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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ALBERTO MORETTO,
ALESSANDRA DE LAZZARI, and LUCIA DICORATO[1]

Appeal 2020-001434
Application 14/356,650
Technology Center 1600

Before ERIC B. GRIMES, JOHN G. NEW, and JAMIE T. WISZ,
Administrative Patent Judges.

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the term "Appellant" to refer to the "applicant" as defined in 37 C.F.R. § 1.142. Appellant states that the real party-in-interest is ZAMBON S.P.A. App. Br. 3.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Non-Final Rejection of claims 1–5, 7–11, 14–15, and 22 as unpatentable under 35 U.S.C. § 103(a) as being obvious over Gruber (US 2009/0175940 A1, July 9, 2009) ("Gruber").

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellant's invention is directed to a pharmaceutical, non-effervescent, solid composition comprising a mixture of a pharmaceutically effective amount of a ibuprofen salt and a pharmaceutically acceptable strong base in a molar ratio of from 1.0:0.01 to 1.0:0.8. Abstr.

REPRESENTATIVE CLAIM

Claim 1 is representative of the claims on appeal and recites:

> 1. A pharmaceutical, non-effervescent, solid composition for immediate oral administration previous dissolution in drinkable water, said composition consisting essentially of
>
> a mixture of a pharmaceutically effective amount of an ibuprofen salt and a pharmaceutically acceptable base in a molar ratio of from 1:0.01 to 1:0.8, wherein the base is selected from an alkaline metal carbonate, an alkaline metal hydroxide and a tribasic metal phosphate; and
>
> one or more pharmaceutically acceptable excipients selected from the group consisting of preservative agents, diluting agents, sweeting agents, aromatic agents and artificial colors,

> said composition being such that, when dissolved in said drinkable water for dilution, imparts a pH value ranging from 9.0 to 9.5 to the obtained solution,
>
> said pH range masking ibuprofen taste in said water solution, avoiding sensory irritation to the oral cavity when swallowed.

App. Br. 14.

ISSUE AND ANALYSIS

We adopt the Examiner's reasoning, findings of fact, and conclusions that the appealed claims are obvious over the cited prior art. We address the arguments raised by Appellant below.

Issue 1

Appellant argues the Examiner erred because the cited prior art does not teach or suggest Appellant's invention. App. Br. 7.

Analysis

The Examiner finds that Gruber teaches compositions comprising solubilized ibuprofen granulate and a base such as sodium carbonate or sodium hydroxide. Non-Final Act. 5 (citing Gruber ¶¶ 64–66). The Examiner also finds that Gruber teaches granulates suitable for sachets that may also contain sweeteners. *Id.* (citing Gruber ¶ 85). The Examiner also finds that Gruber teaches providing enough base to provide a pH of at least 7.5. *Id.* (citing Gruber ¶ 89).

The Examiner acknowledges that Gruber does not expressly teach compositions with a pH of 9.0–9.5. Non-Final Act. 5. However, the

Examiner concludes that it would have been obvious to person of ordinary skill in the art to optimize the constituent concentrations to arrive at the claimed pH range, according to the guidance provided by Gruber. *Id.* at 6 (citing *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) (holding that "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")).

Appellant argues that Gruber provides only for pharmaceutical solid compositions in which ibuprofen is in its native acidic form, and is first reacted with a base to obtain a salt. App. Br. 7 (citing, e.g., Gruber ¶ 28). Specifically, Appellant asserts that paragraph [0028] of Gruber teaches that "[i]t has surprisingly been found that a solubilized ibuprofen can be directly obtained in one step by reacting ibuprofen with a base in essentially dry state." *Id.* In other words, contends Appellant, the paragraphs of Gruber relied upon by the Examiner refer to solubilized ibuprofen granulate comprising a mixed sodium and potassium salt of ibuprofen. *Id.* (citing Gruber ¶¶ 35, 61). Appellant therefore asserts that Gruber teaches the ibuprofen salt only.

In contrast to the teachings of Gruber, argues Appellant, the claimed composition is directed to a mixture of ibuprofen salt with a base, and not to just an ibuprofen salt, as allegedly taught by Gruber. App. Br. 7. According to Appellant, the difference between the claimed invention and the prior art is that, in Appellant's invention, the base is utilized to alkalinize the solution of the ibuprofen salt, whereas Gruber teaches that the base has the function of reacting stoichiometrically with ibuprofen in its native acidic form to obtain a soluble ibuprofen salt. *Id.*

In support of this contention, Appellant points to the Declaration of Dr. Alberto Moretto (the "Moretto Declaration"), filed March 13, 2018. App. Br. 8. Dr. Moretto attests that:

> [T]he pharmaceutical solid compositions described by Gruber only refer to mixtures of ibuprofen in its native acidic form with a base. In contrast, the pharmaceutical composition presently claimed is a mixture of ibuprofen salt with a base.
>
> Thus, in the present application the base is utilized only to alkalinize the solution of the ibuprofen salt, while in Gruber the base has the function of reacting stoichiometrically with ibuprofen in its native acidic form to obtain a soluble ibuprofen salt.
>
> ….
>
> In other words, in Gruber the ibuprofen salt is the result obtained by adding a base to ibuprofen in its native acidic form in order to obtain a soluble form of ibuprofen. On the other hand, in the present application a base is added to the ibuprofen salt to obtain a soluble form of ibuprofen which does not cause oral cavity irritation during therapy.

Moretto Decl. ¶¶ 14–17.

We are not persuaded by Appellant's arguments. Appellant contends that "the pharmaceutical solid composition presently claimed is directed to a mixture of ibuprofen salt with a base, not to just ibuprofen salt as described in Gruber," and that Gruber's "ibuprofen salt is the result obtained by adding a base to ibuprofen in its native acidic form in order to obtain a soluble form of ibuprofen." *See* App. Br. 7; Moretto Decl. ¶ 17. We agree with Appellant that Gruber teaches that "a solubilized ibuprofen can be directly obtained in one step by reacting ibuprofen with a base in essentially dry state." Gruber ¶ 28.

Gruber also specifies that: "In the scope of the present invention, the term 'solubilized ibuprofen' means water-soluble forms of ibuprofen wherein at least part of the ibuprofen is present in salt form. Unless indicated otherwise, 'ibuprofen' refers to the racemic acid form 2-(4-isobutylphenyl) propionic acid." Gruber ¶ 35. So we are in agreement with Appellant, insofar as that Gruber thus teaches that solubilized ibuprofen is synthesized by combining the free-acid form with a base to produce an ibuprofen salt.

However, Gruber also teaches:

> Another aspect of the present invention is a pharmaceutical composition comprising a solubilized ibuprofen or solubilized ibuprofen granulate [i.e., the ibuprofen salt] prepared by the process of the present invention. This pharmaceutical composition *may in addition to the solubilized ibuprofen or ibuprofen granulate also comprise a basic compound which is preferably selected form the group consisting of sodium and/or potassium hydrogencarbonate, sodium carbonate, potassium carbonate, tribasic sodium and potassium phosphates and mixtures thereof*. The pharmaceutical compositions may also comprise one or more pharmaceutically acceptable excipients which are usual for ibuprofen-based compositions.

Gruber ¶ 66 (emphasis added). Gruber thus teaches a composition that, in addition to "an ibuprofen salt" (i.e., the solubilized ibuprofen), *also* contains a base which can be "an alkaline metal carbonate" (i.e., sodium and/or potassium hydrogen carbonate, sodium carbonate, potassium carbonate) or a "tribasic metal phosphate" (i.e., tribasic sodium and potassium phosphates), as required by claim 1.[2] We are consequently not persuaded by Appellant's

[2] *See also* Gruber claims 61 and 62 (emphases added):

arguments that Gruber does not teach a combination of ibuprofen salt and an alkali metal base.

Issue 2

Appellant argues that the Examiner erred because Gruber, unlike Appellant's claimed invention, uses weak bases rather than strong bases, as claimed. App. Br. 11.

Analysis

Appellant argues that Appellant's claims employ strong bases, rather than the weak bases allegedly employed by Gruber. App. Br. 11; *see also* Moretto Decl. ¶ 13 ("The invention is directed to a combination of ibuprofen salt and a strong base…."). Appellant points to *pH (Titration) Curves*, filed October 1, 2018 ("pH Curves"), as demonstrating that strong bases reach alkaline pH (9–9.5) faster and with lower volumes than weak bases. *Id.* Appellant contends that pH Curves teaches that a buffer solution is formed

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61. A pharmaceutical composition comprising the *solubilized ibuprofen* of claim **51**.

62. The pharmaceutical composition of claim **61**, *comprising additionally a basic compound selected from the group consisting of sodium and/or potassium hydrogencarbonate, sodium carbonate, potassium carbonate, tribasic sodium and potassium phosphates* and mixtures thereof.

when weak bases are added to strong acids, i.e., ibuprofen. *Id.* at 12 (citing pH Curves 5[3]).

Appellant argues that pH Curves thus teaches that a buffer solution is formed containing an excess of the weak base and of its salt that resists any large increase in pH. *Id.* Appellant contends that a person of ordinary skill in the art would not have found it obvious to adjust the pH of the composition, nor would it have been routine to adjust the pH levels to the claimed pH range with a reasonable expectation of success. *Id.*

We disagree. As an initial matter, Appellant's claims do not recite "strong bases." Claim 1, the only independent claim on appeal, recites "a mixture of a pharmaceutically effective amount of an ibuprofen salt and a pharmaceutically acceptable base … wherein the base is selected from an alkaline metal carbonate, an alkaline metal hydroxide and a tribasic metal phosphate." As we have explained *supra*, Gruber teaches compositions of an ibuprofen salt and an alkaline metal carbonate (i.e., sodium and/or potassium hydrogen carbonate, sodium carbonate, potassium carbonate) or a tribasic metal phosphate (i.e., tribasic sodium and potassium phosphates). *See* Gruber ¶ 66. Gruber thus expressly teaches two of the bases directly recited by the claims as the group of bases to be combined with an ibuprofen salt. We are consequently not persuaded that Gruber does not teach this limitation of the claims.

[3] pH Curves has no page numbering. We consequently refer to the page number as being the number of the page in numerical order, with the first page designated as page "1."

Issue 3

Appellant argues that the Examiner erred in finding that Gruber teaches the limitation of claim 1 reciting "a mixture of a pharmaceutically effective amount of an ibuprofen salt and a pharmaceutically acceptable base in a molar ratio of from 1:0.01 to 1:0.8." App. Br. 12.

Analysis

Appellant repeats the argument, presented *supra*, that Gruber describes the ratio between ibuprofen and a base, and not the ratio between an ibuprofen salt and a pharmaceutically acceptable base as in the presently claimed invention. App. Br. 12. Appellant therefore argues that there are no similarities between Appellant's claimed composition and those taught by Gruber. *Id.*

We are not persuaded. As we have explained, Gruber expressly teaches compositions comprising solubilized ibuprofen (i.e., the ibuprofen salt) and, additionally, bases within the groups that are expressly recited in the claim. *See* Gruber ¶ 66. We consequently find no merit in Appellant's argument that there are no similarities between the teachings of Gruber and the claimed compositions.

Issue 4

Appellant argues that the surprising and unexpected results of the claimed composition overcome the Examiner's *prima facie* conclusion of obviousness. App. Br. 6.

Analysis

Appellant argues that the addition of a strong, pharmaceutically acceptable base, i.e., an alkaline metal carbonate, an alkaline metal hydroxide, or a tribasic metal phosphate, unexpectedly removes oral cavity irritation when the solid composition comprising ibuprofen salt is dissolved and swallowed as a liquid dosage formulation. App. Br. 6. Appellant argues that this is particularly so when ibuprofen is administered at high dosage and maintains a fast, therapeutic effect. *Id.* at 6–7 (citing, e.g., Spec. 1, 3–4). Appellant argues that the claimed composition completely masks the throat irritating effect of ibuprofen at a dosage of 600 mg in solution. *Id.* at 8 (citing Moretto Decl. ¶ 12).

In support of this contention, Appellant points to the study described in the Moretto Declaration. App. Br. 9 (citing Moretto Decl. ¶ 19). According to Appellant, Dr. Moretto attests that a composition corresponding to an embodiment taught by Gruber comprising ibuprofen and sodium hydroxide at a ratio of 1 to 0.95 was compared to the claimed composition, prepared by mixing 23.74 g of ibuprofen L-arginine salt granulate (22.100 g of ibuprofen L-arginine salt and 1.64 g of sucrose) and 1.8560 g of sodium hydroxide so the molar ratio between Ibuprofen L-arginine salt and sodium hydroxide was 1 to 0.80; both compositions were then dissolved in water at a concentration of 6 mg/ml. App. Br. 10 (citing Moretto Decl. ¶¶ 20, 21). Appellant states that the pH of the Gruber composition was 6.7, whereas that of the claimed composition was 9.4. *Id.* (citing Moretto Decl. ¶¶ 24, 25).

Appellant argues that Dr. Moretto states that test subjects (n = 2) evaluated the Gruber solution as an "irritant" to the throat, noting that the

unpleasant sensation remained for some time after ingestion. *Id.* (citing Moretto Decl. ¶ 26). Dr. Moretto opines that these results demonstrate that only the combination presently claimed is capable of preventing throat irritation following the ingestion of an ibuprofen solution, because inhibition of irritation effects occurs at pH above 9.0. *Id.* at 10–11 (citing Moretto Decl. ¶ 27).

We do not find these results to be probative of unexpected or surprising properties of Appellant's claimed composition. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). We acknowledge that Gruber is the closest prior art to Appellant's claimed composition, but the embodiment selected for the study described in the Moretto Declaration was not the closest embodiment compared to Appellant's composition. We have explained *supra* how Gruber teaches solubilizing ibuprofen with a base, and then secondarily adding additional base(s) of the type recited in claim 1. *See, e.g.*, Gruber Examples 28 and 29. Those embodiments are closer to what Appellant argues is the nature of the claimed composition, yet such embodiments were not employed for comparison in the Moretto study. Indeed, Appellant has not explained which specific embodiment of Gruber is represented in ¶ 20 of the Moretto Declaration, or explained why it should be considered the closest prior art embodiment of the compositions taught by Gruber to the claimed compositions.

Furthermore, and perhaps more importantly, it was generally well known in the prior art that raising the pH solution of an ibuprofen solution

was a way of masking the irritation-inducing effects of ibuprofen, although, prior to Gruber, the use of alkali metal carbonates and phosphates was not thought to be suitable for oral administration because of their high pH. *See* Gruber ¶ 16:

> U.S. Pat. No. 5,262,179 discloses non effervescent water soluble compositions of water soluble ibuprofen salts in which the unpleasant taste of the salt is masked by carbonates, mono hydrogen phosphates and tribasic citrates in aqueous solution.… The alkaline additives have the task of so strongly buffering an ibuprofen salt solution that when drinking the pH does not drop so far in the mouth through saliva that the ibuprofen, which has a low solublitiy [sic] already at a pH value of 5–6, re-precipitates and leads to irritation of the oral mucosa.

We consequently find that the results obtained in the Moretto Declaration are not sufficient indicia of unexpected or surprising results to overcome the Examiner's *prima facie* conclusion that the claims are obvious over the cited prior art. We consequently affirm the Examiner's rejection of claims 1–5, 7–11, 14–15, and 22.

DECISION

The Examiner's rejection of claims 1–5, 7–11, 14–15, and 22 as unpatentable under 35 U.S.C. § 103(a) is affirmed.

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

AFFIRMED

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–5, 7–11, 14–15, 22	103(a)	Gruber	1–5, 7–11, 14–15, 22	