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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/451,918	12/07/2009	Ketan R. Patel	98574.21500	4371

30734 7590 01/29/2020

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EXAMINER	
RODRIGUEZ, RAYNA B	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
01/29/2020	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KETAN R. PATEL

Appeal 2018-006997
Application 12/451,918
Technology Center 1600

Before RICHARD M. LEBOVITZ, RACHEL H. TOWNSEND, and CYNTHIA M. HARDMAN, *Administrative Patent Judges.*

HARDMAN, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 1–5, 18–21, 23, and 25–27. *See* Final Act. 4. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM-IN-PART.

[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 TROIKAA PHARMACEUTICALS LTD. Appeal Br. 3.

CLAIMED SUBJECT MATTER

The claims are directed to a non-aqueous topical solution of a pharmaceutically acceptable salt of diclofenac. Claims 1 and 23, the two independent claims on appeal, are reproduced below:

> 1. A novel composition consisting of:
>
> an effective amount of a pharmaceutically acceptable salt of diclofenac;
>
> a penetration enhancer and solubilizer consisting of 10 to 30% v/v of a lower chain alcohol;
>
> a solvent in an amount greater than or equal to 50% and selected from propylene glycol, glycofurol or mixtures thereof; and
>
> an additional penetration enhancer selected from the group consisting of
>
> oleic acid,
> N-methyl-pyrrolidone (NMP),
> 2-methyl-pyrrolidone, and
> 1-methyl-pyrrolidone;
>
> wherein said composition is a non-aqueous topical solution.
>
> 23. A novel composition comprising:
>
> an effective amount of a pharmaceutically acceptable salt of diclofenac in the range of 1.16% to 5% w/v;
>
> a penetration enhancer and solubilizer in the range of 10 to 20% v/v of a lower chain alcohol;
>
> a solvent in an amount greater than 75% and selected from propylene glycol, glycofurol and mixtures thereof; and
>
> an additional penetration enhancer in the range of 1 to 5% w/v, and selected from the group consisting of
>
> oleic acid,
> N-methyl-pyrrolidone (NMP),
> 2-methyl-pyrrolidone, and
> 1-methyl-pyrrolidone;
>
> wherein the composition is a non-aqueous topical solution.

Appeal Br. 10–12 (Claims Appendix).

The Examiner indicated that the elected species under examination is diethylamine diclofenac as the salt of diclofenac species, propylene glycol as the solvent species, and ethanol as the lower chain alcohol species that is identified as a "penetration enhancer and solubilizer" in claims 1 and 23. Final Act. 2. Accordingly, as to the appealed rejection, we limit our analysis to the patentability of this species, and take no position regarding the patentability of the broader generic claims or the remaining species. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987).

REFERENCES

The Examiner relies on the following prior art:

Name	Reference	Date
Samour	US 5,976,566	Nov. 2, 1999
Zhang	US 2007/0196453 A1	Aug. 23, 2007
H. Trommer & R.H.H. Neubert, *Overcoming the Stratum Corneum: The Modulation of Skin Penetration*, 19(2) Skin Pharmacol Physiol. 106–21 (2006) ("Trommer")		

REJECTION

Claims 1–5, 18–21, 23, and 25–27 stand rejected under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Samour, Zhang, and Trommer. Final Act. 4.

OPINION

Examiner's Findings

The Examiner found that Samour teaches a composition consisting of diclofenac diethylamine, a penetration enhancer, a solvent that is propylene glycol, and ethanol, but "does not teach the penetration enhancer is one of the additional penetration enhancers of claim 1." Final Act. 5. The

Examiner further found that Zhang "suggests a composition comprising a pharmaceutically acceptable salt of diclofenac; ethanol; propylene glycol; and . . . oleic acid," while Trommer "establishes that propylene glycol in combination with oleic acid function synergistically to improve penetration of drugs through the skin." Final Act. 6. The Examiner found that "it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any pharmaceutically penetration enhancer) for another (oleic acid) with an expectation of success, since the prior art establishes that both are suitable for topical compositions." Final Act. 6.

Regarding the amounts of ethanol (the elected species of lower chain alcohol) and propylene glycol recited in claims 1 and 23, the Examiner relied on Samour Figure 1, which is a ternary phase diagram showing the miscibility of the penetration enhancer 2-n-nonyl-1,3-dioxolane at 10 and 2 wt% (squares and circles, respectively), in a vehicle consisting of varying amounts of ethanol, propylene glycol, and water. Final Act. 7; *see also* Samour 8:46–60, Fig. 1. The Examiner found that Samour Figure 1 demonstrates a formulation containing about 83% propylene glycol, 17% ethanol, and 0% water. Final Act. 7. The Examiner found that this formulation includes amounts of ethanol and propylene glycol that fall within the ranges recited in claims 1 and 23. Final Act. 7. The Examiner further found that

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art to utilize the amount of ethanol and propylene glycol taught by Samour as a starting point for optimizing []the amounts of ethanol and propylene glycol in a composition consisting of diclofenac diethylamine; propylene glycol, ethanol; and a

> penetration enhancer, wherein the penetration enhancer is oleic acid.

Final Act. 7.

Regarding the amount of the additional penetration enhancer recited in claim 23 (i.e., "1 to 5% w/v"), the Examiner found that "Samour teaches[]2 to 15% of the skin penetration enhancer (col 4, line 62)," and stated that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art to utilize the amount of penetration enhancer taught by Samour as a starting point for optimizing the amount . . . of penetration enhancer, oleic acid." Final Act. 8.

Appellant's Arguments

With respect to claim 1, Appellant argued that a person of ordinary skill in the art would not have been motivated to change the penetration enhancer in Samour, because Samour consistently describes its inventive compositions as requiring a skin penetration enhancer selected from dioxolane, dioxane, or acetal compounds. Appeal Br. 5–6. Appellant stated that "[r]emoving or replacing these essential penetration enhancing compounds from Samour et al.'s inventive formulations would render it unsatisfactory for its intended purpose of substantially improving flux of NSAIDS," including as compared to a commercially available product that Appellant asserted "includes medium chain triglycerides and polyoxyethylene fatty acid esters that exhibit characteristics of penetration enhancers." Appeal Br. 6 (citations omitted); Reply Br. 2.

With respect to claim 23, Appellant made two arguments. First, Appellant argued that Samour Figure 1 does not disclose a formulation containing the recited amount of propylene glycol. Appeal Br. 7. That is, Appellant argued that Figure 1 depicts the carrier only, and when factoring

in even the minimum amount of active ingredient disclosed by Samour (0.1%) and the penetration enhancer (10%), "the correct maximum amount of propylene glycol . . . in a non-aqueous formulation is 74.62%." Appeal Br. 7. Accordingly, Appellant argued that Samour Figure 1 depicts a formulation that includes less than the claimed amount (i.e., "an amount greater than 75%") of propylene glycol. Appeal Br. 8; *see also* Reply Br. 4.

Second, Appellant argued that Samour fails to teach the amount of penetration enhancer recited in claim 23 (i.e., "1 to 5% w/v"). Specifically, Appellant argued that despite Samour's disclosure of an amount of penetration enhancer that encompasses the claimed range (e.g., 2–15%, *see* Samour 4:62), "the ternary phase diagram requires 10% penetration enhancer to effectuate a non-aqueous formulation, with amounts less resulting in an aqueous formulation." Appeal Br. 8.

Analysis

Claim 1, and Claims that Depend Therefrom

We agree with and adopt the Examiner's findings of fact on the obviousness of claim 1, and determine that the Examiner has presented a prima facie case of obviousness with respect to this claim.

We are not persuaded by Appellant's argument that the Examiner has failed to establish a motivation to modify Samour's penetration enhancer. Importantly, Appellant has not argued that substituting oleic acid for Samour's penetration enhancers would result in miscibility issues, or that Samour Figure 1 is instructive only for formulations containing ethanol, propylene glycol, and the enhancer 2-n-nonyl 1,3-dioxolane. In other words, Appellant has not argued that the phase diagram in Samour Figure 1 is

inapplicable to formulations containing a penetration enhancer other than 2-n-nonyl 1,3-dioxolane.

Rather, with respect to claim 1, Appellant argues only that there was no motivation to change Samour's penetration enhancer because doing so would render the formulation "unsatisfactory for its intended purpose of substantially improving flux[2] of NSAIDS." Appeal Br. 6 (citing Samour 3:50–54); Reply Br. 2–4. We are not persuaded by this argument, because it frames the "intended purpose" of Samour's formulation in an overly narrow way. Appellant cites only one of the disclosed benefits of Samour's formulations (i.e., "substantially improving flux of NSAIDS"). Appeal Br. 6. But elsewhere, Samour more broadly describes the intended purpose of the invention, e.g., stating: "The present invention has as a principal object to provide stable topical compositions effective for the transdermal application of ibuprofen or other NSAID compounds by the application of the composition to the skin." Samour 3:62–65. Appellant has not demonstrated that substituting Samour's disclosed penetration enhancers with oleic acid, based on its functional equivalence to the penetration enhancers of Samour, would render the formulation inoperable for the purpose of providing stable topical compositions effective for the transdermal application of diclofenac.

Moreover, Appellant has not established that using oleic acid in place of Samour's penetration enhancers would have rendered the formulation unsatisfactory even for the purpose of "substantially improving flux of NSAIDS." The comparison present in Samour referred to by Appellant is a

[2] We understand flux in Samour to mean the percutaneous absorption rate of active agent. *See, e.g.*, Samour Example 1.

comparison to commercially available formulations, one of which Appellant contends includes materials that exhibit "characteristics of penetration enhancers" (Appeal Br. 6; Reply Br. 2), but Appellant does not contend that these formulations included oleic acid and propylene glycol. Trommer teaches that propylene glycol and oleic acid function synergistically to improve penetration of lipophilic drugs through the skin. Trommer 112–13. Appellant has not addressed whether one of ordinary skill in the art would have concluded the expected synergy taught by Trommer would not have "substantially improv[ed] flux of NSAIDS." Accordingly, on this record, Appellant has not supported its contention that substituting oleic acid for Samour's penetration enhancers would render the formulations inoperable for the purpose of "substantially improving flux."

For the above reasons, Appellant's arguments do not persuade us of Examiner error, and thus we affirm the rejection of claim 1 as obvious over Samour, Zhang, and Trommer. Claims 2–5, 18–21, and 26 directly or indirectly depend from claim 1. *See* Appeal Br. 10–12 (Claims Appendix). Appellant did not separately argue any of these dependent claims, and instead relied on the arguments it made for claim 1. *See* Appeal Br. 8. Accordingly, dependent claims 2–5, 18–21, and 26 fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2013).

Claim 23, and Claims that Depend Therefrom

With respect to claim 23, we are not persuaded by Appellant's argument that Samour fails to teach the limitation "a solvent in an amount greater than 75%." Appeal Br. 8. Appellant asserts that Samour's ternary phase diagram indicates that the non-aqueous formulation contains 74.62% propylene glycol, which is less than the claimed amount of "greater than

75%." *Id.* at 7–8. However, it is well-settled that absent unexpected results, "where 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 Aller*, 220 F.2d 454, 456 (CCPA 1955). Thus, even accepting Appellant's argument that Samour teaches a formulation containing 74.62% propylene glycol rather than "greater than 75%," Samour indicates that the amount of propylene glycol "may be varied to adjust the initial flux of the NSAID through the skin." Samour Abstract. Accordingly, we agree with the Examiner that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art to utilize the amount of ethanol and propylene glycol taught by Samour as a starting point for optimizing the amount . . . of ethanol and propylene glycol," particularly here, where Samour discloses an embodiment having only slightly less propylene glycol than is recited in claim 23. Final Act. 7.

We are persuaded, however, by Appellant's argument that Samour fails to teach the amount of "additional penetration enhancer" recited in the "non-aqueous topical solution" of claim 23 (i.e., "1 to 5% w/v"). We agree with Appellant that despite Samour's general disclosure of using 2–15% penetration enhancer (*see* Samour 4:62), "the ternary phase diagram requires 10% penetration enhancer to effectuate a non-aqueous formulation." Appeal Br. 8. Samour states that in the phase diagram, "the region below the lines connecting the data points represent the proportions where the vehicle components are immiscible." Samour 8:54–60. The phase diagram shows a single non-aqueous formulation, which contains 10% penetration enhancer; formulations with less than 10% penetration enhancer (i.e., 2%) contain water. *See* Samour Fig. 1. Therefore, an amount of penetration enhancer

less than 10% would be immiscible with the other components and contrary to the desired miscibility described by Samour. Samour 8:33–38. Accordingly, in view of the teachings of Samour Figure 1, the Examiner has not established that in optimizing the amount of penetration enhancer, a skilled artisan would have been motivated to reduce the amount from 10%, with a reasonable expectation of success of achieving the claimed range of "1 to 5% w/v" penetration enhancer *in a non-aqueous formulation*. *See, e.g.*, *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) ("The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the *claimed invention*.") (emphasis added).

For this reason, we determine that the Examiner has not established a prima facie case of obviousness of claim 23, and thus we reverse the rejection of claim 23 as obvious over Samour, Zhang, and Trommer. Claims 25 and 27 depend from claim 23. Appeal Br. 12 (Claims Appendix). Appellant did not separately argue these dependent claims, and instead relied on the arguments it made for claim 23. *See* Appeal Br. 8. Accordingly, for the same reason discussed above with respect to claim 23, we reverse the Examiner's rejection of claims 25 and 27 as obvious over Samour, Zhang, and Trommer. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2013).

CONCLUSION

We affirm the rejection of claims 1–5, 18–21, and 26 under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Samour, Zhang, and Trommer.

We reverse the rejection of claims 23, 25, and 27 under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Samour, Zhang, and Trommer

DECISION SUMMARY

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–5, 18–21, 23, 25–27	103(a)	Samour, Zhang, and Trommer	1–5, 18–21, 26	23, 25, 27

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-IN-PART