BL01 001 83

PATENTS ACT. 1949

IN THE MATTER OF an application
for Letters Patent No 1489532
in the name of Nippon Shinyaku
Company Limited

and

IN THE MATTER OF an opposition
thereto by Essential Sterolin Products
(Pty) Limited

DECISION

The application is opposed on the grounds of prior publication in UK specification 1298047 and Agr. Biol. Chem. (Japan) Vol 30 pages 770-778 and Vol 31 pages 1244-1247; obviousness having regard to the disclosure in the aforementioned publications; and insufficient and unfair description.

At the hearing before me on 2 November 1982, Mr H Laddie appeared as counsel for the applicants. The opponents were not represented.

In the course of the proceedings before the hearing further evidence, namely a second affidavit by Mr M Kawamata, was submitted by the applicants under Rule 43. It was referred to by Mr Laddie and I have decided to admit it formally to the proceedings.

The applicants' invention relates to amorphous steryl glucoside palmitates and processes for producing them. The steryl glucoside palmitates are defined at lines 17 to 22 on page 1 of the specification in suit as "6-O-mono-palmitates of β-sitosteryl-β-D-glucoside, stigmasteryl-β-D-glucoside, campesteryl-β-D-glucoside and cholesteryl-β-D-glucoside and mixtures of such steryl-β-D-glucoside palmitates extracted from vegetables" and are conveniently referred to thereinafter and will likewise be referred to in this decision, as SGP. The specification continues "Said SGP widely exists together with other fatty acid esters in vegetables. They are obtained together with various fatty acid esters from natural substances such as soy beans, cotton seeds and rape-seeds according to, for example, a method of T Kiritsuchi, et al. [Agr. Biol. Chem. Vol 13, No 8, 770-778 (1966)]. SGP is synthesized from steryl glucosides according to, for example, the method of T. Kiritsuchi, et al [Agr. Biol. Chem., Vol 31, No 10, 1244-1247 (1967)], said steryl glucosides being obtained from natural materials or obtained by a known process for steryl glucoside synthesis (for example, Chem.

Ber. 105, 1097-1121). SGP having a strong hemostatic activity is a pharmacologically important substance." It is then explained that a serious defect of SGP in relation to its use in medicines has been poor adsorbability through digestive tracts due to insolubility in water. However, "It has now been found by thermal analysis that SGP has polymorphism." and that ..... "amorphous SGP exhibits the equivalent pharmacological activity in an amount of $\frac{1}{2}$ - $\frac{1}{4}$ of the crystalline SGP". The applicants' invention is for such amorphous SGP and claim 1 reads:-

"Amorphous steryl glucoside palmitates (SGP) as hereinbefore defined."

The remainder of the claims are concerned with two distinct methods of preparing this material. Thus according to Claim 2, amorphous SGP is prepared by heating the crystalline variety above 110°C, but below the decomposition temperature, the preferred range being 125 to 145°C (Claim 3); whereas in Claim 4 amorphous SGP is obtained by dissolving crystalline SGP in an organic solvent and then evaporating the solution, eg by distillation, spray- or freeze-drying (Claim 6). Specified solvents are chloroform, dichloroethane, benzene and hexane (Claim 5) and there are further claims (7 - 10) relating to the use in either process of a mixture of crystalline SGP with a powdered inert organic or inorganic compound. Claim 11 is an omnibus claim linked to the Examples.

In para 5(i) of their counterstatement the applicants admit there is an error in one of the references to Agr. Biol. Chem. in their specification, and with their agents' letter of 28 April 1978 they have filed a printed copy of the specification showing the required correction in red ink. The sole correction requested is the replacement of "Vol 13" by "Vol 30" in the first reference to the said journal. From the context this amendment is clearly allowable and indeed is confirmed by the opponents' Notice, in which the same references have been cited.

PRIOR PUBLICATION

The cited pages 770-778 of Agr. Biol. Chem. (Japan) Vol 30, No 8 (hereinafter Kiribuchi I) comprise an article entitled "Separation of Soybean Sterols by Florisil Chromatography and Characterization of Acylated Steryl Glycoside". The article is adequately summarized in the abstract preceding it which reads:-

"Florisil column chromatography was demonstrated to be effective in differentiation between different forms of sterols. Sterols of ground soybeans are in four forms, free, ester, and free and acylated glucosides, as analyzed on acetone extracts. In soybean oil foots, steryl ester is present in negligibly small amount. The acylated steryl glucosides were isolated from oil

foots in a crystalline state. A chemical structure, steryl 6-acyl D-glucoside, was assigned to the compound, and its probable identity with the glucosides reported by Lepage is discussed. The acylated glucoside preparation was shown to be heterogeneous in composition, carrying palmitic, stearic, oleic, linoleic and linolenic acids as the main acyl moieties and campesterol, stigmasterol and β-sitosterol as steryl moieties. The presence of the three sterols is common to three other forms of sterols".

On page 775 under the heading "Characterization and Structural Determination of the Acylated Steryl Glucosides" there occurs the passage:-

"The acylated steryl glucoside fractions obtained from ten batches of eluate from the Florisil chromatography of the acetone extracts of soybean oil foots were combined to yield 4.68 g of the crude preparation. After five recrystallizations from acetone, 2.83 g of colorless crystalline plates were obtained". The melting point of this product was 130 - 150°C.

On page 776, reference is made to the alkaline hydrolysis of the crystalline acylated steryl glucosides and a gas chromatogram of their fatty acid components shows 42.7% of the fatty acids to be palmitic acid.

The cited pages 1244-1247 of Agr. Biol. Chem. (Japan), Vol 31, No 10 (hereinafter Kiribuchi II) comprise an article entitled "Synthesis of 6-O-Palmitoyl-β-D-Glucosyl β-Sitosterol". The article confirms that β-sitosterol and palmitic acid have been shown to be the major components in soybean steryl 6-acyl-D-glucoside then goes on to describe the title synthesis. The last step of this synthesis is given in the passage common to pages 1245 and 1246 and reads "To 826 mg of β-sitosteryl β-D-glucoside dissolved in dry pyridine, 400 mg of palmitoyl chloride in dry benzene was added dropwise, and the mixture was kept standing for 3 hours at room temperature. After acidification with diluted sulfuric acid the reaction mixture was extracted with chloroform. The chloroform layer was washed twice with water and evaporated in vacuo". Then after describing how a small portion of the residue, which is shown to be a mixture of mono-, di- and tetra- palmitates, the monoester predominating, was subjected to thin layer chromatography, it says "The monopalmitate was isolated from the main portion of the residue by Florisil chromatography; yield, 250 mg. Recrystallization from acetone gave 145 mg of pure monopalmitoyl-glucosyl β-sitosterol. By periodate oxidation, it was confirmed that the palmitoyl residue was linked to C-6 of the glucose moiety."

UK Specification 1298047 (hereinafter 047), published in November 1972, discloses

a therapeutic composition comprising either a glycoside or glycoside ester of β-sitosterol and a carrier. The specific disclosure of glycosides and glycoside esters is limited to β-sitosterol-β-D-glucoside and its tetra-acetate. In Example 3 it is stated "The β-sitosterol glucoside (sterolin) or its esters may be introduced into foodstuffs in any possible manner, preferably in as fine a form as possible so as to enhance its absorbability. The concentration of the compounds depends on their state of dispersion (mono-molecular or molecular aggregates of any size of either an amorphous or crystalline nature). The coarser or more crystalline the particle size, the less effectively is the sterolin or its esters absorbed," and then, later, "The substances may be added as a finely divided, preferably amorphous, powder ....."

At the hearing Mr Laddie largely confined his remarks on prior publication, and indeed on obviousness, to the cited UK specification, and I will therefore consider this document first.

The opponents' sole witness, Dr K H Pegel, a senior lecturer in chemistry at the University of Natal, and the inventor of 047, says in paragraph 5 of his first affidavit that a common ester in the field of organic pharmaceutical chemistry and particularly steroid chemistry is the palmitate, and that a person in this art, on reading a publication which refers to esters, would automatically consider palmitates as falling under the generic term "esters". In reply, Mr M Kawamata, a senior manager in the pharmaceutical department of the applicant company and a co-inventor of the invention in suit, responds in paragraph 4 of his first affidavit by citing the British Pharmacopoeia, in which no palmitate is included among the 22 steroid esters mentioned and he contends that the assertion that the term "ester" indicates "palmitate" is nothing but an arbitrary decision, pointing out that the only steryl glucoside ester described in 047 is the tetra-acetate. This is undoubtedly so and I do not find anything in 047 which leads me to believe that the informed reader of that specification would be clearly directed to palmitates when encountering the various references to "esters".

In his address, Mr Laddie took the argument a stage further in referring to E I Du Pont de Nemours & Co (Witsiepe's) application (1982) FSR 303. Basing himself on the House of Lords' judgement in that case, he contended that there was no suggestion that the particular esters selected by the applicants had been made or used and no suggestion of the advantages they allege for amorphous SGP. In any event, even on pre-"Du Pont" law, there was no anticipation by reason of 047. I fully accept this argument. As indicated above, the only specific

reference to an ester in the cited document is that to a tetra-acetate and I do not see that the disclosure of 047 could constitute a prior publication of the mono-palmitate ester, irrespective of the particular physical form presently under consideration.

Regarding the two Kiribuchi citations, I was invited by Mr Laddie to dismiss them out of hand, but this I am unable to do, since they are both concerned with SGP as the specification in suit clearly acknowledges, and the question to be asked is whether they disclose the applicants' amorphous SGP.

In Kiribuchi I, it is manifest from the Abstract, quoted earlier, that the acylated steryl glucosides are isolated in a crystalline state and this is confirmed in the experimental section (page 775), which refers to acetone extraction and chromatography of soybean oil foots followed by recrystallisation of the combined acylated steryl glucoside fractions using the same solvent. There is no indication in the article that SGP could exist in an alternative form.

Again in Kiribuchi II, the opening sentence "Acylated steryl glucosides have been isolated from soybean oil foots in a crystalline state ....." sets the picture, and in the synthesis described on pages 1245-6 6-O-palmitoyl-β-D-glucosyl-β-sitosterol (one of the applicants' SGP) is isolated by chromatography and recrystallised from acetone. In neither paper do I perceive any clear and unmistakeable directions to produce an amorphous variety of SGP, and it would seem that Dr Pegel appreciated the opponents' difficulty in this respect, since in his second affidavit he makes some attempt to show that the applicants' own SGP may not be amorphous, but another crystalline form. Thus in paragraph 11 he is surprised that Mr Kawamata did not support his statement concerning their amorphous nature by reference to X-ray diffraction pictures. In response, Mr Kawamata provides such X-ray data in his Rule 43 evidence. There has been no formal rebuttal of this evidence and because the opponents elected not to be represented at the hearing I have nothing before me to suggest that Mr Kawamata's evidence might not be conclusive, and I therefore dismiss this aspect of the opponents' case.

Thus I conclude that there is no prior publication of the invention claimed in any of the claims of the application in suit by reason of UK specification 1298047 or the Kiribuchi documents.

OBVIOUSNESS

The opponents' case, as I understand it, is that since crystalline SGP is a

known material and various methods for preparing amorphous products closely related to SGP are known. and in addition the pharmacological superiority, from the point of view of absorption into the digestive tract, of amorphous over crystalline products closely related to SGP is also recognised, it would be obvious to prepare and use amorphous SGP.

At the hearing, after reminding me that the standard for assessing obviousness in these proceedings was equivalent to "clearly obvious", Mr Laddie stressed the advantage achieved by the applicants' invention, namely the large increase per unit weight in pharmacological activity shown by amorphous SGP over the crystalline form. According to the Examples of the specification in suit, an activity equivalent to that of the crystalline form is exhibited by the amorphous variety when used in amounts varying from one half to an eighth of the former.

The same three documents cited as prior publications form the basis for the opponents' attack. The two Kiribuchi papers, published in 1966 and 1967 respectively. deal principally with the structure elucidation and the synthesis of 6-O-palmitoyl-β-D-glucoside and related substances. The papers are not concerned with the industrial or medical application of these compounds and, as indicated earlier, there is no suggestion or pointer in either regarding amorphous forms. The opponents have not supported their allegation here with expert testimony, and in consequence I do not find that they have established a prima facie case on obviousness which necessitates further consideration.

There remains 047, and it will be recalled that the disclosure relates to β-sitosteryl glycosides and their esters generally. There are no grounds for a mosaic with the Kiribuchi documents, and putting it at its highest, the case on 047 seems to reside in the passages quoted earlier from Example 3, which indicate firstly, that irrespective of whether it is amorphous or crystalline, as fine a form as possible is preferred so as to enhance absorbability of the sterolin (β-sitosterol glucoside) or its esters; and secondly, that the active material is added as a finely-divided, preferably amorphous powder, or in the form of a hot concentrated solution in ethanol or as an emulsion. Thus, the use of an amorphous powder is only one of several alternatives, and the emphasis is upon the state of sub-division rather than the particular physical form.

A study of the specification as a whole shows that it is concerned almost exclusively with sterolin itself, the only specified ester being the tetra-acetate in Example 5 and there is no further reference to the use of amorphous material. In passing, it is to be observed that there seems to have been no

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specific attempt by the inventor of 047, Dr Pegel himself, to prepare an amorphous version of either β-sitosterol β-D-glucoside or its tetra-acetate.

In his evidence for the opponents Dr Pegel quotes from two other specifications, his own UK 1365661 published in 1974 and an earlier German Patentschrift 1031933, but neither of these is formally cited and, having studied them I can find in neither clear support for the view that at the relevant date it was common knowledge in the art to which the applicants' specification relates that an amorphous sterol glycoside or an ester thereof would have greater solubility than a corresponding crystalline version and therefore greater absorption into the digestive tract. The German Patent not only relates to cardenolide glycosides rather than sterol glycosides but also, as a perusal of the whole document, rather than a selection of isolated passages quoted by the witness, seems to show, it is dealing with the somewhat specialized case of making solid solutions of the glycosides or their genins with other substances, and it is the presence of these other substances which increases the absorbability rather than the form of the glycosides or genins themselves.

When looking at UK 1365661, I note that at lines 19-30 on page 1 it says "The intermolecular bonding forces in either crystalline or amorphous glycoside aggregates make the abstraction of single molecules prior to any biological utilisation very difficult if not impossible. Thus for maximum utilisation and effectiveness these glycosides must or should be presented in monomolecular dispersed forms. It is, therefore, important to break up molecular aggregates to sterol or steroid glycosides and distribute them in a medium as isolated units or in continuous monolayers." This passage does not appear to tie up completely with Dr Pegel's own conclusions and certainly does not suggest to me the superior absorbability of an amorphous over a crystalline product.

Before leaving the matter of obviousness, it is observed that Mr Kawamata in his first affidavit asserts that polymorphism (in the applicants' sense) is a physical property not common to steroid glucoside or aglycon thereof, and that crystalline β-sitosterol β-D-glucoside when subjected to the solvent/ evaporation treatment is recovered unchanged. Dr Pegel does not disagree with the first statement though he does say that if a particular compound is capable of existing in an amorphous form it will be easier to obtain it in such form if the molecule is made more complex, by derivatization, eg by the addition of a long ester chain. It has not been made plain that this information was in the realm of public general knowledge at the relevant time, but if the notional skilled worker was aware of it, he would I think find little encouragement to consider an amorphous form of SGP, the chances of whose existence at all,

particularly if he knew that the facts concerning β-sitosterol β-D-glucoside, would have appeared to be somewhat unlikely.

To my mind, the opponents have failed to demonstrate that any of their citations form a satisfactory basis from which a man skilled in the art, if faced with the applicants' problem, would be led by the teaching to contemplate the amorphous form of SGP.

INSUFFICIENCY

There are six limbs to the opponents' attack of insufficiency. The first is that there is inaccuracy in the reference to Agr. Biol. Chem. in the specification and that the alleged invention is not adequately differentiated from the disclosures in the Agr. Biol. Chem. articles. The proposed red ink amendment disposes of the inaccuracy point and in view of my rejection of the allegation of prior publication based on these articles I do not find the other matter to be of any substance.

The second limb is that the review of the prior art in the specification is misleading and incomplete, and should include a reference to the cited UK 1298047. In my opinion such a reference is not required. I do not think it can be said that the applicants' invention cannot be performed without there being a substantial risk of infringement of any of the claims of 1298047 and a Section 9 type reference would not therefore appear to be necessary, and there is no other reason that warrants an acknowledgement of the cited patent.

The third limb is that the term "polymorphism" is inaccurate when used to describe the property of a substance which can be crystalline or amorphous. On page 340 of the Science Dictionary published 1965 by Evans Brothers Limited (Exhibit KHP2 to Dr Pegel's second affidavit) "Polymorphism" is defined as "The property of certain chemical substances of CRYSTALLIZING in two or more different ways, forming substances which are seemingly different." On a strict interpretation of the term, I accept that this is so; however, I do not consider that in the present specification, particularly given the passage on page 1 lines 66-72 of the printed version, the applicants' use of the term gives rise to any ambiguity and accordingly I find that no action is called for.

The fourth limb is that the passage at lines 80-82 on page 1 of the specification, which reads "Accordingly the present invention is amorphous steryl glucoside palmitates (SGP) as hereinbefore defined" is misleading. because there is no previous definition of what is meant by "amorphous steryl glucoside palmitates"

I reject this attack, because at lines 17-22 on the same page already quoted, the applicants in my view clearly define what they mean by SGP, and "amorphous" must be taken to have its dictionary definition of a non-crystalline form.

The penultimate allegation of insufficiency is concerned with the passage at lines 72-79 on page 1 of the specification in suit, which reads "Amorphous SGP obtained according to the process embodiments of the present invention is in the form of glassy blocks or is in resinous form. Both forms must be pulverized before processing them into preparations but mechanical pulverization of them is difficult because of their high coherence". The opponents say that the specification gives no directions as to how this pulverization problem has been solved. In Example 1 the semi-transparent glassy amorphous product is "pulverized by a suitable method". I do not regard this as a serious defect in the specification, particularly since pulverization is not a characteristic feature of the invention as claimed. Pulverization is not said to be impossible, merely difficult. Perhaps this is "know-how" that the applicants have withheld, but I cannot see how its absence can amount to insufficiency. In the other examples it would appear that the product can be used directly in pharmacological tests and there would appear to be no insufficiency in this respect.

The final allegation is that the meaning of "different" at page 5, line 11, is wholly ambiguous. The passage in which this word occurs reads "Fig 6 is differential thermal analysis chart of crystalline steryl glucoside monopalmitate. Figs 7, 8, 9 and 10 are different thermal analysis charts of the amorphous products obtained by the present invention." (emphasis added). It appears to me that the word should be "differential", and perusal of the original specification indeed confirms that this is so, "different" having resulted from a printers' error.

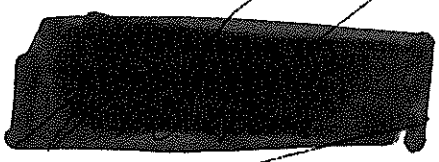
In the result, therefore, I find that the opponents have not succeeded on any of the grounds they have advanced and accordingly the opposition is dismissed. I direct that the application be amended in the manner proposed by the applicants and shown in red ink in the printed copy of the specification accompanying this decision.

As regards the question of costs, Mr Laddie drew attention to the great expense and inconvenience to which the applicants had been put, firstly, because of the opponents' failure to respond to the Rule 43 evidence submitted by Mr Kawamata on 2 June 1980 and the resulting delay in bringing the issue to a hearing and secondly, because of their failure not only to attend the hearing but also to make clear until very shortly beforehand whether it was their intention to withdraw

or merely not be represented.

In making an award of costs I have taken these circumstances into account and I award the applicants (Nippon Shinyaku Company Limited) the sum of six hundred pounds (£600) towards their costs in these proceedings and direct that this sum be paid to them by the opponents, Essential Sterolin Products (Pty) Limited.

Dated this 10th day of January 1983



N B DEAN

Superintending Examiner, acting for the Comptroller

PATENT OFFICE