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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CAROLINE ROBIC and MARC PORT

Appeal 2020-000689
Application 14/762,064
Technology Center 1600

Before RICHARD M. LEBOVITZ, JASON V. MORGAN, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant[1] seeks our review,[2] under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 1–19. We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

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[1] We use the word "Appellant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party-in-interest as Guerbet. (Appeal Br. 4.)

[2] We consider the Non-Final Office Action issued October 26, 2017 ("Non-Final Act."), the Final Office Action issued July 13, 2018 ("Final Act."), the Appeal Brief filed April 26, 2019 ("Appeal Br."), and the Examiner's Answer issued on August 1, 2019 ("Ans.").

The Examiner rejected claims 1–19 under 35 U.S.C. § 103(a) as being obvious over Jarzyna[3] and Port.[4] (*See* Final Act. 2–6.) Appellant argues the merits of the patentability of the claims as a group, focusing on claim 1. (*See* Appeal Br. 7.) Accordingly, we focus on claim 1 in our analysis.

Appellant's Specification is directed to magnetic nanoemulsions that are used as contrast agents in magnetic resonance imaging ("MRI"). (Spec. 1:3–4.)

Appellant's claim 1, with additional indentations to clarify claim elements, recites:

> An oil-in-water nanoemulsion composition, comprising:
> 50 to 90% by weight of aqueous phase;
> 9.5 to 49.5% by weight of lipid phase nanodroplets,
> wherein the lipid phase nanodroplets comprise an oil and magnetic particles,
> wherein the oil comprises at least 70% by weight of C6-C18 saturated fatty acid glycerides, and
> wherein the magnetic particles comprise an iron compound and are covered with one or more C8-C22 fatty acids; and
> 0.38 to 4.95% by weight of a mixture of surfactants at the interface between the aqueous and lipid phases,
> wherein the mixture of surfactants comprises at least one amphiphilic lipid and at least one amphiphilic targeting ligand, and
> wherein the mixture of surfactants is 4 to 10% by weight of the oil;

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[3] Jarzyna et al., *Iron oxide core oil-in-water emulsions as a multifunctional nanoparticle platform for tumor targeting and imaging*, 30 BIOMATERIALS 6947–54 (2009).

[4] Port et al., International Patent Application Publication WO 2012/084981 A1, published June 28, 2012), cited to as U.S. Patent 9,770,520 B2, issued Sept. 26, 2017.

wherein the composition comprises more than 100 mmol of iron per liter of composition.

(Appeal Br. 21.)

The Examiner finds that Jarzyna teaches iron oxide oil-in-water emulsions that are multifunctional nanoparticles useful for imaging. (*See* Non-Final Act. 3.) The Examiner finds further that the oil-in-water emulsions of Jarzyna are composed of a hydrophobic oil core component, including nanocrystals of iron oxides, and that the oil droplets are stabilized by a lipid mixture of DSPC and PEG-DSPE to favor formation of small particles in a size range of 30–100 nm. (*See* Non-Final Act. 3, citing Jarzyna 6947–48 and Fig. 1A.) Figure 1A of Jarzyna is reproduced below.

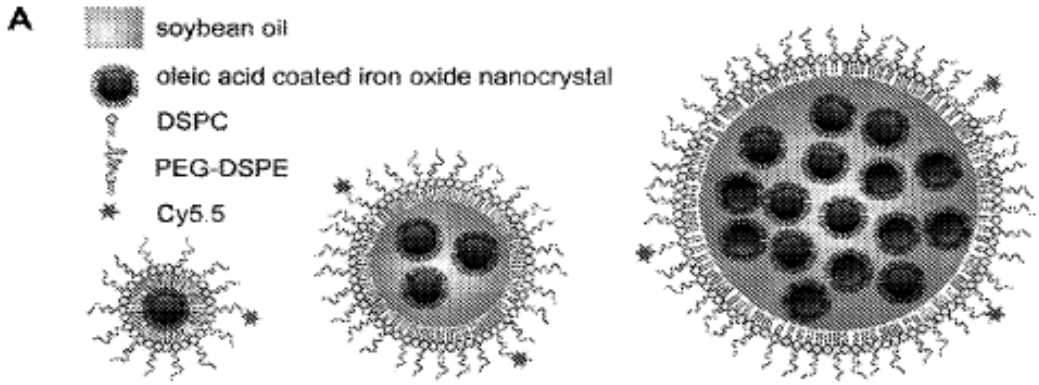

Figure 1A depicts a schematic diagram of different sized nanoemulsions including soybean oil, oleic acid coated iron oxide nanoparticles, and the lipids DSPC and PEG-DSPE. (*See* Jarzyna 6948.) Cy5.5, a near infrared fluorophore, is incorporated into the nanoemulsion for optical imaging. (*See id.*)

Jarzyna teaches several different compositions for the synthesis of nanoemulsions. (*See* Jarzyna 6949.) But, as the Examiner finds, Jarzyna does not teach an emulsion composition comprising a lipid phase of oil that

is 70% by weight of C6–18 saturated fatty acid glycerides and does not teach an amphiphilic targeting ligand. (*See* Non-Final Act. 4.)

Port teaches an oil-in-water nanoemulsion composition for MRI comprising an aqueous phase that is 70% to 90% by weight of the composition, a lipid phase comprising an oil, which is 9.5% to 29.5% by weight of the composition, and a surfactant at the interface between the aqueous and lipid phases. (*See* Port Abstract and 4:30–53.) Port teaches further that the surfactant of the oil-in-water emulsion comprises at least one amphiphilic paramagnetic metal chelate and optionally an amphiphilic lipid, with the total content of surfactant being between 4% and 10% by weight relative to the oil and between 0.35% and 2.95% by weight relative to the composition. (*See id.*) The oil of the nanoemulsion composition of Port can comprise at least 70% of saturated C6–C18. (*See id.*)

Port teaches, further, that nanoemulsions can include, in the surfactant layer, one or more targeting biovectors or ligands that specifically recognize a receptor or enzyme. (*See* Port 3:53–63.) Port teaches that amphiphilic biovectors are 0.01% to 10% by weight of the total amount of surfactants. (*See* Port 5:41–43.) Port teaches "selecting optimized compositions comprising sufficient surfactant to stabilize the size of the nanoparticles, but not too much so as to avoid insufficient incorporation of the biovectors." (Port 4:15–18.)

The Examiner finds that it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute an oil comprising at least 70% by weight of C6–C18 saturated fatty acid glyceride for the soybean oil in the nanoemulsions taught by Jarzyna because Port teaches that compositions using polyunsaturated oils pose several technical

problems, including long term stability problems due to oxidation. (*See* (Non-Final Act. 6–7, citing Port 2:47–58.) The Examiner also finds that it would have been obvious to include an amphiphilic targeting ligand because amphiphilic biovectors allow for access to physiological zones such as the blood brain barrier in order to locate a pathological area. (Non-Final Act. 6–7, citing Port 5:53–62 and 5:25–28.)

The Examiner finds further that it would have been obvious to arrive at the claimed concentrations of the aqueous phase, oil, surfactant, and iron by routine optimization because these concentrations are result-effective variables. (*See* Non-Final Act. 7–8.) Specifically, the Examiner finds that the prior art shows that relaxation rates of a paramagnetic metal ion are a function of the metal concentration, indicating to one of ordinary skill in the art that metal concentration is a result-effective variable, which may be optimized to determine the most favorable concentration for imaging. (*See* Final Act. 4, citing Port 69:1–16.)

Appellant argues that a skilled artisan would not have been motivated to modify the nanoemulsion of Jarzyna to include an amphiphilic targeting ligand as taught in Port because doing so would interfere with the intended purpose of Port. (*See* Appeal Br. 11–12.) According to Appellant, fluorescent agents as taught in Jarzyna prevent the inclusion of vectorising agents, such as amphiphilic targeting ligands. (*See id.*) Appellant cites to the discussion of Jarzyna in the Specification in support of this argument. (*See* Appeal Br. 11, n.19.) Specifically, the Specification states:

> In Jarzyna et al (Biomaterials, 30, 6947-6954, 2009) are described iron nanoparticle emulsions notably consisting of magnetite (Fe_3O_4) covered with oleic acid, the oily phase of these emulsions being mainly made from soya bean oil (in this

> case a polyunsaturated oil. These nanoemulsions are coupled with a fluorophore Cy5.5, a fluorescent agent belonging to cyanines. *This type of compound does not give the possibility of vectorising a nanosystem. This just gives the possibility of being able to ascertain that what is seen in imaging is visible in fluorescence.* The described nanoemulsions have a reduced iron loading capacity (not more than 15 mmol of iron per liter of emulsion) and therefore do not give the possibility of obtaining MRI images of sufficient quality.

(Spec. 3:15–23.) We do not read this portion of Appellant's Specification to indicate that the fluorescent agent of Jarzyna would interfere with an amphiphilic targeting agent. Rather, this disclosure indicates that Jarzyna's agent does not by itself provide for amphiphilic targeting. Appellant does not point to any explanation, either in the Specification or elsewhere, that supports an interpretation of this portion as meaning that a fluorescent agent would interfere with an amphiphilic targeting agent. Appellant does not direct us to any evidence to explain why both could not exist in the same nanoemulsion. Accordingly, this argument does not persuade us that the Examiner erred.

Appellant also argues that a skilled artisan would not have been motivated to replace the soybean oil of Jarzyna with the oil used in Port. (*See* Appeal Br. 12–15.) First, Appellant argues that the iron oxide nanocrystal nanoemulsions of Jarzyna are "entirely distinct" from the metal chelate nanoemulsions of Port. (*See id.* at 12–13.) In support, Appellant points to the statement in Port that the "nanoemulsion does *not* comprise any metallic nanocrystals." (*See id.* citing Port 4:58–59.) Appellant does not explain this statement in Port any further. Thus, it is not clear if metallic nanocrystals are excluded for technical reasons or for other reasons. It is

also not clear how this statement establishes that metallic nanocrystals nanoemulsions are "entirely distinct" from metal chelate nanoemulsions.

Second, Appellant argues that the Examiner is incorrect in finding that a skilled artisan would have been motivated to replace the soybean oil of Jarzyna with the oil of Port. (*See* Appeal Br. 13–14, citing Non-Final Act 6–7.) Appellant argues that the soybean oil emulsion of Jarzyna is injectable and, thus, compatible with crossing biological barriers of organs without toxic effects. (*See* Appeal Br. 13, citing Jarzyna sections 2.8, 3.3, and 3.4.) This argument is not persuasive because it does not address the teaching in Port that unsaturated oils, such as the type of soybean oil used in Jarzyna, are sensitive to oxidation resulting "firstly in a problem of stability of the emulsion over time, especially for storage for several months (typically 3 years for injectable contrast agents), and secondly in a risk (associated with the presence of oxygen) of impairment of the paramagnetic behavior of the product for medical imaging MRI examinations." (Port 2:52–58.) Thus, the evidence supports the Examiner's determination that one of ordinary skill in would have had reason to have substituted the soybean oil in Jarzyna with the oil of Port.

Appellant's argument that the statement in Port does not apply to the nanoemulsions of Jarzyna because they are taught to be stable for at least three months, is similarly unpersuasive because Port addresses longer term stability "typically 3 years." (*See* Appeal Br. 13.) Appellant's argument that the concern about oxidation taught in Port is irrelevant to the metallic oxide nanoparticles of Jarzyna, is also unpersuasive because Port specifically addresses the unsaturated oils, not the metallic portion of the nanoparticles. (*See* Appeal Br. 14.)

Appellant argues further that the teachings in Port regarding problems of polyunsaturated oils were made with respect to lanthanide chelate emulsions disclosed by U.S. Patent Application Publication 2007/0148194 ("Amiji"), not with respect to soybean oil in metallic oxide nanocrystal emulsions. (*See* Appeal Br. 14–15.) We are not persuaded by this argument because regardless of the disclosure of Amiji, Port states that "unsaturated oils are sensitive to oxidation" resulting in stability problems and impairment in MRI examinations and soybean in one such oil. (Port 2:52–58.)

Appellant's arguments fail to persuade us that the problem of long term stability due to oxidation of nanoemulsions made with unsaturated oils is not a reason expressly taught in Port that would motivate one of ordinary skill to look for a substitution. In light of this express teaching, we are not persuaded that the Examiner resorted to hindsight reasoning to find a motivation, as Appellant argues. (*See* Appeal Br. 15.)

Appellant argues that the Examiner erred because the combined teachings of Jarzyna and Port do not teach or suggest an oil-in-water nanoemulsion with more than 100 mmol iron per liter because they do not encompass or overlap the claimed concentration. (*See* Appeal Br. 15–19.) Appellant argues that although Port may teach that relaxation rate is a function of gadolinium concentration in metal chelate emulsions, Jarzyna teaches that the relaxation rate (relaxivity) is dependent upon the *size* of the nanoparticles. (*See* Appeal Br. 16, citing Jarzyna 6950 ("Interestingly, we observed r_1 and r_2 to be size dependent . . ."), Fig. 1.) According to Appellant, this renders the finding that metal concentration is a result-effective variable irrelevant to metal particle nanoemulsions. (*See id.*) We

are not persuaded by Appellant's argument because, while particle size may be one result-effective variable, this does not mean that additional variables would be excluded from affecting the efficacy of the emulsion in imaging.

Furthermore, Jarzyna teaches that iron content affects relaxation rate, wherein "[t]he high payload potential of the nanoemulsions allowed us to load high quantities of iron oxide nanocrystals, causing an remarkably high transverse relaxivity (r_2), which is desirable forT_2(*)-weighted MRI." (Jarzyna 6953; *see* Ans. 7.) Thus, Jarzyna teaches that high quantities of iron oxide nanocrystals are desirable.

Appellant argues further that the Examiner erred in determining that an ordinarily skilled artisan would achieve the claimed metal concentration of 100 mmol of iron per liter of composition by routine optimization because the "general conditions" of claim 1 are not disclosed in Jarzyna or Port. (*See* Appeal Br. 16–18.) According to Appellant, Jarzyna teaches a composition with a maximum of 15 mmol of iron per liter and Port teaches a composition of only 0.1 to 2.5 mmol of gadolinium and that the "extremely large difference" between the claimed concentration and the range taught in Jarzyna cannot support a finding of obviousness. (Appeal Br. 17.) Appellant argues further that because the concentration taught in Jarzyna would have been too low to obtain quality MRI images, the Jarzyna composition was not vectorized, and the Port disclosure is directed to a metal chelate nanoemulsion, the Examiner's determination that the iron concentration is a result-effective variable suitable for optimization through routine experimentation is a reversible error. (*See* Appeal Br. 18.)

We are not persuaded by Appellant's arguments. The cited prior art indicates that it was known in the art that increased iron concentrations

allow increased relaxivity in emulsions for MRI.[5] (*See* Jarzyna 6953; Port 69:1–4.) Because Port teaches an oil-in-water emulsion with many of the same conditions recited in claim 1 (an aqueous phase, a lipid phase with C6–C18 saturated fatty acids, and surfactants at the interface between the aqueous and lipid phases comprising at least one amphiphilic paramagnetic metal chelate) we are not persuaded that the Examiner improperly relied on *In re Aller*, 220 F.2d 454, 456 (CCPA 1955), to find that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable range by routine experimentation."[6]

Appellant argues further that even if the iron concentration is a result-effective variable that could be determined by routine optimization, the claimed iron concentration, increasing the iron concentration nearly seven times to yield a vectorized nanoparticle emulsion with enough iron to produce "very great quality" MRI is a different in new and unexpected result

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[5] We note that Appellant's Specification refers to a 2009 publication, which the Specification states "the nanoemulsions described in this document also have a reduced iron loading capacity (not more than 80 mmol of iron per liter of emulsion) and therefore do not give the possibility of obtaining an optimum sensitivity in MRI." (*See* Spec. 3:25, citing "Senpan et al (JACS, Vol. 3, No. 12, 3917–3926, 2009" (the correct citation appears to be "Senpan et al., ACS Nano. 3(12):3917–3926 (2009)").)

[6] Appellant also cites to *E.I. DuPont de Nemours & Company v. Synvina C.V.*, 904 F.3d 996, 1011 (Fed. Cir. 2018), for the reversal of a Board decision of non-obviousness where the prior art taught the same oxidation reaction and taught conditions identical to or overlapping with those of the claims. (*See* Appeal Br. 18.) We do not see how this case is persuasive of Appellant's argument, where claims were held to be obvious. Appellant does not point to a statement by the court that obviousness can be determined *only* when claims are identical or overlapping with the prior art.

in kind, not in degree. (Appeal Br. 19, citing Spec. 4:8–20.) Appellant does not direct us to evidence to support the assertion that this result would have been unexpected by those of ordinary skill in the art. "Attorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). Nor does Appellant compare the quality of the MRI results obtained by the claimed emulsion with any of the prior art or direct us to evidence that 100 mmol is a critical concentration. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("However, when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

Conclusion

Upon consideration of the record and for the reasons given, we affirm the Examiner's rejection.

In summary:

Claims Rejected	**35 U.S.C. §**	**Reference(s)/Basis**	**Affirmed**	**Reversed**
1–19	103	Jarzyna, Port	1–19	

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

AFFIRMED