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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER
SHIN, MONICA A

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HILTRUD LINDENBLATT, THOMAS T. FRANK, and REINER VONDERSCHMITT

Appeal 2021-000577
Application 15/645,436
Technology Center 1600

Before DONALD E. ADAMS, ULRIKE W. JENKS, and RACHEL H. TOWNSEND, *Administrative Patent Judges.*

TOWNSEND, *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 to a solid pharmaceutical preparation of levothyroxine sodium and methods of making such a composition as being obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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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 Merck Patent GmbH. (Appeal Br. 1.)

STATEMENT OF THE CASE

Levothyroxine sodium is used to treat thyroid hormone deficiency. (Spec. 1.) Storage stability of pharmaceutical preparations of this compound is important to avoid dosage variations. (*Id.*) Appellant's invention is directed to a solid pharmaceutical preparation of levothyroxine sodium having improved stability. (*Id.*)

Claims 1–10, 12–17, 20, and 21 are on appeal. Claims 1 and 13, reproduced below, are illustrative of the claimed subject matter:

> 1. A solid pharmaceutical preparation comprising levothyroxine sodium, 2-10% by weight based on the preparation of gelatine, 0.2 to 3% by weight based on the preparation of citric acid, and a filler that is 50 to 80% by weight, based on the preparation, of mannitol, sucrose or lactose, and 10 to 30% by weight, based on the preparation, of maize starch.
>
> 13. A process for the production of a solid pharmaceutical preparation according to Claim 7, comprising suspending
>
> (a) levothyroxine sodium and optionally liothyronine sodium in an aqueous gelatin solution,
>
> (b) spraying the suspension obtained in (a) onto the filler in a fluidized bed granulation and drying to form granules, citric acid being either dissolved in the aqueous gelatine solution or admixed with the granules,
>
> (c) collecting the granules obtained in (b) and optionally,
>
> (d) mixing a disintegrant and optionally a lubricant with the granules obtained in (c), and (e) compressing a mixture obtained in (d) to give tablets.

(Appeal Br. 9–10.)

The prior art relied upon by the Examiner is:

Name	Reference	Date
Kahn	WO 95/20954	Aug. 10, 1995
Kun et al.	US 6,017,958	Jan. 25, 2000
Schreder et al.	US 6,646,007 B1	Nov. 11, 2003
Hanshew, JR et al.	US 2004/0013725 A1	Jan. 22, 2004

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

Claims 1–4, 6–10, 13, 14, 16, 17, and 21 under 35 U.S.C. § 103(a) as unpatentable over Khan and Schreder.

Claim 15 under 35 U.S.C. § 103(a) as unpatentable over Khan, Schreder, and Kun.

Claims 5, 12, and 20 under 35 U.S.C. § 103(a) as unpatentable over Khan, Schreder, and Hanshew.

DISCUSSION

The Examiner found that Khan teaches a solid pharmaceutical composition that includes the ingredients and the ranges recited in claim 1, where Khan calls the sugar or sugar alcohol a diluent instead of a filler, and citric acid is provided as a flavoring agent. (Final Action 4 (citing Khan, 2:24–33, 3:40–4:4, 5:19–32, 9 (Example 1), 6:7–25.) The Examiner recognized, however, that the use of gelatin as a binder is only suggested as among the possible "suitable additional pharmaceutically acceptable ingredients" in a tablet formulation. (Final Action 4–5.)

The Examiner relied on Schreder "for the motivation to specifically select and use gelatin in Khan's tablets." (*Id.* at 5.) In particular, the Examiner found that Schreder discloses levothyroxine sodium tablets that

comprise gelatin and fillers and also discloses that when gelatin is used as a binder, the "preparation has a surprising stability." (*Id.* (citing Schreder 1:66–67, 4:15–29 (Example 3)).) The Examiner found that one of ordinary skill in the art would have had a reasonable expectation of success given that "both Khan and Schreder are directed to levothyroxine sodium tablets and Khan discloses that binders such as gelatin are suitable for inclusion in their tablets." (*Id.* at 6.)

The Examiner further found that Schreder teaches a process for producing the pharmaceutical preparation as substantially set forth in claim 13. (*Id.* at 5–6 (citing Schreder 2:27–43, 3:11–37).) The Examiner found that one of ordinary skill in the art would have found it obvious to use Schreder's method to make the levothyroxine sodium tablets including gelatin. (*Id.* at 6.) The Examiner explained that

> One of ordinary skill in the art would have been motivated with a reasonable expectation of success in doing so as both Schreder and Khan are directed to levothyroxine sodium tablets; Khan discloses generally mixing all of the components together before compressing the mixture into a tablet; and Schreder generally discloses that ingredients outside of gelatin, active agent, and filler(s) are mixed in with the formed granules prior to compressing the mixture into a tablet.

(*Id.*)

We agree that the Examiner set out a prima facie case of obviousness in the initial rejection of the claims. However, we conclude that Appellant has provided evidence of unexpected results sufficient to establish the non-obviousness of the claimed invention. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a

person of ordinary skill in the relevant art would have found surprising or unexpected.")

Appellant's argument that one of ordinary skill in the art would not have added a stability-inducing agent such as gelatin to Kahn because the goal of Khan is to produce an essentially unstable tablet that can dissolve in the mouth (Appeal Br. 2–3, 5) is not persuasive. In particular, while Kahn is concerned with a composition that can easily dissolve in the mouth, such does not indicate that Kahn is not interested in a product that has a stable shelf life until inserted into the mouth of a patient. Schreder suggests such stability can be provided by gelatin (Schreder 1:66–67), and Kahn does teach that binders such as "starch, gelatin or natural and synthetic gums" are pharmaceutically acceptable ingredients that "[t]he solid oral dosage forms of the invention may further comprise." (Kahn 6:7–11.)

Despite the foregoing, however, Appellant has provided evidence demonstrating that at the time the invention was made, it was known that citric acid (and tartaric acid) is a pH modifier that reduces the stability of levothyroxine sodium pentahydrate in tablets. (Appeal Br. 4 (citing Patel[2]).) Patel describes tablet formulations of levothyroxine sodium pentahydrate including 10% pH modifier and the diluent dibasic calcium phosphate. (Patel 38, 41.) Formulations that included basic pH modifiers provided greater storage stability of the levothyroxine sodium pentahydrate in the tablets than did citric acid. (*Id.* at 41 (Table 3).) And formulations that included no pH modifiers provided greater storage stability of levothyroxine

[2] Himanshu Patel et al., *The effect of excipients on the stability of levothyroxine sodium pentahydrate tablets*, 264 Int'l J Pharm. 35–43, 41 (Table 3) (2003).

sodium pentahydrate in tablets than the formulations that included citric acid. (*Id.*) In addition, Appellant has provided testing results demonstrating the instability of levothyroxine sodium tablets that include 1.5 % by weight citric acid, which is within range recited in claim 1. (*Id.* (citing 2018 Declaration[3]).) The Storage and Stability Testing data provided in the 2018 Declaration demonstrates that the stability of levothyroxine sodium in a composition that includes 1.5% by weight citric acid is worse than the stability of levothyroxine sodium in a composition that does not include citric acid. (2018 Declaration 4 (15 tablets of each group were subjected to assay/purity determination)[4].) Thus, Appellant's data indicates that even with lower percentages of citric acid than was used in the Patel formulations, the same negative impact on stability arises.

The 2018 Declaration also provided data showing the stability of levothyroxine sodium in a tablet composition that includes 1.5% by weight citric acid together with 5% by weight gelatin. (*Id.*) Appellant provided additional data showing the stability of levothyroxine sodium in a tablet composition that includes gelatin but no citric acid. (Appeal Br. 4 (citing 2020 Declaration[5]).) The data provided in the 2020 Declaration included

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[3] Declaration Under 37 C.F.R. § 1.132 of Daniel Schwartz, dated November 27, 2017, and submitted by Appellant to the Office in 2018.

[4] Thus, even though there is only a single assay result reported each for 7, 14, and 28 days storage, that data point is based on a number of tablets having been tested. As such, we do not find the Examiner's concern regarding the absence of margin of error (Ans. 9) to be an appropriate reason to discount Appellant's data.

[5] Declaration Under 37 C.F.R. § 1.132 of Daniel Schwartz, dated April 16, 2020. The 2020 Declaration is not paginated, we assume the first page is page 1, and number the remaining pages consecutively.

stability results for the Comparison Example 1 composition described in Appellant's Specification. (2020 Declaration 2–3.) The Specification discloses that Comparison Example 1 is a tablet formulation that includes 5% by weight gelatin and no citric acid. (Spec. 17.) The 2020 Declaration demonstrates that the levothyroxine sodium in a tablet composition that includes no citric acid and 5% by weight gelatin is more stable than the tablet composition that has no gelatin and no citric acid, both of which are more stable than the tablet composition that has 1.5% citric acid and no gelatin. (2020 Declaration 3 (20 tablets of Comparison Example 1 were used in the assay determination).) The 2020 Declaration also shows that the levothyroxine sodium in a tablet composition that includes 1.5% citric acid and 5% by weight gelatin is more stable than the tablet composition that has 5% gelatin and no citric acid. We agree with Appellant that the stability results observed with the combination of gelatin and citric acid would not have been expected by one having ordinary skill in the art because citric acid by itself has been reported in the literature, and shown by Appellant, to negatively affect the stabilization of levothyroxine sodium in a tablet. That is, one of ordinary skill in the art would not have expected the combination of citric acid and gelatin to provide better stabilization of levothyroxine sodium in a tablet composition than the stabilization provided by gelatin alone, "**citric acid not being recognized as having any stability-enhancing ability.**" (Appeal Br. 4.) Contrary to the Examiner's apparent position (Ans. 9) that synergy must be established to rebut the Examiner's prima facie case, "it is well settled that comparative test data showing an unexpected result will rebut a prima facie case of obviousness." *In re Fenn*, 639 F.2d 762, 765 (CCPA 1981).

For the foregoing reasons, we do not affirm the Examiner's rejection of claims 1–4, 6–10, 12, 13, 14, 16, 17, and 21 as being obvious from Khan and Schreder.

The Examiner's reliance on Kun and Hanshew to address dependent claim limitations does not address the data supporting unexpected results of better storage stability of the levothyroxine sodium in a tablet that includes both gelatin and citric acid than in gelatin alone. Thus, we reverse the Examiner's rejection of claim 15 as being obvious from Khan, Schreder, and Kun and of claims 5, 12, and 20 as being obvious from Khan, Schreder, and Hanshew.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	References/Basis	Affirmed	Reversed
1–4, 6–10, 13, 14, 16, 17, 21	103(a)	Khan, Schreder		1–4, 6–10, 13, 14, 16, 17, 21
15	103(a)	Khan, Schreder, Kun		15
5, 12, 20	103(a)	Khan, Schreder, Hanshew		5, 12, 20
Overall Outcome				1–10, 12–17, 20, 21

REVERSED