutes** (see especially (A4), right-hand column: "Effervescent Tablets").

3.5 In conclusion, on the basis of the above considerations, the board has no reasonable doubts that the skilled person is able on the basis of the original disclosure and his common general knowledge properly to carry out the invention and to achieve the desired result as evidenced by the experimental results submitted on the part of the appellants. The allegations of insufficiency under Article 83 EPC are thus defeated.

4. *Novelty (Article 100(a) in conjunction with Article 54 EPC)*

Respondents 02 had already withdrawn their opposition on the ground of lack of novelty during the proceedings before the opposition division. Since the novelty of the claimed subject-matter in the patent in suit is no

longer disputed, there is no need for further detailed substantiation of this matter.

5. *Inventive step (Article 100(a) in conjunction with Article 56 EPC)*

5.1 The board concurs with the opinion of the opposition division in the impugned decision that citation (2) represents the closest state of the art. The appellants similarly agreed in their submissions, both in writing and during the oral proceedings, with the board's opinion in this respect. The disclosure of citation (2) is already referred to in the introductory part of the contested patent at lines 37 to 44 on page 2. It, too, is concerned with the provision of an effervescent pharmaceutical composition which was specifically designed for the oral administration of ibuprofen or a pharmaceutically active salt thereof in liquid form.

Moreover, citation (2) already addresses the problem that ibuprofen, on the one hand, is a versatile and most valuable pharmaceutical agent endowed with strong analgesic and antipyretic properties but, on the other, suffers the considerable disadvantage of very limited solubility in water giving rise to serious difficulties in the oral application of this medicament to patients in need of it. The cited document, like the contested patent, proposes a solution for overcoming the above-mentioned difficulties associated with the insolubility of ibuprofen in water. The effervescent composition disclosed in (2) was moreover not only designed to facilitate the oral application but also to minimise the amount of ibuprofen left in the glass after consumption of the medicament so that the required dose of ibuprofen can reliably be administered (see (2), especially page 2, lines 16 to 24). According to the respondents' assertion during the oral proceedings the product according to the prior art of (2) is perfectly palatable and was successfully put on the market.

Citation (1), which was alternatively considered by the respondents to be the closest state of the art, is the original patent covering ibuprofen and salts thereof. Although reference is made in line 21 on page 6 that oral compositions may include effervescent granules and that these may comprise a combination of effervescent agents well known in the art (cf. page 6, lines 43 to 44), the skilled person is given no instructions in (1) as to how he could indeed prepare such effervescent granules, let alone, as to how he could arrive at palatable solutions of ibuprofen.

Citation (3), which was likewise suggested by the respondents in a further alternative to be taken as the closest state of the art, discloses an effervescent composition in the form of a tablet or powder comprising a therapeutic agent, a granulating agent, a microparticulate effervescent component and an effervescent system which dissolve rapidly in water to yield an effervescent solution containing a completely dissolved therapeutic agent. The therapeutic agent that may be used in the composition disclosed in (3) may in fact be selected from any stable therapeutic agent and combination of therapeutic agents (see especially page 5, lines 3 to 5), regardless of their particular chemical structure and behaviour towards an acid or basic environment. Ibuprofen as such (cf. page 5, line 30; page 6, line 27) is only mentioned as one example in the long list of potentially suitable therapeutic agents that may be employed in the composition disclosed in (3) without giving any further details of a composition containing ibuprofen as the active ingredient. The list mentioned above includes among a certain number of other categories of therapeutic agents antitussives, antihistamines, decongestants, alkaloids, mineral supplements, laxatives, vitamins, antacids, ion exchange resins, anti-cholesterolemic and anti-lipid agents, antipyretics, analgesics, appetite suppressants, anti-inflammatory agents, antibiotics, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, etc., (see page 5, line 8, to page 6, line 18).

In view of the fact that citation (2) is explicitly and directly concerned with the provision of an effervescent formulation of ibuprofen for oral administration and that (2) rather than (1) and (3) already addresses certain specific problems which are inherently associated with the oral administration of ibuprofen such as its unpalatability or its water insolubility, the board is of the opinion that citation (2) is a technically more realistic starting point for the assessment of the technical problem the claimed invention sets out to solve, and hence for the assessment of inventive step, than is citation (3).

5.2 The pharmaceutical composition disclosed in (2) effervesces, when added to water, thereby forming an aqueous suspension of ibuprofen suitable for oral administration. According to the statement in lines 4 and 5 on page 2 of citation (2), such aqueous suspensions are convenient to use and are advantageous over solid monolithic dosage forms, eg tablets or capsules, for the application to patients having difficulty in swallowing tablets or capsules, for example, children and elderly patients. The inventors of (2) have found that the inclusion of a water-insoluble hydrophilic polymer, for example starch, cellulose or water-insoluble cellulose derivatives, or cross-linked polyvinylpyrrolidone in the compositions disclosed in (2) gives an improved suspension of ibuprofen or salt thereof when such compositions are added to water.

In spite of the progress which has been achieved by the provision of the orally administrable form of ibuprofen disclosed in (2), the appellants see a serious drawback to this liquid pharmaceutical dosage form in the fact that ibuprofen, when added to water, is present in suspension in the solid state, ie undissolved, in water. As is already stated in the contested patent (see page 2, lines 42 and 43) and has been repeated by the appellants at several occasions during the entire proceedings, the presence of the drug in undissolved form in the said suspension is still met with some measure of discomfort to patients, because it prevents at least to a certain extent elimination of the problems of poor organoleptic properties, especially bad taste, burning of the throat and irritation of the intestinal mucosa frequently experienced with the application of ibuprofen.

5.3 Thus, in the light of the closest state of the art according to citation (2), the technical problem to be solved may be seen as that of providing of an improved pharmaceutical dosage form of ibuprofen which is just as easy to swallow as the one disclosed in (2) but which obviates the above-mentioned disadvantages associated with the application of ibuprofen in the solid state, more specifically in suspension.

In the contested patent the appellants propose to solve this problem by the provision of a pharmaceutical composition which contains ibuprofen or its sodium salt in admixture with sodium bicarbonate and citric acid in certain specified ratios and which effervesces, when added to water, thereby forming a **clear aqueous**

solution of the sodium salt of ibuprofen suitable for oral administration. With reference to the conclusions reached in point 3 (above) regarding sufficiency of disclosure and reproducibility of the invention, the board is satisfied that the claimed pharmaceutical compositions in the contested patent represent an adequate solution to the technical problem defined above.

5.4 The board adopts the view expressed in decision T 60/89 (OJ EPO 6/1992, 268, see especially reasons, point 3.2.5) that the same level of skill has to be applied when, for the same invention, the two questions of sufficient disclosure, on the one hand, and inventive step, on the other, have to be considered.

Thus, in the present case the skilled person knew from his general specialist knowledge that ibuprofen is soluble in aqueous solutions of sodium hydroxide and sodium carbonates in the form of its sodium salt, see eg citation (6). He likewise knew, that the combination of citric acid, on the one hand, and sodium bicarbonate, on the other is the most widely used effervescent couple for the preparation of pharmaceutical effervescent compositions (see, for example, citation (A1), page 987, right-hand column, paragraph 2, page 989, left-hand column, paragraph 7).

Moreover, the skilled person starting from the effervescent composition of (2) and faced with the technical problem defined above was aware that this problem might be solvable, if an excess of bicarbonate is used in order to render the solution alkaline and so

to facilitate the dissolution of the active ingredient ibuprofen which is present in the effervescent suspension in (2) in acid form (see A1, the paragraph bridging pages 991 and 992).

5.5 If, on the basis of his common general knowledge, the skilled person still encountered certain difficulties in the preparation of an effervescent composition solving the technical problem at issue, he would have learned from citation (3) that effervescent compositions exist which dissolve rapidly in water to yield an effervescent palatable solution containing a completely dissolved therapeutic agent, in particular analgesic agents. He would moreover have learned how such compositions can be prepared, even if the therapeutic agent used is only sparingly soluble in water.

Ibuprofen is explicitly referred to on page 5, line 30 and on page 6, line 27, and is claimed in claim 21 as a suitable analgesic therapeutic agent to be provided in the form of a water soluble effervescent composition. Citric acid and sodium bicarbonate form also in (3) the preferred effervescent couple.

Citation (3) teaches an effective method for producing therapeutic effervescent compositions which dissolve rapidly in cold water to form a clear palatable solution. Said method comprises the steps of preparing a pre-blended mixture of the granulated therapeutic agent having a particle size of about 100 to about 600 microns and a component of the effervescent couple having a particle size of about 50 to about 600 microns

and blending this pre-mix with the effervescent system, and as such was likewise **readily applicable** to the preparation of the claimed effervescent compositions.

Once effervescent water-soluble compositions comprising ibuprofen as the active agent along with sodium bicarbonate/citric acid as the effervescent couple and, moreover, a suitable method for preparing such compositions became obvious from the cited prior art, determination of suitable proportions or ratios of the ingredients required to achieve optimal dissolution of ibuprofen in water was then, contrary to the appellants' assertions in this respect, merely a matter of routine experimentation for the skilled formulator in the pharmaceutical industry being aware of the technical teaching of (2) in combination with that of (3).

5.6 In view the above considerations, the claimed compositions cannot be regarded as involving an inventive step within the meaning of Article 56 EPC in the absence of the demonstration of any unexpected advantageous properties or capabilities. These conclusions apply not only to the claims of the main request but extend also to those of the auxiliary request. The auxiliary request differs from the main request merely in that the proportions of the individual ingredients are more exactly defined in claim 1.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon