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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte KARL-HEINZ WOELLER, LUDGER KOLBE, CATHRIN SCHERNER, and RAINER WOLBER

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Appeal 2020-000492
Application[1] 15/641,451
Technology Center 1600

_____

Before DONALD E. ADAMS, JOHN E. SCHNEIDER, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating a local pigmentation disorder by applying a self-adhesive transdermal therapeutic system to affected skin, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

Melanin "brings about a more or less pronounced brownish to brown-black skin color." (Spec. 1.) "Problems with hyperpigmentation of the skin

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Beiersdorf AG. (Appeal Br. 3.)

have a wide variety of causes and/or are accompanying phenomena of many biological processes." (*Id.* at 2.) Active ingredients and preparations which counteract skin pigmentation are known. (*Id.* at 3.) 4-n-Butylresorcinol is known to inhibit the production of melanin. However, the compound itself "has a tendency to discolor - and to discolor cosmetic or dermatological preparations comprising it." (*Id.* at 4.) Appellant's invention is directed to a system to deliver 4-n-butylresorcinol transdermally and "provide remedies for the disadvantages of the prior art." (*Id.*)

Claims 21 and 26–40 are on appeal. Claim 21 is representative and reads as follows:

> 21. A method for the treatment of a local pigmentation disorder, wherein the method comprises applying to skin affected by the disorder a transdermal therapeutic system, which comprises 4-n-butylresorcinol as an active ingredient, the transdermal therapeutic system being employed in the form of a matrix system selected from nonpolar matrices based on synthetic and natural rubber, polar wet adhesive films based on polyacrylic acid/polyvinyl alcohol, nonpolar matrices based on polyacrylic acid copolymers, polar anhydrous gel matrices based on polyacrylic acid/polyvinylpyrrolidone, nonpolar polyisobutylene matrices and polar water gel matrices based on agar agar/polyacrylic acid.

(Appeal Br. 17.)

The prior art relied upon by the Examiner is:

Name	Reference	Date
Torihara et al.	US 4,959,393	Sept. 25, 1990
Wang et al.	US 5,508,038	Apr. 16, 1996
Woeller et al.	US 2005/0281881 A1	Dec. 22, 2005
L. Panigrahi et al., *The Effect of pH and Organic Ester Penetration Enhancers on Skin Permeation Kinetics of Terbutaline Sulfate From Pseudolatex-Type Transdermal Delivery Systems Through Mouse and Human Cadaver Skins*, 6(2) AAPS PharmSciTech E167–173 (2005)		

The following grounds of rejection by the Examiner are before us on review:

Claims 21, 26, 28–35, and 38–40 under 35 U.S.C. § 103(a) as unpatentable over Torihara and Wang.

Claims 21, 27, 28, and 29 under 35 U.S.C. § 103(a) as unpatentable over Torihara and Woeller.

Claims 36 and 37 under 35 U.S.C. § 103(a) as unpatentable over Torihara, Woeller, and Panigrahi.

Claims 29–40 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1–19 of U.S. Patent No. 9,801,971.[2]

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[2] Appellant argues that "[t]his rejection is not presented for review" and does not otherwise respond to the merits of the rejection. (Appeal Br. 15.) We note that the rejection has not been withdrawn by the Examiner in the Answer and conclude that Appellant has waived any argument as to the merits of the rejection. Consequently, we summarily affirm the Examiner's obviousness-type double patenting rejection. MPEP § 1205.02 ("If a ground of rejection stated by the examiner is not addressed in the appellant's brief, appellant has waived any challenge to that ground of rejection and the Board may summarily sustain it, unless the examiner subsequently withdrew the rejection in the examiner's answer.")

DISCUSSION

Obviousness: Torihara and Wang

The Examiner notes that Torihara states "there is a strong demand for agents which enable acquired deposition sites, such as spots or freckles, to be restored to a normal skin color." (Final Action 4 (emphasis omitted).) The Examiner finds that Torihara discloses 4-n-butylresorcinol is a skin depigmental agent for topical application and that it can be used along with any cosmetic base ordinarily used for skin depigmental agents. (*Id.*) The Examiner further finds that Torihara teaches "that the amount of the resorcinol derivative is in the range of from 0.01 wt% to 15 wt% of the total amount of a cosmetic composition." (*Id.*) The Examiner recognizes that Torihara does not expressly teach that the resorcinol derivative is placed in a matrix as claimed for topical application. (*Id.*) However, the Examiner finds that such would have been obvious in light of the teachings of Wang.

The Examiner finds that Wang teaches polyisobutylene (PIB) adhesives useful in transdermal drug delivery systems, and that the thickness of the adhesive layer will generally be between 0.0254 mm and 0.381 mm when used with a rate-controlling membrane. (*Id.* at 5.) The Examiner further finds that Wang teaches "that the composition and thickness of the adhesive layer will be adjusted so that the adhesive layer does not constitute a significant permeation barrier to the passage of the agent to be delivered as compared to that of the rate-controlling membrane." (*Id.*)

The Examiner concludes that one of ordinary skill in the art to would have been motivated to combine Wang with Torihara to take advantage of transdermal active agent delivery. (*Id.*) The Examiner also concludes that there would have been a reasonable expectation that the PIB based system of

Wang could be used with 4-n-butylresorcinol given that the "LogP, a parameter measuring polarity data of active agents" of 4-n-butylresorcinol is between the LogP of nicotine and benztropine, two of the active ingredients that Wang specifically identifies as active agents that can be used with the PIB adhesives described. (Ans. 6–7.) The Examiner explains that nicotine has a lower logP than 4-n-butylresorcinol and is thus more polar and hydrophilic than 4-n-butylresorcinol, while benztropine has a higher logP than both 4-n-butylresorcinol and nicotine and is more non-polar and hydrophobic than either of those two compounds. (*Id.* at 7.) Given the large difference between the logP of nicotine and benztropine, the Examiner finds that it would have been understood "that the transdermal matrix of Wang can accommodate a variety of active ingredients." (*Id.*)

We agree with the Examiner's factual findings and conclusion of obviousness. Wang teaches that "[t]he characteristics of the adhesives of this invention . . . make them particularly useful as in-line adhesives in rate controlled transdermal delivery devices" (Wang 3:34–36) and that transdermal delivery devices can be applied by a patient anywhere "from several hours up to a week depending upon the agent being delivered and the condition being treated" (*id.* at 3:42–46). Torihara, as the Examiner explains, teaches 4-n-butylresorcinol is a skin depigmental agent that can be applied topically. (*See, e.g.*, Torihara cols. 1–2.)

We agree that these teachings provide sufficient reasoning to establish a motivation to combine. "[I]nterrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all [can provide] an apparent reason to combine the

known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Indeed, the obviousness analysis "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* And we note "[t]he 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).

Contrary to Appellant's argument, Wang does not "recommend" the PIB adhesive "for use in combination with only non-polar active agents" (Appeal Br. 7 (emphasis omitted)). Rather, we conclude that Wang simply discloses that there is an advantage to use with such ingredients. It is true, as Appellant indicates, that Wang teaches that the disclosed PIB adhesive "finds particular use" (*id.*) for delivering oily nonpolar agents such as nicotine, benztropine, secoverine, dexsecoverine, and arecoline. (Wang 5:12–29.) Regarding those agents, Wang notes that they have a low solubility in the PIB adhesives disclosed and thus the concentration of those agents "is significantly reduced as compared to that observed in prior art non-PIB adhesives" and thus the degradation of adhesive is reduced where such oily, non-polar oily agents were known to degrade the typical non-PIB adhesives in which they were highly soluble. (*Id.*)

However, Wang does not teach that the PIB adhesive can *only* be used with oily, non-polar agents, just because a particular benefit is obtained with certain oily, non-polar agents. *Accord Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be

considered" (citation omitted) (alteration in original)). Wang specifically does not limit the agents that can be included with the matrix noting that they can be:

> any beneficial agent or compound that can be delivered by a device herein to produce a beneficial and useful result. The term includes medicines, organic and inorganic drugs, hormones, nutrients, vitamins, food supplements, and other agents that benefit an animal or human.

(Wang 3:48–53.) For this reason, we also do not find persuasive of non-obviousness Appellant's argument that 4-n-butylresorcinol is "structurally and chemically completely different" (Appeal Br. 7–8) from the non-polar agents nicotine, benztropine, secoverine, dexsecoverine, and arecoline. "Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988). That Wang suggests its transdermal system can be used with a variety of beneficial agents without restricting such agents to oily non-polar agents provides a reasonable expectation of success that 4-n-butylresorcinol could be delivered with a transdermal system that used the disclosed PIB adhesive.

Appellant separately argues claims 38–40. (Appeal Br. 9–11.) These claims recite different release rates for 4-n-butylresorcinal from the therapeutic system. Appellant argues that Wang teaches adhesive layer thickness ranges when used with a rate controlling membrane and argues that Wang "makes it clear that when a rate-controlling membrane is present, the release rate of the drug is controlled by the rate-controlling membrane, not by the (thickness of the) adhesive layer." (*Id.* at 10.) According to Appellant, "it is impossible to draw any conclusions regarding the release

rate of a drug in the device of WANG based on the thickness of the adhesive layer, at least when a rate-controlling membrane is present." (*Id.*) We do not find this argument persuasive of non-obviousness because the claims do not exclude the presence of a rate-controlling membrane and Wang makes it clear that the composition and thickness of the adhesive layer is a result-effective variable with respect to passage of the agent to be delivered. (Wang 4:33–45 ("The composition and thickness of the adhesive layer *will be adjusted* such that the adhesive layer does not constitute a significant permeation barrier to the passage of the agent to be delivered as compared to that of the rate-controlling membrane. . . . the thickness is also preferably selected so that the adhesive does not contain a substantial amount and preferably less than about 15% of the total amount of agent in the device, particularly in rate-controlled delivery devices.") (emphasis added).)

Claim 21, from which claims 38–40 depend, recites that the transdermal therapeutic system "comprises" a particular active ingredient and that the system is "employed in the form of a matrix system selected from" a number of types of materials types matrices. "'Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997). Thus, we do not consider that the therapeutic system is in the "form of a matrix system" to limit the composition of the elements that make up that system to only the active ingredient recited and the group of matrix materials identified from which to select. Consequently, that Wang teaches release rate can be controlled in part by a rate-controlling membrane does not establish non-obviousness of the claimed invention.

Furthermore, "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012). The motivation to optimize comes from the natural desire of those skilled in the art to experiment with, and improve upon, known conditions taught in the prior art. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). That a number of elements may need to be adjusted to arrive at the claimed rate of release does not establish non-obviousness.

In addition, we note that Wang is also not limited to a transdermal delivery device that has a release rate-controlling membrane. (*See* generally Wang 4:46–51; 5:2–8.) Moreover, claims 38–40 are not limited to a particular concentration range of active to achieve the claimed rate of release.

In light of the foregoing, we affirm the Examiner's rejection of claims 21, 26, 28–35, and 38–40 as being obvious over Torihara and Wang.

Obviousness: Torihara and Woeller

The Examiner's findings regarding Torihara are discussed above. The Examiner finds that Woeller discloses a self-adhesive polymer matrix that can be a medical patch or bandage. (Final Action 7.) The Examiner further finds Woeller teaches:

> [T]he . . . polymer matrix comprises (a) at least one polymer which forms a gel in water, (b) water, (c) a sea algae extract, and (d) at least one alcohol which is a monohydric or polyhydric alcohol and, in one aspect of the polymer matrix, component (a) may comprise a polyacrylic acid polymer or copolymer.

(*Id.* at 7–8 (emphasis omitted).) The Examiner also finds that Woeller teaches "component (c) may comprise **agar-agar** and/or carrageenan." (*Id.* at 8.)

The Examiner further finds that Woeller teaches topical administration of drugs provides the following two advantages:

(1) first-order release kinetics of the active substance, thereby allowing a constant level of active substance to be maintained in the body over a very long period of time;

(2) the path of uptake through the skin avoids the gastrointestinal tract and also the first pass through the liver. (*Id.*) Thus, the Examiner concludes that it would have been obvious to one having ordinary skill in the art to "choose self-adhesive polymer matrix taught by Woeller as the particular drug delivery system to be incorporated into the invention of Torihara." (*Id.*)

We agree with the Examiner's factual findings and conclusion of obviousness.

Appellant's argument that "none of the examples of pharmaceutical active substances which are mentioned in col. 5, lines 24–30 and claim 6 of WOELLER shows any structural or other resemblance with 4-n-butylresorcinol"[3] and that "[t]he same applies to the active ingredients which are employed in Examples VII-IX of WOELLER" (Appeal Br. 12 (emphasis omitted)) is not persuasive of non-obviousness. Woeller teaches the gel

[3] We note that Woeller, US 2005/0281881 A1, relied on in the Examiner's rejection does not have column and line numbers. Moreover, claim 6 of Woeller does not recite any particular active components, though claims 18 and 27 do.

matrix taught can be doped "with hydrophilic active substances, or else, in the case of an appropriate solubilizer, with hydrophobic active substances for wound healing or skin care." (Woeller ¶ 75.) Woeller essentially teaches that any active substance for topical application for wound healing or skin care is capable of being added to the disclosed matrix. Furthermore, the actives recited in claims 18 and 27 include menthol and ketoprofen both of which include cyclic carbon structures and OH substituents, which 4-n-butyl resorcinol also includes. Even if it were true, it is not dipositive that none of the examples of pharmaceutical active substances which are specifically mentioned in Woeller shows any structural or other resemblance with 4-n-butyl resorcinol. "It is well settled that a prior art reference is relevant for all that it teaches to those of ordinary skill in the art." *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992).

Appellant's argument that "it would be impossible for one of ordinary skill in the art to predict whether the matrix materials disclosed in WOELLER can successfully be used in combination with 4-n-butylresorcinol as active agent" (Appeal Br. 13; *see also id.* at 14) is similarly unavailing. Woeller provides a reasonable expectation of success with any hydrophilic or hydrophobic active substance. And Appellant has not provide any scientific reasoning or evidence as to why certain active substances would not reasonably be expected to work. "Attorney argument is not evidence." *Icon Health & Fitness v. Strava*, 849 F.3d 1034, 1043 (Fed. Cir. 2017) *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989) ("Attorneys' argument is no substitute for evidence.")

Woeller teaches that "transdermal therapeutic systems for delivering active substances into and/or through the skin have been known for a long

time and constitute patch-like systems which in particular are doped with drugs" (Woeller ¶ 6.) Such systems provide "time-dependent release" of the drug and amount released per unit time and the duration of activity of the drug is influenced directly by the composition of the matrix. (Woeller ¶¶ 8, 10–11.) Whether or not Woeller specifically addresses particular release rates (Appeal Br. 13) is immaterial as none of the rejected claims requires any particular release characteristics. Woeller generally teaches that transdermal therapeutic systems are beneficial because they provide "time-dependent" drug release and that the amount of drug release per unit time and the duration of activity is "influenced directly" by the composition of the matrix. (Woeller ¶ 11.)

Finally, that "[n]othing is mentioned in [paragraph 217] of WOELLER regarding the treatment of (local) pigmentation disorders" (Appeal Br. 13) is not persuasive of nonobviousness. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). The references must be read, not in isolation, but in combination for what they fairly teach as a whole. *Id.* The Examiner relied on Torihara for the fact that the active agent 4-n-butyl resorcinol is a skin depigmental agent that can be applied topically to restore age spots or freckles to a "normal skin color." (Torihara 1:9–16.) Woeller provides a reason to apply 4-n-butyl resorcinol with an adhesive transdermal patch system. In particular, Woeller teaches the benefits of transdermal therapeutic systems, stating that they

> avoid the need for frequently repeated administration and avoid burdening the skin with high concentrations of active substances, and so reduce irritation to the skin, which is

> unavoidable in the event of repeated administration of liquid and semisolid administration forms. . . .
>
> In summary, the advantages . . . lie in a distinctly improved compliance on the part of users, which is attributable to the simple and rapid administration and to the long-lasting efficacy of transdermal therapeutic systems.

(Woeller ¶¶ 14–15).

Thus, we affirm the Examiner's rejection of claims 21, 27, 28, and 29 as being obvious over Torihara and Woeller.

Appellant does not separately argue the rejection of claims 36 and 37 other than to say that "PANIGRAHI is unable to cure the noted deficiencies of TORIHARA and WOELLER." (Appeal Br.15.) Because we do not find any deficiency in the Examiner's obviousness rejection of the claims over Torihara and Woeller, we affirm the rejection of claims 36 and 37 as being obvious over Torihara, Woeller, and Panigrahi.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
21, 26, 28–35, 38–40	103	Torihara, Wang	21, 26, 28–35, 38–40	
21, 27, 28 29	103	Torihara, Woeller	21, 27, 28, 29	
36, 37	103	Torihara, Woeller, Panigrahi	36, 37	
29–40		Obviousness-Type Double Patenting	29–40	
Overall Outcome			21, 26–40	

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED