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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SAMUEL KYEREMATENG, GERD WOEHRLE, SVENJA WARNECKE, SIMON KULLMANN, ULLRICH WESTEDT, and JÜRGEN WEIS

Appeal 2019-006437
Application 14/346,686
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and ELIZABETH A. LAVIER, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from Examiner's decision to reject claims 1, 4, 8–10, 15, and 19 (Appeal Br. 2).[2] We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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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 "AbbVie Deutschland GmbH & Co. KG" (Appellant's April 30, 2019 Appeal Brief (Appeal Br.) 2).

[2] Pending claims 16–18 and 22–24 stand withdrawn from consideration (*see* Appeal Br. 2).

STATEMENT OF THE CASE

Appellant's disclosure "relates to formulations comprising a solid dispersion product of an active agent having at least one hydrogen bond donor moiety or proton donor moiety and a pharmaceutically acceptable polyvinyllactam polyvinylacetate poly(alkylene glycol) graft copolymer, and methods for preparing such formulations" (Spec.[3] 1: 3–6). Appellant's claim 1 is reproduced below:

> 1. A formulation comprising a solid dispersion product comprising
>
> (a) an active agent having a proton donor moiety which comprises an acidic hydrogen atom bound to a heteroatom,
>
> (b) a pharmaceutically acceptable polyvinyllactam polyvinylacetate poly(alkylene glycol) graft copolymer, and
>
> (c) a pharmaceutically acceptable acidic pH modifier selected from the group consisting of citric acid, sorbic acid, gluconic acid, lactic acid, glycolic acid, malonic acid, maleic acid, tartronic acid, mucic acid, glutamic acid, and aspartic acid;
>
> wherein the active agent is selected from pharmaceutically active agents, cosmetically active agents and nutritional supplements, and is a compound with a solubility in water at 25°C and pH 7.0 of 0.01 g/100 ml or less.

(Appeal Br. 15.)

[3] Appellant's March 21, 2014 Specification.

Ground of rejection before this Panel for review:

Claims 1, 4, 6, 8–10, 15, and 19 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Westedt,[4] Hardung,[5] Tran,[6] Babcock,[7] and Breitenbach.[8]

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness?

FACTUAL FINDINGS (FF)

FF 1. Examiner finds that Appellant's "elected species of active agent . . . [is] fenofibric acid (a cholesterol reducing agent)" (Ans.[9] 3).

FF 2. Westedt "relates to a method for the transmucosal administration of fibrate compounds . . . to a drug delivery system suitable for such a route of administration and to a process for manufacturing the drug delivery system" (Westedt 1: 3–5; *see id.* at 3: 9–11 (Westedt discloses "[p]referably, the fibrate compound is selected from the group consisting of fenofibric acid . . . , the physiologically acceptable salts and derivatives thereof."); *see* Final Act.[10] 4).

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[4] Westedt et al., WO 2008/037809 A1, published April 3, 2008.
[5] Hendrik Hardung, Ph.D. et al., *Combining HME & Solubilization: Soluplus® - The Solid Solution*, 10 Drug Delivery Technology XX (2010).
[6] Phuong Ha-Lien Tran et al., *Dissolution-modulating mechanism of pH modifiers in solid dispersion containing weakly acidic or basic drugs with poor water solubility*, 7 Expert Opin. Drug Deliv. 647–661 (2010).
[7] Babcock et al., US 2004/0013734 A1, published Jan. 22, 2004.
[8] Breitenbach et al., WO 2011/101352 A1, published Aug. 25, 2011.
[9] Examiner's June 27, 2019 Answer.
[10] Examiner's May 1, 2018 Final Office Action.

FF 3. Westedt discloses that "parenteral administration of fibrate compounds generally suffers from the intrinsic problems of poor solubility of the drugs" (Westedt 2: 23–25; *see* Tran 648: col. 1 ("Generally poorly water-soluble drugs are weakly acidic or basic compounds and, hence, show pH-dependent solubility"); Final Act. 9).

FF 4. Westedt discloses that its "delivery system comprises a solid dispersion product wherein the fibrate compound is distributed homogenously in a polymer matrix" (Westedt 5: 17–19; *see* Final Act. 4–5 (citing Westedt 6: 24 and 35; *id.* at 7: 4; *id.* at 19: 15–19 and 45–46; *id.* at 20: 1–5; *id.* at 21: 29–37)).

FF 5. Examiner finds that Westedt discloses that it compositions may comprise solubilizers (Final Act. 5 (citing Westedt 9: 8–9)).

FF 6. Examiner finds that although Westedt discloses "the formation of solid dispersions comprising fenofibric acid, solublizers and polymers," Westedt "does not expressly teach a solid dispersion comprising fenofibric acid, a pH modifier and [Soluplus®[11]]" (Final Act. 5).

FF 7. Hardung discloses that "Soluplus outperforms many of the well-known surfactants and solubilizers for poorly soluble compounds and is

---

[11] Appellant discloses:

> In a preferred embodiment of the invention, the polyvinyllactam polyvinylacetate poly(alkylene glycol) graft copolymer[, as set forth in Appellant's claim 1,] is a polyvinylcaprolactam polyvinylacetate poly(ethylene glycol) graft copolymer having a number average molecular weight determined by gel permeation chromatography in the range of 90,000 to 140,000 and a glass transitions temperature of 70°C such as Soluplus® (available from BASF AG, 10 Ludwigshafen, Germany).

(Spec. 7: 5–10)

potentially applicable to solid oral dosages" (Hardung, Introduction; *see id.* at Conclusion ("Soluplus is especially designed to solubilize poorly soluble [active pharmaceutical ingredients] (APIs) and has demonstrated an excellent capability to form solid solutions with many crystalline APIs"); *see also* Final Act. 5).

FF 8. Hardung discloses the "impact of pH on solublization using different buffer media," wherein "Soluplus was capable of acting as a solubilizer and increasing the saturation solubility of various actives at all pH values examined," specifically pH 1.2, 7, and 9 (Hardung, Results; *see* Final Act. 5–6).

FF 9. Tran discloses that "[a]lthough the solid dispersion method has been known to increase the dissolution rate of poorly water-soluble drugs by dispersing them in hydrophilic carriers, one obstacle of the solid dispersion method is its limited solublization capacity, especially for pH-dependent soluble drugs" (Tran, Abstract; *see generally* Final Act. 6).

FF 10. Tran discloses:

> For a weakly basic drug that is deprotonated and non-ionized in intestinal fluid, an acidifier is commonly used to enhance the drug dissolution rate by decreasing the pH_m[12] of the dosage forms. On the other hand, an alkalizer is a suitable pH modifier to increase the pH_m of a solid dosage form containing a weakly acidic drug. However, in reality, this rule is not applicable in every case. For example, an acidifier is not as effective as an alkalizer for enhancing the dissolution of a drug such as telmisartan, which is poorly soluble in intestinal fluid. Hence,

[12] Tran defines the term "pH_m . . . as the pH of the saturated solution in the immediate vicinity of the drug particles and has been used to modify the dissolution of ionizable drugs from pharmaceutical formulations in a predictable manner" (Tran 648).

> the optimal choice is dependent on the specific drug and can be screened in a preliminary solubility study.

(Tran 648; *see id.* 658: Fig. 4 (Tran provides a flow chart outlining the "[t]ypical pharmaceutical process for studying a solid dispersion system incorporating a pH modifier with a weakly basic drug or weakly acidic drug"); *see* Final Act. 6.)

FF 11. Tran discloses that citric acid is a typical acidic type of pH modifier (Tran 655, Table 1; *see* Final Act. 6).

FF 12. Babcock discloses:

> It is known that solid amorphous dispersions comprising a low-solubility drug in a polymer can increase the maximum concentration of drug that will dissolve in an aqueous solution in in vitro tests, or that will dissolve in body fluids such as those present in the gastrointestinal (GI) tract in in vivo tests, and, in turn, enhance the bioavailability of the drug.

(Babcock ¶ 3; *see generally* Final Act. 6.)

FF 13. Babcock discloses that pH modifiers can be added to solid dispersions to modify its dissolution rate (*see* Babcock ¶ 94; *see also id.* ¶ 104 ("At least one function of inclusion of such pH modifiers is to control the dissolution rate of the drug, polymer, or both, thereby controlling the local drug concentration during dissolution"); *see* Final Act. 6).

FF 14. Babcock discloses that "[e]xemplary pH modifiers include acids such as citric acid" (Babcock ¶ 104; *see* Final Act. 6).

FF 15. Examiner finds that Breitenbach discloses that "Soluplus is a graft copolymer of 13 [wt%] . . . PEG 6000, 57 wt% N-vinylcaprolactam and 30 wt% vinyl acetate" (Final Act. 7 (citing Breitenbach 8: 7–10)).

ANALYSIS

Based on the combination of Westedt, Hardung, Tran, Babcock, and Breitenbach, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to replace the polymer matrix of Westedt's solid dispersion with Soluplus, to enhance the solubilization of the active agent, fenofibrinic acid, as taught by Hardung, and include a pH modifier, such as citric acid, to modulate the dissolution rate of the solid dispersion taught by the combination of Westedt, Hardung, Tran, Babcock, and Breitenbach (*see* Final Act. 7; *see also* FF 1–15).

As Examiner explains, "the pH modifiers of Tran and Babcock [were never asserted to] fall within the scope of [Westedt's] solubilizers" (Ans. 4). Therefore, we are not persuaded by Appellant's contention that "Examiner uses the mention of a 'solublizer' in Westedt as the basis for combining the pH modifiers allegedly taught in Tran and Babcock" (Appeal Br. 5; *see also id.* at 5–6). In addition, Hardung discloses that "Soluplus outperforms many of the well-known surfactants and solubilizers for poorly soluble compounds" (FF 7). Therefore, we are not persuaded by Appellant's contention that "[t]he record fails to show why one skill in the art would (a) not use the polymer(s) explicitly disclosed in Westedt and[, instead,] (b) use" Hardung's superior Soluplus® product (*see* Reply Br. 3).

In the context of solid dispersions, Tran discloses the general rule that "[f]or a weakly basic drug that is deprotonated and non-ionized in intestinal fluid, an acidifier is commonly used to enhance the drug dissolution rate by decreasing the pH_m of the dosage forms," whereas "an alkalizer is a suitable pH modifier to increase the pH_m of a solid dosage form containing a weakly acidic drug" (FF 10). Tran, however, makes clear that

> in reality, this rule is not applicable in every case. For example, an acidifier is not as effective as an alkalizer for enhancing the dissolution of a drug such as telmisartan, which is poorly soluble in intestinal fluid. Hence, the optimal choice is dependent on the specific drug and can be screened in a preliminary solubility study.

(FF 10.) Thus, Tran supports a conclusion that those of ordinary skill in this art would have tested the performance of a solid dispersion for a particular active to determine whether drug dissolution rate would be effectively modified by an acidic or basic pH modifier. Therefore, we are not persuaded by Appellant's contention that "performing a pre-screening assay for pH modifiers, without narrowing the scope of the same, would represent undue experimentation" (Appeal Br. 10). To the contrary, Tran makes clear that those of ordinary skill in this art would have found it routine to identify the appropriate pH modifier for a particular active agent solid dispersion (*see* FF 10).

For the foregoing reasons, we are not persuaded by Appellant's contention that when considering Hardung's disclosure in isolation, one of ordinary skill in this art would have concluded that

> (1) formulations comprising Soluplus and basic drugs (such as clotrimazole, keoconezole and cinnerizine) would benefit from being in an acidic environment and (2) formulations comprising Soluplus and acidic drugs likely would not significantly benefit from pH modulation; however, solubility is modestly increased in basic environments. This guidance is directly contrary to what is instantly claimed where a poorly soluble acidic active is in a Soluplus formulation with an acidic pH modifier, which the inventors surprisingly discovered had an improved drug release profile.

(Appeal Br. 7 (citing Appellant's Fig. 6); *see id.* (Appellant contends that "one skilled in the art would not be motivated to combine the Soluplus

teachings of Hardung and pH modifier teachings in Tran/Babcock because Hardung teaches that modification of pH would not significantly impact the solubility of acidic actives when Soluplus is employed").)

Tran and Babcock in combination suggest, in general, that the dissolution rate of solid dispersions comprising a poorly water-soluble acidic active agent, such as Appellant's elected species of active agent, fenofibric acid, can benefit from the addition of an appropriate pH modifier (*see* FF 1 and 9–14). Therefore, we are not persuaded by Appellant's intimation that person of ordinary skill in this art would not have sought to obtain a beneficial dissolution rate of a poorly water-soluble acidic active agent from Hardung's Soluplus® by adding a pH modifier to the solid dispersion as suggested by Tran and Babcock (*see* FF 1–14; *cf.* Appeal Br. 7–9).

For the foregoing reasons, we are not persuaded by Appellant's contention that the combination of Westedt, Hardung, Tran, Babcock, and Breitenbach fails to provide a person of ordinary skill in this art with a reasonable expectation of success in formulating a solid dispersion comprising fenofibric acid, Soluplus®, and a pH modifier, such as citric acid, as set forth in Appellant's claimed invention (*see* FF 1–14; *cf.* Appeal Br. 12).

Given that each of Westedt, Hardung, Tran, Babcock, and Breitenbach published after the 2000 disclosure of Leuner,[13] we are not persuaded by Appellant's contention that

> [i]f performing a pre-screening test with pH modifiers[, as suggested by the combination of Westedt, Hardung, Tran, Babcock, and Breitenbach,] was as routine as suggested by the

[13] Leuner et al., *Improviding drug solubility of oral delivery using solid dispersions*, 50 Eur. J. Pharma and Biopharma 47–60 (2000).

> Examiner, Leuner . . . would not characterize the effort as "one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry."

(Appeal Br. 11.) The state of the art after Leuner's disclosure and prior to the filing date of the instant application, as reflected in the evidence relied upon by Examiner, supports a conclusion that pre-screening with pH modifiers is a routine endeavor in this field (*see generally* FF 10).

For the foregoing reasons, we are not persuaded by Appellant's contention that Examiner's conclusion of obviousness is based in improper hindsight reasoning or that the prior art relied upon by Examiner teaches away from Appellant's claimed invention (*see* Appeal Br. 12–13).

Given that the combination of Westedt, Hardung, Tran, Babcock, and Breitenbach suggests that the use of pH modifiers in solid dispersions benefits the dispersions dissolution rate, identifies the pH modifiers typically used with solid dispersions, including citric acid, and makes clear that it is routine to screen solid dispersion formulations with pH modifiers to determine the appropriate pH modifier for a particular solid dispersion formulation, we are not persuaded by Appellant's contention that it was surprising that Appellant "found that the addition of an acidic pH modifier to a formulation comprising Soluplus and a poorly-soluble acidic active improved solubility" (Appeal Br. 13; *see also* Reply Br. 5 (Appellant contends that "[a] skilled artisan would recognize that the addition of citric acid had a substantial effect on the drug release profile of fenofibric acid")). To the contrary, Appellant did no more than combine familiar elements according to known methods to achieve a predictable result. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness. The rejection of claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Westedt, Hardung, Tran, Babcock, and Breitenbach is affirmed. Claims 4, 6, 8–10, 15, and 19 are not separately argued and fall with claim 1.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 4, 6, 8–10, 15, 19	103	Westedt, Hardung, Tran, Babcock, Breitenbach	1, 4, 6, 8–10, 15, 19	

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).

AFFIRMED