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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KATARINA E. A. LINDELL, ANETTE K. SCHLUTER,
GUNNAR A. BERGENGREN,
and BENGT A. BOSSON

Appeal 2017-004832
Application 13/871,476[1][2]
Technology Center 1600

Before TONI R. SCHEINER, DEMETRA J. MILLS, and JOHN G. NEW, *Administrative Patent Judges.*

MILLS, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a). The Examiner has rejected The pending claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] This application is related to United States applications 11/686,842 (Appeal 2017-001569) and 12/619,851.
[2] According to Appellants, the Real Party in Interest is McNeil AB of Helsingborg, Sweden.

STATEMENT OF CASE

The following claim is representative.

1. A liquid pharmaceutical formulation for use in the treatment of addiction to tobacco or nicotine, comprising:

(i) nicotine in free nicotine base form; and

(ii) a buffering agent,

(iii) the liquid pharmaceutical formulation being adapted for administration to the oral cavity of a subject by spraying, dropping or pipetting, and

(iv) the liquid pharmaceutical formulation being adapted so as to achieve a tmax of nicotine in venous blood of the subject within from about 3 to about 20 minutes after an incidence of administration of 200 microliters of the liquid pharmaceutical formulation.

Additional claims on appeal are found in the Claims Appendix to the Appeal Brief.

Cited References

Ferno et al. (hereinafter "Ferno")	U.S. 4,579,858	Apr. 1, 1986
Rose et al. (hereinafter "Rose")	U.S. 4,920, 989	May 1, 1990
Prencipe et al. (hereinafter "Prencipe")	U.S. 5,000,944	Mar. 19, 1991
Jones	U.S. 5,656,255	Aug. 12, 1997
Monte	U.S. 5,810,018	Sept. 22, 1998
Von Wielligh	U.S. 6,024,097	Feb. 15, 2000

McCoy et al. WO 00/47203 Aug. 17, 2000
(hereinafter "McCoy")

Harris et al., *Drug Delivery via the MucoU.S. Membranes of the Oral Cavity*, Vol. 81 Number 1, J. PHARMACEUTICAL SCIENCES 1–10 (Jan. 1992). (Hereinafter "Harris").

Tomar et al., *Review of the Evidence that pH is a Determinant of Nicotine Dosage from Oral Use of Smokeless Tobacco*, TOBACCO CONTROL 6:219–225 (1997). (Hereinafter "Tomar").

Richard A. Frazier et al., *Development of a Capillary Electrophoresis Method for the Simultaneous Analysis of Artificial Sweeteners, Preservatives and Colours in Soft Drinks,* JOURNAL OF CHROMATOGRAPHY A, 876, 213–220 (2000). (Hereinafter "Frazier").

Grounds of Rejection

1. Claims 1–3, 5–8, 10, 11, 12, 13, and 15–18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Von Wielligh in view of Rose and Tomar.
2. Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Von Wielligh in view of Rose, Tomar, and Prencipe.
3. Claim 9 is rejected under 35 U.S.C. §103(a) as being unpatentable over Von Wielligh in view of Rose, Tomar, and Jones.
4. Claim 12 is rejected under 35 U.S.C. §103(a) as being unpatentable over Von Wielligh in view of Rose, Tomar, McCoy, Monte, and Frazier.
5. Claims 1–3, 5, 7–10, 12, 13, 17, and 18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Monte and Tomar.

6. Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Monte in view of Tomar and Prencipe.
7. Claims 6 and 11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Monte in view of Tomar, and Rose.
8. Claims 15 and 16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Monte in view of Tomar, and Von Wielligh.
9. Claim 12 is rejected under 35 U.S.C. §103(a) as being unpatentable over Monte, Tomar, McCoy, and Frazier.
10. Claims 1–3, 6, 7, 8, 10, 12, 11, 13, and 17–19 are rejected under 35 U.S.C. §103(a) as being unpatentable over in view of Tomar.
11. Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Rose, Tomar, and Prencipe.
12. Claim 5 is rejected under 35 U.S.C. §103(a) as being unpatentable over Rose, Tomar, and Monte.
13. Claim 9 is rejected under 35 U.S.C. §103(a) as being unpatentable over Rose, Tomar, and Jones.
14. Claim 12 is rejected under 35 U.S.C. §103(a) as being unpatentable over Rose, Tomar, Monte, Frazier, and McCoy.

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Answer at pages 2–43. The following facts are highlighted:

1. Rose teaches a method for delivering nicotine to a subject, the method comprising the steps of administering a liquid pharmaceutical composition comprising nicotine into the oral cavity of a subject by

spraying, i.e., via oral transmucosal delivery without chewing or sucking (Rose, column 16, line 66). Rose does not teach an alkaline pH for the composition or the presence of a buffer in the composition used in the method. Ans. 7.

2. Monte teaches a method for delivering nicotine to a subject, the method comprising: administering a liquid pharmaceutical composition comprising nicotine into the oral cavity of a subject by spraying, dropping or pipetting thereby providing oral transmucosal delivery of nicotine to the subject without chewing or sucking, said composition having an alkaline pH and further comprising one or more buffers present in an amount sufficient to confer sufficient buffering capacity on the composition such that administration of the composition transiently increases the pH of liquid in the oral cavity of said subject by about 0.3 to about 4 pH units and reduces the subject's urge to smoke within 30 minutes of administration by allowing the nicotine to be systematically absorbed by buccal uptake. (Monte, col. 2, 11. 25–30; col. 4, 11. 15–20; col. 5, 11. 39).
3. Monte teaches a concentration of 0–2% for the nicotine but does not teach the spray volume. *Id.* at Col. 3, 11. 50–60; Ans. 20.
4. Rose teaches that for a concentration range similar to that of Monte (i.e., 0.01 %–3%; column 16, line 58 and column 8, line 61), a volume of 0.27 microliters to 300 micro liters is used for the spray because the desired dose of nicotine is 0.008 mg to 0.03 mg per inhalation (Rose, col. 9, 1. 44).
5. Rose teaches nicotine in free base form. *Id.* at Col. 14, 11. 28–30.

6. Monte teaches nicotine in free base form. Monte, Col. 4, Ex. 1.
7. Von Wielligh teaches a method for delivering nicotine to a subject, the method comprising administering a liquid pharmaceutical composition comprising nicotine (Von Wielligh, col. 4, 1. 35) by spray.
8. Tomar teaches that the absorption of nicotine in the oral mucosa is enhanced at alkaline pH (abstract) and that the inclusion of buffering agents (i.e., sodium carbonate and bicarbonate) in nicotine-containing gum chewed orally for nicotine replacement therapy increases the pH of the oral environment and thus facilitates the absorption of nicotine (Tomar, "nicotine replacement studies;" page 223, left column). In particular, Tomar teaches that oral mucosal uptake of nicotine is increased by 30% from pH 7 to pH 9 (*id.*, "human studies," page 222, left column).
9. Prencipe teaches that sodium hydroxide is useful to adjust the pH of a solution for oral use to 8.5, i.e., to an alkaline condition (Prencipe, column 9, lines 43-44).
10. McCoy teaches that poloxamers enhance the oral absorption of pharmaceutical agents by modifying the surface membrane of the oral mucosa (McCoy, abstract).
11. The oral formulation of McCoy "contains the surfactant at 0.1 % to 20% by weight (McCoy, page 7, lines 24-24) and 0.12% sweetener (i.e., about 0.2%. ...)." Final Act. 11.
12. Frazier teaches that the most commonly used artificial sweeteners in soft drinks (i.e., oral compositions) are aspartame, acesulfame k, and saccharin. Frazier, 214, left column.

PRINCIPLES OF LAW

In making our determination, we apply the preponderance of the evidence standard. *See, e.g.*, *Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Moreover, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

Obviousness Rejection

We select claims 1, 4, 5, 6, 9, 12, and 15, as representative claims for purposes of this decision. Appellants do not present separate arguments for each of the 14 grounds of rejection listed above, in the Brief, rather, Appellants appear to group all rejections together in the Appeal Brief and present group arguments that apply to all of the rejections. For expediency and avoidance of redundancy in this Decision, Rejections 1–14, as set forth in the grounds of rejection, are combined, and addressed below. Arguments not shared by all of the rejections, or arguments with respect to individual references will appear separately, in specific paragraphs. Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(iv).

Essentially, Rose, Monte, and Von Wielligh teach liquid formulations of nicotine. FF 1, 2, and 5. Rose and Monte additionally teach that the nicotine may be in the form of a free base. FF 5, 6. The Examiner relies on Tomar for the teaching that it was known in the art to adjust the pH of nicotine to increase its absorption rate. Tomar 222, col. 1.

Appellants contend that the prior art of Jones and Ferno teaches away from the claimed invention. App. Br. 9–11. Appellants argue that Jones expressly taught acidic, not alkaline compositions for nicotine delivery. *Id.* Appellants argue that Ferno mandated use of an acidic nicotine delivery environment over an alkaline one. *Id.* Appellants repeat this argument for each of the combinations of primary references.

The Examiner responds, arguing that the art of record does not teach away from the proposed reference combinations. The Examiner argues that the disclosure of Ferno is limited to nasal administration and that side effects of administration of Ferno's composition include nasal burning and intensive sneezing. Ans. 34. The Examiner argues that Appellants have provided no evidence or reasoning for why this might be the case, or given specific examples of the kind of adverse effects that could actually be expected when orally consuming an alkaline solution. *Id.*

The primary issue before us is: Does the evidence of record teach away from the claimed invention?

ANALYSIS

We agree with, and adopt, the Examiner's fact findings, statement of the rejection and responses to Appellants' arguments as set forth in the

Answer. We find that the Examiner has provided evidence to support a prima facie case of obviousness. We provide the following additional comment to the Examiner's argument set forth in the Final Rejection and Answer.

We are not persuaded by Appellants' arguments that Jones and Ferno teach away from the claimed invention. Appellants have not established with evidence that the nasal symptoms or side effects of acidic nicotine compositions would also be present in the oral cavity with administration of a nicotine composition buffered to pH levels of 8–9. Attorney argument cannot take the place of evidence. *See In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984) (Arguments and conclusions unsupported by factual evidence carry no evidentiary weight). In addition, Tomar indicates that oral delivery of nicotine with increased alkalinity promotes the absorption of nicotine and increases its physiological effects. Tomar further states that, "In a . . . study, Beckett, Gorrod, and Jenner examined the buccal absorption of various tobacco alkaloids and found a strong effect of increased pH on absorption of nicotine—virtually none was absorbed at pH 5.5, about 10% at pH 7, and more than 30% at pH 9." Tomar, p. 222, col. 1. Tomar further suggests the buffering of nicotine with sodium carbonate. Tomar, p. 223, col. 1. One of ordinary skill in the art would have readily recognized under scientific pH principles that more buffering of nicotine would decrease the acidity of nicotine in a formulation, as well alter some of the side effects associated with acidic formulations of nicotine. Moreover, one of ordinary skill in the art would have optimized the result effective variable of pH to balance the nicotine absorption rate with side effects associated with acidic

pH. ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." (citations omitted)). *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

In the present case, "[t]he fact that the motivating benefit comes at the expense of another benefit . . . should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be weighed against one another." *Medichem S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). Therefore, the motivating benefit of increased nicotine absorption at a higher pH would tend to reduce side effects associated with acidic formulations like those of Jones and Ferno. The benefit of increased nicotine absorption would have been weighed against side effects by one of ordinary skill in the art, who desires to find the best formulation balance.

We also find that the Examiner never stated that Jones teaches away from the claimed invention in the manner suggested by Appellants. In the Final Rejection dated June 15, 2015, p. 22, the Examiner stated that Jones was only cited for peak blood nicotine levels occurring around 15 minutes after administration and other references were relied on to teach an alkaline nicotine composition for oral delivery. Final Act. 22-24, 33. We agree with the Examiner and do not find that the Examiner agreed that Jones taught away from the claimed invention.

With respect to Tomar, Appellants argue that none of Tomar's examples address buffered oral nicotine sprays. App. Br. 15. Appellants argue that Tomar does not contemplate liquid formulations that include free base nicotine and a separate buffer. The Examiner responds, arguing that

> Tamar [sic, Tomar] generally teaches that nicotine absorption in mucosal tissue is enhanced at higher pH, which clearly provides motivation to increase the pH of any formulation used to deliver nicotine to the oral mucosa as relied on in the rejection, not only for gum formulations. Appellant has not provided any reasoning or rationale for why the general teaching of Tamar [sic, Tomar] regarding pH sensitivity of nicotine delivery to the oral mucosa would not motivate one of ordinary skill in the art at the time of invention to adjust the pH of an oral spray formulation, which also delivers nicotine to the oral mucosa . . .

Final Act. 30, et. seq.; Tomar, p. 222, col. 1.

Tomar states that, "Beckett and Hossie noted that the oral mucosa behaves similarly to other biological lipoidal membranes relative to its penetration by drugs." Tomar, p. 222, col. 1. The Examiner argues that, Tomar "generally teaches that nicotine absorption in mucosal tissue is enhanced at higher pH; this mechansism [sic, mechanism] is not dependent on the particular dosage form because it depends on the oral pH." Ans. 40. The Examiner relies on Rose and Monte for free base, liquid, nicotine formulations for oral delivery, not Tomar. In addition, Appellants err in attacking the references individually, as the rejection is based on a combination of references. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). The references cannot be read in isolation, but must be read for what they teach in combination with the prior art as a whole. *See id.*

Appellants argue that the Examiner did not honor the well-settled rule, including the rule that "a compound can be patented on the basis of its properties." *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987). Appellants further cite *Ex Parte Vigano*, No. 2010-007666, 2011 WL6960346, *2–3

(BPAI 2011) in support of this proposition. App. Br. 19–20. We are not persuaded by Appellants' argument. We find that the Examiner has established a prima facie case of obviousness on the cited combinations of references, and that the Examiner properly shifted the burden of proof to Appellants to show that the oral, liquid, nicotine formulations of Rose, Monte and Von Wielligh, at the buffered nicotine pH range suggested by Tomar, would have untoward side effects in the oral cavity at the buffered pH ranges of Tomar. Appellants failed to provide such evidence. The evidence of Jones and Ferno is insufficient to show side effects in the oral cavity at the buffered pH range suggested by Tomar.

Appellants argue that the Examiner misinterprets the reference and Appellants' disclosure, and misapplies the doctrine of inherency. App. Br. 19, 22. Appellants argue, in particular, that Figure 3 of

> Rose provides some disclosure related to craving reduction. But (1) that figure relates to the effect of transdermal - *not* oral - administration of nicotine to a subject and (2) that figure shows that transdermal administration of 8 mg of nicotine resulted in a craving reduction of ***less than* 5% *within 30 minutes of administration,*** which is far inferior to appellants' claimed reduction of ***20% within 2 minutes of administration.*** Thus, Rose does not provide any disclosure regarding appellants' claimed craving reduction as a function of time based on oral administration of nicotine.

App. Br. 19.

The Examiner responds arguing,

> it is not necessary for Rose to provide any disclosure regarding appellants' claimed craving reduction as a function of time based on oral administration of nicotine, because these properties would necessarily be associated with performing the method of the rejection. . . . [C]lear and specific motivation is

> provided by Tamar [sic, Tomar] to modify the Rose to arrive at the claimed invention, and thus the elements of the claimed subject matter, i.e., oral nicotine spray and inclusion of a buffer in an oral dosage form to increase oral pH and thereby increase nicotine absorption across the oral mucosa, were known at the time of invention. Because the structure of the obvious composition is substantially identical to that of the claimed composition, it would necessarily have the same properties.

Ans. 55.

Therefore, in this case, obviousness is not predicated on what was not known at the time of invention. We find no misapplication of the principle of inherency.

> *Where ... the claimed and prior art products are identical or substantially identical,* or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product .... Whether the rejection is based on "inherency" under 35 U.S.C. § 102, on "prima facie obviousness" under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d 1252, 1255 (CCPA 1977) (emphasis added.)

The Examiner finds that,

> the composition used in the method of the prior art as applied in the rejection in the instant case is not structurally different from the composition used in the claim method; it has exactly the same active agent in the same amount and it has the same species of buffer considered by Appellant to give rise to the claimed functional properties, i.e., rapid uptake of nicotine.

Ans. 55-56. The Examiner properly shifted the burden of proof to Appellants to show that the liquid nicotine compositions of Rose, Monte and

Von Wielligh, at the pH range of Tomar, would not possess the same craving control reduction as that of claim 35. Appellants did not provide appropriate rebuttal evidence.

Appellants argue that Tomar teaches nicotine gums bound to ion exchange resins and that the nicotine is not in free base form. App. Br. 13.

The Examiner response, that,

> Tamar [sic, Tomar] generally teaches that nicotine absorption in mucosal tissue is enhanced at higher pH, which clearly provides motivation to increase the pH of any formulation used to deliver nicotine to the oral mucosa as relied on in the rejection, not only for gum formulations. Appellant [sic] has not provided any reasoning or rationale for why the general teaching of Tamar [sic, Tomar] regarding pH sensitivity of nicotine delivery to the oral mucosa would not motivate one of ordinary skill in the art at the time of invention to adjust the pH of an oral spray formulation, which also delivers nicotine to the oral mucosa . . . The paragraph of Tamar [sic, Tomar] on page 223, left column, discussing the use of buffers in gums to increase the pH explicitly concludes with "The experiments confirmed that the pH of the oral environment, and not merely rinsing, can control the absorption of nicotine through the oral mucosa." Given this explicit statement (and the fact that the entire reference of Tamar is about absorption of nicotine and not about release of nicotine from a matrix), it is clear that Tamar [sic, Tomar] is actually referring to the use of buffers in the gum to increase salivary pH ("nicotine gum buffered with sodium bicarbonate and bicarbonate to increase salivary pH level" from the same paragraph of page 223, left column) to enhance absorption across the oral mucosa, and not to release nicotine from an exchange resin.

Ans. 40.

We find that the Examiner has the better argument, and agree with the Examiner that one of ordinary skill in the art would read

Tomar to describe the generic principle that the pH sensitivity of nicotine affects nicotine absorption when delivered to the oral mucosa. This disclosure in Tomar provides motivation to one of ordinary skill in the art to buffer nicotine administered to the oral mucosa.

Appellants' Brief provides no comment or analysis of the Frazier, Prencipe, or McCoy cited references, or of the separate 14 rejections as set forth in the grounds of rejection. Unargued rejections are summarily affirmed. Furthermore, "[T]he reply brief [is not] an opportunity to make arguments that could have been made in the principal brief on appeal to rebut the Examiner's rejections, but were not"); *see also* 37 C.F.R. § 41.67(c)(vii) ("Any arguments *or authorities* not included in the [Appeal] brief … will be refused consideration by the Board"), *see Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (Informative) ((emphasis added); *and* 37 C.F.R. § 41.41(b) (A reply brief shall not include any new or non-admitted amendment, or *any new or non-admitted affidavit or other Evidence*) (emphasis added). Arguments not made are waived.

CONCLUSION OF LAW

The cited references support the Examiner's obviousness rejections, which are affirmed for the reasons of record. All pending, rejected claims fall.

AFFIRMED