

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte DAVID F. WOODWARD and GYORGY AMBRUS

Appeal 2008-4070
Application 10/136,240
Technology Center 1600

Decided: September 12, 2008

Before TONI R. SCHEINER, ERIC GRIMES, and FRANCISCO C.
PRATS, *Administrative Patent Judges*.

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DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a liquid composition containing a cationic therapeutic component in an ion-pair complex with an efficacy enhancing component. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

Claims 1, 3, 7-11, 13, 16, 17, 19, 20, 22, 25-28, and 40 are pending and on appeal (App. Br. 5). Claims 1, 11, 20, and 40 are the appealed independent claims. Claim 20 is representative and reads as follows:

20. A liquid composition comprising:
an ophthalmically acceptable cationic therapeutic component selected from the group consisting of NMDA antagonists, antibacterials, antihistamines, decongestants, antiinflammatories, antiparasitics, miotics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics, and mixtures thereof
provided in a therapeutically effective amount; and
an efficacy enhancing component having one, two, or three negative charges provided in an amount greater than 0.2% (w/v) and less than about 10% (w/v) and being effective to enhance the pharmacokinetic disposition of the therapeutic component, to enhance the movement of the therapeutic component across a lipid membrane, or a biological membrane under physiological conditions, and to enhance the permeability of the therapeutic component, from about 80% to about 100% of the therapeutic component present in complex with the efficacy enhancing component, the efficacy enhancing component being present in an ion-pair complex with the therapeutic component so that a ratio of electrical charge from the efficacy enhancing component to electrical charge from the therapeutic component is at least about 1:1 the complex remaining substantially intact in an aqueous environment, and each of the enhanced effects being relative to the effect obtained with the therapeutic component without the efficacy enhancing component.

Claims 1, 3, 7-11, 13, 16, 17, 19, 20, 22, 25-28, and 40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Maurer¹ (Ans. 3-6).²

OBVIOUSNESS

ISSUE

The Examiner cites Maurer as disclosing “a quinoxaline containing composition and the composition comprises [a] pharmaceutically acceptable carrier such as hydroxypropylmethyl cellulose, sodium chloride (Example 6). Hydroxypropylmethyl cellulose is a non-ionic polymer and meets the limitation of efficacy enhancer and solubilizer in claims 1, 11, 16, 20, 25 and 40” (Ans. 3). The Examiner points out that the “quinoxaline compounds are formulated as compositions containing pharmaceutically acceptable carriers (column 8, lines 46-60) and the carriers suitable for the quinoxaline compositions” include stearic acid (*id.* at 3-4 (citing Maurer, col. 8, l. 62, through col. 9, l. 9)).

Based on these teachings, the Examiner finds that “[t]he quinoxaline, an N-methyl-D-aspartate (NMDA) antagonist meets the limitation of NMDA antagonist recited in the amended claims 1, 11, 20 and 40 and claims 3, 13, and 22” (*id.* at 4). The Examiner also finds that “[s]tearic acid, a fatty acid, having one carboxylic acid group and hydroxypropylmethyl cellulose meet the limitation of the efficacy-enhancing component” (*id.*). The

¹ U.S. Patent No. 5,834,470, issued Nov. 10, 1998.

² The Examiner’s Answer also contains a provisional obviousness-type double patenting rejection over certain claims of Application Serial No. 09/847,935 (Ans. 6-7). Our review of that application, however, indicates that the conflicting application was abandoned on July 11, 2008. The provisional double patenting rejection is therefore moot, and will not be discussed further.

Examiner reasons that the claimed ion-pair complex “reads on a mixture containing a therapeutic agent and efficacy enhancing component and specifically, the instant specification does not teach how such a complex is formed except that it appears to be formed by bringing the TC [(therapeutic component)] and EEC [(efficacy enhancing component)] in a solution” (*id.*).

The Examiner concedes that, while Maurer’s composition contains an efficacy enhancing component and a quinoxaline therapeutic component, Maurer does not disclose the molar ratio of the two ingredients (*id.* at 5). However, the Examiner contends, “since an ion-pair complex forms between the therapeutic component (TC) and the efficacy enhancing component (EEC) by combining the EEC and the TC, it flows that a certain amount of TC combines with a certain amount of the EEC” (*id.*).

Thus, the Examiner contends, the disclosed ingredients when combined would have yielded the claimed molar ratio of therapeutic component to efficacy enhancing component because the “claims broadly claim a large number of classes of therapeutic components, [including] the class of NMDA antagonists [which] reads on the quinoxaline of Maurer. Secondly, the efficacy enhancing component has one, two or three negative charges and read[s on] hydroxypropylmethyl cellulose or stearic acid” (*id.*).

Specifically, the Examiner contends, “the stearic acid which has one anionic charge would combine with one cationic drug in a 1:1 ratio; the hydroxypropylmethyl cellulose having three negative charges would combine with a cationic drug that has one cationic side/end” (*id.* at 5-6). The Examiner concludes that “[i]t therefore flows that [the claimed] molar ratio combination between the cationic drug and the EEC would be obvious” (*id.* at 6).

Appellants contend that the Examiner has not established a prima facie case of obviousness because the hydroxypropylmethyl cellulose used in Maurer's compositions is not an anionic compound capable of complexing with the quinoxaline in those compositions (*see* App. Br. 16), and because the stearic acid used in Maurer's compositions is only used in solid compositions, not liquid compositions as recited in the claims on appeal (*see id.* at 17).

The issue with respect to the obviousness rejection, therefore, is whether the Examiner has made a prima facie case that one of ordinary skill in the art would have considered claims 1, 3, 7-11, 13, 16, 17, 19, 20, 22, 25-28, and 40 obvious in view of Maurer.

FINDINGS OF FACT

1. Maurer discloses "substituted 6-(2-imidazolinylamino)quinoxaline compounds. The compounds have been found to be selective alpha-2 adrenoceptor agonists and are useful for treatment of one or more of respiratory disorders, particularly nasal congestion; ocular disorders, particularly glaucoma; and gastrointestinal disorders, particularly diarrhea" (Maurer, col. 1, ll. 9-15).

2. With respect to suitable carriers for its therapeutic compounds, Maurer discloses:

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; *solid lubricants, such as stearic acid* and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols

such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

(Maurer, col. 8, l. 61, through col. 9, l. 9 (emphasis added).)

3. Maurer discloses that tablets containing its therapeutic compounds “typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc” (Maurer, col. 9, ll. 29-34).

4. Example 3 of Maurer discloses a tablet that contains stearic acid (Maurer, col. 12, ll. 24-39).

5. Appellants state, and the Examiner does not dispute, that “stearic acid has a melting temperature of 69.6 °C (157.3 °F)” (App. Br. 19).

6. Maurer discloses that sublingual and buccal dosage forms of compositions containing its therapeutic compounds “typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose” (Maurer, col. 9, l. 65, through col. 10, l. 2).

7. Example 6 of Maurer discloses an intranasal gel composition that contains hydroxypropyl methylcellulose (Maurer, col. 13, ll. 1-16).

8. In finding that Maurer disclosed compositions having the nonionic solubilizer recited in claim 7, the Examiner found that “[h]ydroxypropylmethyl cellulose is a non-ionic polymer” (Ans. 3).
9. In describing compounds useful as solubilizers, the Specification states “[e]xamples of nonionic solubilizer components include, without limitation, poly(oxyethylene)- poly(oxypropylene) block polymers, polysorbate 80, polyvinyl alcohol, polyvinylpyrrolidone, *hydroxypropylmethyl cellulose* and the like and mixtures thereof” (Spec. 23 (emphasis added)).
10. In describing compounds useful as efficacy enhancing agents, the Specification states “[e]xamples of anionic polymers which may have multiple anionic charges include: . . .

cellulose derivatives:

carboxymethylcelluloses

metal carboxymethylhydroxyethylcelluloses

hydroxypropylmethylcelluloses”

(Spec. 16-17.)

PRINCIPLES OF LAW

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. “[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.”

In re Fritch, 972 F.2d 1260, 1265 (Fed. Cir. 1992) (citations omitted, bracketed material in original). Furthermore, “[e]ven when obviousness is based on a single prior art reference, there must be a showing of a suggestion

or motivation to modify the teachings of that reference.” *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000).

Thus, as the Supreme Court recently pointed out:

[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007).

When evaluating claims for obviousness, “the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill.” *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). Moreover, “[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.” *Id.* (quoting *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965)). The test of obviousness, therefore, is “whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention.” *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991).

ANALYSIS

We agree with Appellants that the Examiner has not made a prima facie case that one of ordinary skill in the art would have considered the rejected claims obvious in view of Maurer.

Each of independent claims 1, 11, and 20, recites a liquid composition that contains a cationic therapeutic component and an efficacy enhancing

component that contains one, two, or three negative charges. Independent claim 40 recites a liquid composition that contains a cationic therapeutic component and an efficacy enhancing component that contains a fatty acid.

We agree with the Examiner that stearic acid is a fatty acid that has a single negative charge, and that Maurer discloses stearic acid as a suitable carrier for its therapeutic quinoxaline compounds (*see* FF 2, 3). However, we do not agree with the Examiner that one of ordinary skill in the art would have been prompted by Maurer to combine stearic acid with the disclosed quinoxaline compounds when making a liquid composition, as recited in the appealed claims.

Specifically, Maurer discloses stearic acid as a “solid lubricant[]” (Maurer, col. 8, l. 67 (FF 2)) that is used as an adjuvant ingredient when making tablets (FF 3, 4). Maurer does not include stearic acid in any liquid formulations. Moreover, as Appellants point out, and the Examiner does not dispute, stearic acid has a relatively high melting point of 69.6 °C (157.3 °F) (*see* FF 5). We therefore agree with Appellants that Maurer does not provide a teaching that would have suggested to one of ordinary skill that it would be suitable or desirable to prepare a liquid formulation that contains stearic acid in combination with a quinoxaline compound, as recited in the appealed claims.

The Examiner argues that the claims do not exclude meltable compounds, and that “substances such as stearic acid, though having a melting point 160 °F as stated by appellant can be dissolved in suitable solvents for use” (Ans. 9). The Examiner also argues that “Appellant’s contention about the melting point of stearic acid would also apply to appellant’s use of fatty acids in composition of claim 16. It is also noted that

appellant's specification at page 14, line 23 names stearic acid as a fatty acid" (*id.* at 9-10).

We are not persuaded by these arguments. The Examiner does not point to any teaching in Maurer suggesting that it would be suitable or desirable to provide the disclosed compositions at a temperature that would be sufficient to melt stearic acid. Moreover, while it may be true that compounds such as stearic acid can be converted to a liquid form at lower temperatures given the appropriate solvent, the Examiner has not explained where or why Maurer would have suggested to one of ordinary skill that it would be desirable to convert Maurer's stearic acid carrier to a liquid form using a solvent.

We therefore do not agree with the Examiner that one of ordinary skill would have been prompted to include stearic acid in the liquid formulations of Maurer. The Examiner points to no other teaching or suggestion in Maurer of combining its quinoxaline compounds with a fatty acid in a liquid composition, as required by claim 40. We therefore reverse the Examiner's rejection of claim 40 as obvious over Maurer.

With respect to independent claims 1, 11, and 20, the Examiner urges that Maurer's hydroxypropyl methylcellulose (HPMC) meets the limitation requiring the composition to contain an efficacy enhancing ingredient that has one, two, or three, negative charges (Ans. 7-8). Specifically, the Examiner urges that HPMC must meet that limitation because it is listed in the Specification at pages 16-17 (FF 10) as being an efficacy enhancing component that has multiple anionic charges (*id.*).

We are not persuaded by this argument. We note that the Specification lists "hydroxypropylmethylcelluloses" among "cellulose

derivatives” that “may have *multiple* anionic charges” (Spec. 16-17 (FF 10) (emphasis added)). However, claims 1, 11, and 20 each require the efficacy enhancing component to have one, two, or three negative charges.

The Examiner has not explained how the Specification’s inclusion of hydroxypropyl methylcelluloses in a group of derivatives that may have multiple anionic charges demonstrates that one of ordinary skill would have recognized that Maurer’s hydroxypropyl methylcellulose necessarily has one, two, or three negative charges.

Rather, when considering the obviousness of the claimed compositions, the Examiner explicitly states that “[h]ydroxypropylmethyl cellulose is a non-ionic polymer” (Ans. 3 (FF 8)). Moreover, in describing compounds useful as solubilizers, the Specification lists hydroxypropylmethyl cellulose as being a “nonionic solubilizer” (Spec. 23 (FF 9)). In our view, the most reasonable reading of the Specification’s characterization of HPMC as nonionic and “hydroxypropylmethyl-celluloses” as cellulose derivatives that “may have multiple charges” is that HPMC itself is nonionic but derivatives of hydroxypropylmethylcellulose (i.e., “hydroxypropylmethylcelluloses”) can have multiple anionic charges. The Examiner has not explained why one of ordinary skill viewing Maurer would have considered it obvious to use a hydroxypropyl methylcellulose derivative having one, two, or three negative charges in Maurer’s compositions.

Given these facts, we find that a preponderance of the evidence does not support the Examiner’s assertion that hydroxypropyl methylcellulose meets the limitation in claims 1, 11, and 20 requiring an efficacy enhancing component with one, two, or three negative charges. Moreover, as discussed

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above, we do not agree with the Examiner that one of ordinary skill viewing Maurer would have considered it obvious to include stearic acid in the liquid composition of claims 1, 11, and 20. We therefore reverse the Examiner's rejection of claims 1, 11, and 20, and their dependent claims 3, 7-10, 13, 16, 17, 19, 22, and 25-28, as being obvious over Maurer.

SUMMARY

We reverse the Examiner's rejection of claims 1, 3, 7-11, 13, 16, 17, 19, 20, 22, 25-28, and 40 under 35 U.S.C. 103(a) as being unpatentable over Maurer.

REVERSED

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