



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/695,848	04/03/2007	Hans-Ulrich Petereit	306430US0	3381
22850	7590	01/28/2013	EXAMINER	
OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P. 1940 DUKE STREET ALEXANDRIA, VA 22314			DICKINSON, PAUL W	
			ART UNIT	PAPER NUMBER
			1618	
			NOTIFICATION DATE	DELIVERY MODE
			01/28/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HANS-ULRICH PETEREIT, HEMA RAVISHANKAR, and
SHRADDH BODINGE

Appeal 2011-002497
Application 11/695,848
Technology Center 1600

Before DEMETRA J. MILLS, RICHARD M. LEBOVITZ, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF CASE

Claim 1. A pharmaceutical preparation comprising a core that is enveloped by a coating;

wherein said core comprises an active ingredient, which has a solubility in water of at least 10 g/l at 20°C, and an organic acid, a salt of an organic acid, or both; and

wherein said coating comprises silicon dioxide particles having an average particle size ranging from 1 to 50 µm, and one or more (meth)acrylate copolymer(s), where at least 60% by weight of said copolymer(s) are free-radically copolymerized units containing 93 to 98% by weight C₁- to C₄-alkyl esters of acrylic or of methacrylic acid monomers and 2% to 7% by weight (meth)acrylate monomers having a quaternary ammonium group in the alkyl radical;

wherein said preparation contains said coating in an amount ranging from 10 to 200 wt. % based on the weight of the core; and wherein said pharmaceutical preparation exhibits sigmoidal active ingredient release characteristics with a lag phase, a pulse phase and a run-out phase, characterized by an active ingredient release in the paddle apparatus at 100 rpm in buffer of pH 6.8 according to the European pharmacopoeia of approximately 10% during the lag phase and a subsequent active ingredient release of approximately a further 80% within less than 4 hours in the pulse phase.

Cited References

Panoz et al.	US 4,663,150	May 5, 1987
Noda et al.	US 5,395,628	Mar. 7, 1995
Seth	US 6,368,628 B1	Apr. 9, 2002
Mandrea	US 2006/0183767 A1	Aug. 17, 2006
Addington	US 2008/0200401 A1	Aug. 21, 2008

Grounds of Rejection

Claims 1-11, 13-14, 16, and 19-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Noda in view of Seth as evidenced by Addington.

Claims 1-14 and 16-20 are rejected under 35 U.S.C. § 103(a) as being

unpatentable over Noda in view of Seth and Panoz as evidenced by Addington.

Claims 1-11 and 13-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Noda in view of Seth and Mandrea as evidenced by Addington.

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Answer at pages 4-9.

The Examiner required an election of species of both the organic acid and the active ingredient in an office action dated July 29, 2008. Appellants elected succinic acid as the organic acid and phenylephrine as the active ingredient. (Office Action dated August 29, 2008.)

When the examiner has required the applicant to elect single chemical species for examination, the issue on appeal is the patentability of the single elected species. It is appropriate to limit discussion to that single issue and take no position respecting the patentability of the broader generic claims, including the remaining, non-elected species. *See Ex parte Ohsaka*, 2 USPQ2d 1461 (BPAI 1987).

We therefore to limit our discussion in this Decision to that single issue and take no position respecting the patentability of the broader generic claims, including the remaining, non-elected species. *See Ex parte Ohsaka*, 2 USPQ2d 1461 (BPAI 1987).

Discussion

ISSUE

The Examiner concludes that Noda teaches much of the disclosed claim, except

Seth discloses that hydrophilic silicon dioxide is a well known anti-tacking agent (agglomeration inhibitor) (see col 3, lines 3-5). Seth discloses drug particles coated with acrylate polymers wherein Syloid® 244FP is incorporated into the acrylate polymer to deagglomerate the particles (see col 2, line 14 to col 3, line 5; Examples). Syloid® 244FP is comprised of silicon dioxide particles having an average particle size of 5.5 microns (see Addington; paragraph 250).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to incorporate Syloid® 244FP as the agglomeration inhibitor in the composition taught by [Noda], to deagglomerate the particles. The expectation of success is high, as Noda discloses incorporation of agglomeration inhibitors, and Seth discloses that silicon dioxide is a well known anti-tacking agent and that Syloid® 244FP is an effective agglomeration inhibitor used in drug particles coated with acrylate polymers.

The above references do not teach sigmoidal release of the active ingredient. Although the references do not disclose all the characteristics and properties of the composition disclosed in the present claims, based on the substantially identical process using identical components, the Examiner has a reasonable basis to believe that the properties claimed in the present invention would be inherent in the composition made by combining Noda and Seth as described above. Because the PTO has no means to conduct analytical experiments, the burden of proof is shifted to [the] Applicant to prove that the properties are not inherent.

(Ans. 5.)

Appellants argue that

Noda does not teach that talc and colloidal silica are “functional equivalents in their ability to act as agglomeration inhibitors” in its coating films, most especially in its coating films comprising Eudragit RS 30 D® or Eudragit RS® as the acrylic polymer. Nor does Noda suggest adding colloidal silica to its coating films, most especially to its coating films comprising Eudragit RS 30 D® or Eudragit RS® as the acrylic polymer, to persons having ordinary skill in the art. Noda states that colloidal silica may be added to the core.

Nor does Noda teach that its “active ingredient ... [must have] a solubility in water of at least 10 g/l at 20°C,” as Applicant's claims require. Applicant's Specification teaches that theophylline, the active agent in the pharmaceutical preparations Noda describes in its Examples 1, 3, 4, and Experiment, has a solubility in water of 8.4 g/l at 20°C (Spec., p. 23, l. 22). The significance of the required solubility limitation on the active ingredient employed in Applicant's claimed pharmaceutical preparations is stated in the Specification (Spec., p. 7, ll. 16-17; emphasis added), “The effect according to the invention surprisingly occurs only with active ingredients which have a solubility in water of at least 10 g/l “ In support of that statement, the results from Applicant's Examples 6-8 reported in Tables 1 and 2 (Spec., pp. 24-25) show that Noda's theophylline with a solubility in water of 8.4 g/l at 20°C (Spec., p. 23, l. 22) is not sigmoidally released as required from Applicant's claimed pharmaceutical preparations whereas the results from Applicant's Examples 1-3 and 10 reported in Tables 1 and 2 (Spec., pp. 24-25) show that phenylephrine hydrochloride and terbutaline sulphate with a solubility in water of 500 g/l at 20°C (Spec., p. 23, ll. 24-26) are sigmoidally released as required from Applicant's claimed pharmaceutical preparations.

(App. Br. 9-10.)

Appellants argue that “Seth teaches away from combining Noda's acrylic polymers containing a trimethylammonium-ethyl group (available under

the name Eudragit RS®) with colloidal silica because the combination would have no desired effect.” (App. Br. 17.)

The issue with respect to each of the obviousness rejections is: Is there sufficient evidence to support the Examiner’s conclusion that the claimed invention is obvious in view of the cited prior art? Has the Examiner adequately addressed Appellants’ evidence of unexpected results?

PRINCIPLES OF LAW

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.” *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a *prima facie* case of obviousness has been established, we consider the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

After a *prima facie* case of obviousness has been established, the burden of going forward shifts to the applicant. Rebuttal is merely a “showing of facts supporting the opposite conclusion,” and may relate to any of the *Graham* factors including so-called secondary considerations.

If rebuttal evidence of adequate weight is produced, the holding of *prima facie* obviousness, being but a legal inference from previously uncontradicted evidence, is dissipated.

In re Piasecki, 745 F.2d 1468, 1472 (Fed. Cir. 1984) (citations omitted).

“[T]he Board must weigh each reference for its power to suggest solutions to an artisan of ordinary skill.” *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991). “If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed.” *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986).

The burden of demonstrating unexpected results rests on the party asserting them, and “it is not enough to show that results are obtained which differ from those obtained in the prior art; that difference must be shown to be an *unexpected* difference.” *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972). “Unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice.” *In re DeBlauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). “[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).

Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Companies, Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Instead, evidence of secondary considerations are but a part of the “totality of the evidence” that is used to reach the ultimate conclusion of obviousness. *Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1151 (Fed. Cir. 1983)

Additionally,

In order for a showing of “unexpected results” to be probative evidence of non-obviousness, it falls upon the applicant to at least establish: (1) that there actually is a difference between the results obtained through the claimed

invention and those of the prior art . . .; and (2) that the difference actually obtained would not have been expected by one skilled in the art at the time of invention.

In re Freeman, 474 F.2d 1318, 1324 (CCPA 1973) (citations omitted).

“The 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).

ANALYSIS

We find that the Examiner has provided evidence to support a prima facie case of obviousness. In particular, Noda discloses a pharmaceutical preparation comprising a core containing an active substance and an organic acid and a coating. (Abstract.) The Examiner finds that “Noda discloses (+)-(2S,3S)-3-acetoxy-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4-(5H)-one maleate, which meets the criteria of an active ingredient which has a solubility in water of at least 10 g/l at 20 °C.” (Ans. 13, Noda, col. 5, l. 5-16.)

Noda discloses

a coating film formed on the surface of the core comprising an acrylic polymer containing a trimethylammoniumethyl group (see abstract; col 1, line 57 to col 2, line 13). In one embodiment, the coating comprises a copolymer of ethyl acrylate, methyl methacrylate and trimethylammonium-ethyl methacrylate chloride, wherein the trimethylammonium-ethyl methacrylate chloride is present in about 0.025-0.033 mol per 1 mol of remaining neutral acrylic monomers (see col 2, lines 37-42). This corresponds to a polymer comprising 4.9-6.3% by weight trimethylammonium-ethyl methacrylate monomers based on the total weight of the polymer (4.9% calculated from

$(5.2 \text{ g}/(101 \text{ g} + 5.2 \text{ g})) \times 100\%$ where 5.2 g is calculated from $(0.025 \text{ mol})(207 \text{ g/mol})$ where 207 g/mol is the molecular weight of trimethylammonium-ethyl methacrylate and 101 g is calculated from $(1 \text{ mol})(101 \text{ g/mol})$ where 101 g/mol is the molecular weight of both ethyl acrylate and methyl methacrylate (the remaining neutral acrylic monomers); 6.3% is obtained by a similar calculation). The organic acid may be succinic acid (see col 2, line 51).

(Ans. 4.)

Importantly, the Examiner finds that the coating may further comprise agglomeration inhibitors (Ans. 12, *see* Noda, col. 4, lines 39-44 disclosing agglomeration inhibitors such as talc and titanium dioxide). The Examiner acknowledges that Noda does not disclose the specific silicon dioxide agglomeration inhibitor claimed. Seth is relied on by the Examiner to show that silicon dioxide is a known, conventional agglomeration inhibitor. The Examiner concludes that

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to incorporate Syloid® 244FP as the agglomeration inhibitor in the composition taught by [Noda], to deagglomerate the particles. The expectation of success is high, as Noda discloses incorporation of agglomeration inhibitors, and Seth discloses that silicon dioxide is a well known anti-tacking agent and that Syloid® 244FP is an effective agglomeration inhibitor used in drug particles coated with acrylate polymers.

(*Id.* at 5.)

We agree with the Examiner that Noda essentially teaches each element claimed, including the use of agglomeration inhibitors in the coating. We find that it would have been *prima facie* obvious to incorporate

a conventional, pharmaceutical agglomeration inhibitor such as silicon dioxide for the agglomeration inhibitor disclosed in the coating of Noda for its known and expected properties.

Thus, the burden of coming forth with evidence to rebut the Examiner's prima facie case of obviousness has shifted to Appellant. *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977).

Appellants argue that “Noda does not teach that talc and colloidal silica are ‘functional equivalents in their ability to act as agglomeration inhibitors’ in its coating films, most especially in its coating films comprising Eudragit RS 30 D® or Eudragit RS® as the acrylic polymer.” (App. Br. 9.)

Appellants argue that “based on Applicant's Examples 4, 7, and 9 (Spec., p. 24-25; Tables 1-2), the evidence of record proves that combinations of Eudragit RS® and talc which are exemplified and most preferred by Noda do not provide for sigmoidal release of active ingredients having a solubility in water of at least 10g/l at 20°C as Applicant's claims require.” (*Id.* at 16.) Appellants argue that the “comparative compositions that contained talc instead of silicon dioxide (Examples 4, 7, and 9) show a much longer time-release in the pulse phase.” (*Id.* at 27.)

Appellants argue that the results and distinctions in Table 2 of the Specification were unexpected. (Br. 27.) Appellants indicate in the Specification at page 7, line 15, that the effect according to the invention “surprisingly occurs.”

The closest inventive examples in Table 2 of the Specification, page 25, are Examples 2, 3, and 10, which, according to the invention, contain silicon dioxide as the agglomeration inhibitor combined with Eudragit, and

comparative Examples 4 and 9 containing talc as the agglomeration inhibitor combined with Eudragit.

Inventive Example 3, for example, with silicon dioxide shows a pulse phase of 3.5 hours and comparative Example 4 with talc shows a pulse phase of 4 hours with approximately an additional 80% release of drug. (*See* Table 2.) Appellants therefore contend that the difference between 3.5 hours and 4 hours is a much longer time-release in the pulse phase, and therefore unexpected.

Appellants argue:

Table 2 of the Specification . . . shows that preparations representative of the claimed invention (Examples 1, 2, 3, and 10) provide a sigmoidal release of the active ingredient where approximately a further 80% of the active ingredient is released within less than 4 hours in the pulse phase. The comparative compositions that contained talc instead of silicon dioxide (Examples 4, 7, and 9) show a much longer time-release in the pulse phase. That is, the compositions of Examples 4, 7, and 9 did not release at least 80% of the active ingredient within less than 4 hours in the pulse phase of sigmoidal release. The results and the distinctions were unexpected.

(App. Br. 27.)

In response to Appellants' evidence of unexpected results, the Examiner finds that "The data is not commensurate in scope with the elected embodiment nor to the overall scope of the claims. Regarding the elected embodiment, the elected species of organic acid is succinic acid, while the data is drawn to sodium succinate." (Ans. 14.) The Examiner also argues that "the data is drawn to a composition which comprises additional ingredients to those claimed: povidone and Aerosil 200." (*Id.*)

We are not persuaded by the Examiner's arguments concerning Appellants' evidence of unexpected results. The Examiner has not shown that succinic acid and sodium succinate would have reasonably been expected by one of ordinary skill in the art to provide different results in the Examples. In addition both inventive Example 3 in Table 2 and comparative Example 4 both include povidone and Aerosil 200. So all things being equal, these ingredients would not have been expected to affect the end result.

"If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed." *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986). This the Examiner did not do.

Appellants came forward with data showing a difference between an embodiment of the claimed invention and the closest prior art. (Spec. Table 2.) While we recognize that the data shows a difference in pulse release rate between the claimed invention and the prior art comparative example, we have not, without the benefit of the Examiner's review, concluded that such data provides evidence of unexpected results. We do find, however, that the Examiner has failed meet the burden of showing that Appellants' proffered evidence of unexpected results is not convincing. Having no proper rebuttal to Appellants' evidence of unexpected results, we reverse the obviousness rejections with respect to the elected species.

Appeal 2011-002497
Application 11/695,848

CONCLUSION OF LAW

The cited references support a prima facie case of obviousness, however the Examiner has not provided rebuttal argument to Appellants' evidence of unexpected results. The obviousness rejections are reversed.

REVERSED

cdc