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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HASSAN MOHAMMAD[1]

Appeal 2019-000223
Application 13/992,946
Technology Center 1600

Before DONALD E. ADAMS, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1]We use the word "Appellant" to refer to the "applicant" as defined in 37 C.F.R. § 1.142. Appellant identifies Euro-Celtique S.A. as the real party-in-interest. App. Br. 3.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 1, 3, 7, 11, 12, 14, 21, 22, 24–28, 30, 31, and 53–55 as unpatentable under 35 U.S.C. § 103(a) over the combination of Hayes (US 2007/0298103 A1, December 27, 2007) ("Hayes"), Noack et al. (US 2004/0228915 A1, November 18, 2004) ("Noack"), and Arkenau-Maric et al. (US 2009/0004267 A1, January 1, 2009) ("Arkenau-Maric").

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

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellant's invention is directed to a dosage form comprising: (1) non-stretched melt extruded particulates comprising a drug selected from an opioid agonist, a tranquilizer, a CNS depressant, a CNS stimulant or a sedative hypnotic; and (2) a matrix in which the melt extruded particulates are present as a discontinuous phase. Abstr.

REPRESENTATIVE CLAIM

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

1. A dosage form comprising:

> non-stretched, melt-extruded particulates comprising a drug which is an opioid agonist; and a matrix;
>
> wherein said melt-extruded particulates have an average diameter of 200-800 μm and are present as a discontinuous phase in said matrix;

> said matrix comprises a continuous phase comprising a gel-forming agent; and
>
> said melt-extruded particulates further comprise a copolymer of acrylic acid alkyl esters and methacrylic acid alkyl esters or mixtures thereof;
>
> and wherein said dosage form comprises 35-45 % wt of said melt-extruded particulates and 45-65 % wt of said matrix, based on the total weight of the dosage form.

App. Br. 27.

ISSUES AND ANALYSES

We adopt the Examiner's findings, reasoning, and conclusion that the claims on appeal are *prima facie* obvious over the cited prior art. We address the arguments raised by Appellant below.

A. Claims 1, 3, 7, 11, 12, 14, 21, 22, 24–28, 30, 31, and 53–55

Issue 1:

Appellant argues the Examiner erred in finding that the combined cited prior art teaches or suggests the limitation of claim 1 reciting: "dosage form comprises 35-45 % wt of said melt-extruded particulates" and "45-65 % wt of said matrix, based on the total weight of the dosage form." App. Br. 12.

Analysis

The Examiner finds that Hayes teaches particulates produced by melt extrusion (abstract), particulates with a diameter of 0.1mm, comprising a matrix of Eudragit NE 30 D and NE 40 D. Final Act. 4 (citing Hayes ¶¶ 10,

14. The Examiner finds that Hayes teaches that the matrix comprises a pharmaceutically active agent, including a combination of opioid agonist and opioid antagonist (e.g., oxycodone HCL), a rate controlling polymer (e.g., ethyl cellulose), a plasticizer (e.g., stearyl alcohol), and a lubricant (e.g., glycerol dibehenate). *Id.* (citing Hayes ¶¶ 106, 94, 47, 49, 50). The Examiner finds that Hayes teaches dosages comprising up to 50% oxycodone, and further teaches alteration of the diameter of the particulate, spherical particles, and formulation as a tablet. *Id.* (citing Hayes ¶¶ 54, 79–81, 86, 96).

The Examiner finds that Hayes does not teach or suggest a tablet comprising particulates within a matrix, nor does it expressly teach 35–45% wt particles and 45–65% wt matrix. Final Act. 4. However, the Examiner finds, Noack teaches tablets comprising particulates, and a matrix material, including hydroxypropylmethyl cellulose ("HPMC"), which corresponds to the claimed gel-forming agent. *Id.* (citing Noack, Abstr., ¶ 44). The Examiner also finds that Noack also teaches melt-extruded particles mixed with a matrix and processed into a tablet. *Id.* (citing Noack ¶ 43). The Examiner finds that Noack teaches exemplary embodiments of particles comprising 200 mg microcrystalline cellulose ("MCC," i.e., binder), 40 mg croscarmellose sodium (i.e., disintegrant), 1.6 mg magnesium stearate (i.e., lubricant), and further teaches that this matrix is mixed with an equal amount of particles. *Id.* at 4–5. The Examiner finds that Noack thus teaches 50% matrix and 50% particulates, and further teaches up to 25% binder, 10% lubricant, and 10–80% additional excipient. *Id.* at 5.

The Examiner further finds that, although Hayes does not teach a combination of oxycodone and naloxone, Arkenau-Maric teaches the

combination of an opioid agonist and an opioid antagonist, in which the opioids include oxycodone, and the opioid antagonists include naloxone. Final Act. 5 (citing Arkenau-Maric ¶¶ 46, 25, 63).

The Examiner concludes that it would have been obvious to a person of ordinary skill in the art to combine the particulate formulations of Hayes with up to 25% HPMC as a matrix material, as taught by Noack, to arrive at Appellant's claimed invention. The Examiner finds that a skilled artisan would have been motivated to combine the teachings of Hayes and Noack because both references are drawn to particulates in a tablet formulation; specifically, Noack teaches a plurality of multiparticulates commingled with extra-multiparticulate HPMC and compressed into a tablet. *Id.* Therefore, concludes the Examiner, it would have been obvious to combine the teachings of Noack with the formulations of Hayes to achieve a multiparticulate formulation including HPMC, and then tableting that formulation. *Id.*

The Examiner further concludes that it would have been obvious to a skilled artisan at the time of Appellant's filing to produce the formulations of Hayes with oxycodone and naloxone, as taught by Arkenau-Maric, and that a person of ordinary skill would have been motivated to do so because both references are drawn to particles comprising an opioid, oxycodone, Arkenau-Maric further teaches that naloxone is a known opioid antagonist that may be used in combination with oxycodone. Final Act. 6–7.

Appellant argues that the Examiner acknowledges that Hayes neither teaches nor suggests: (1) the melt-extruded particulates are present as a discontinuous phase in a matrix; (2) the matrix comprises a continuous phase

comprising a gel-forming agent; (3) the dosage form comprises 35–45 % wt of melt-extruded particulates based on the total weight of the dosage form; (4) the dosage form comprises 45–65 % wt of said matrix based on the total weight of the dosage form; and (5) the melt-extruded particulates have an average diameter of 200–800 μm. App. Br. 12.

Appellant contends that the teachings and suggestions of Noack do not cure the alleged deficiencies of Hayes. App. Br. 12. Appellant points to the Declaration of Dr. Harjit Tamber, filed September 11, 2017 (the "Tamber Declaration") as opining on the state of the art in formulating dosage forms at the time of invention, and providing an expert opinion on the teachings of Noack. *Id.*

Appellant argues further that, although Noack teaches particles in a matrix, generally, the tablets of Noack are designed to disintegrate rapidly when administered and, to achieve this, Noack teaches that the amount of extra-multiparticulate (i.e., matrix) material in the dosage form should be minimized. App. Br. 12 (citing Noack ¶¶ 10–11). Appellant contends that the multiparticulate formulations of Noack are therefore no different from the prior art multiparticulate formulations discussed in the Tamber Declaration. *Id.* at 12–13 (citing App. Br. 4–5; Tamber Decl. ¶ 4). According to Appellant, the prior art teaches that melt-extruded particulates are compressed to form tablets using a small amount of filler or diluent and, when orally taken, disintegrate rapidly into the individual multiparticulates. *Id.* at 13. Appellant contends that this is a different concept from the dosage forms in the claims on appeal, as noted by the Tamber Declaration at ¶ 5. *Id.*

Appellant also argues that, contrary to the Examiner's findings, Noack teaches the exemplary production of tablet formulations from three different sets of multiparticulates with masses of: (1) 814.92 mg; (2) 837.76 mg, and (3) 875.83 mg, respectively. App. Br. 13 (citing Noack 7, Table 1). In each case, asserts Appellant, the multiparticulates are mixed with extra-multiparticulate material consisting of 200 mg microcrystalline cellulose, 40 mg croscarmelose sodium and 1.6 mg magnesium stearate, i.e., a total of 241.6 mg matrix material. *Id.* Appellant therefore contends that Noack discloses tablets comprising, respectively: (1) 77.1 wt% particulates and 22.9 wt% matrix; (2) 77.6 wt% particulates and 22.4 wt% matrix; and (3) 78.4 wt% particulates and 21.6 wt% matrix. *Id.* However, Appellant argues, none of the examples of Noack teaches a tablet comprising 50 wt% matrix and 50 wt% particulates. *Id.* (citing Noack 7; *see also* Tamber Decl. ¶ 8).

Appellant further disputes the Examiner's finding that paragraph [0078] of Noack teaches a 50/50 mixture of particulates and matrix. App. Br. 13. Appellant asserts that paragraph [0078] of Noack states that: "The weight was adjusted to match the yield of material obtained in step 10." *Id.* However, Appellant argues, paragraph [0078] of Noack teaches that it is the weight of the matrix materials (referred to in Noack as extra-multiparticulate ingredients) which is adjusted, and not the weight of the melt-extruded particulates. *Id.* at 14. Therefore, Appellant contends, the entire quantity of the coated melt-extruded particulates obtained in step 10 is mixed with the matrix materials. *Id.* Appellant asserts that the quantity of coated melt-extruded particulates obtained in step 10 differs slightly for each of the three formulations in Table 1 because a different thickness of coating is used in

each case, varying from 758.07 mg (7% weight gain) to 814.2 mg (15% weight gain). *Id.*

Appellant further disputes the Examiner's interpretation of Example 2 of Noack. App. Br. 14. Appellant notes that, as the Examiner has acknowledged, microcrystalline cellulose ("MCC") is used in the matrix as an extra-multiparticulate binder. *Id.* Appellant points to paragraph [0044] of Noack as teaching that no more than 25 wt% of extra-multiparticulate binder should be included in the dosage form. *Id.* Appellant argues that, in the Examiner's reading of Example 2, 241.6 mg of matrix material, containing 200 mg of MCC, is mixed with an equal amount, i.e., 241.6 mg, of coated particulates from step 10. *Id.* However, Appellant argues, if this was the case, then there would be 200 mg of extra-multiparticulate binder in a dosage form with a total weight of 483.2 mg, equating to 41% wt of extra-multiparticulate binder. *Id.* Appellant contends that is far more than is expressly taught by Noack as the highest proportion of extra-multiparticulate binder that should be included in the dosage form. *Id.*

Appellant argues, rather, that the correct interpretation of paragraph [0078] of Noack is that the quantity of matrix material is varied with the variation in the quantity of coating used in step 10 to produce the three different dosage forms (7%, 10%, and 15% weight gain). App. Br. 15. According to Appellant, the purpose of Example 2 of Noack is to produce dosage forms containing melt-extruded particulates with varying thicknesses of coating; these are then tested in Example 3 to see how the thickness of the coating affects the rate of release of the drug from the dosage form. *Id.* (citing Noack ¶¶ 64, 84). Appellant asserts that the effect of using different thicknesses of coating in each of the three dosage forms of Example 2 is that

the overall mass of the coated particulates varies slightly in each of the three cases, as set out in Table 1, and that the weight of matrix material used in making the dosage form is varied based on the quantity of material obtained in step 10. *Id.* Significantly, argues Appellant, this is the step involving covering the multiparticulates with differing thicknesses of coating, and hence is where the variation in weight between the three sets of particulates is introduced. *Id.* at 15–16 (citing Noack ¶ 75).

Appellant contends that it therefore follows that the variation in the weight of matrix material used is linked to the variation in weight of the particulates resulting from the different amounts of coating. App. Br. 16. Appellant contends that the "adjusting" of the weight of the matrix material compensates for variation in the weight of coated particulates obtained in step 10 and not so that equal weights of particulates and matrix material are used. *Id.*

Appellant further disputes the Examiner's finding that Noack teaches that its tablets may comprise up to 25% binder and up to 10% lubricant. App. Br. 16 (citing Noack ¶¶ 44, 46). Appellant asserts that paragraph [0044] of Noack teaches that the amount of extra multiparticulate binder present in the tablets disclosed therein is 0.5 to 25%, preferably about 0.75 to about 15%, and more preferably about 1 to about 10%, based on the total weight of the composition. *Id.* at 17. Appellant also contends that paragraph [0046] of Noack specifies that in addition to a binder, the extra-multiparticulate material may comprise a lubricant in an amount of 0.1 to about 10%, preferably about 0.2 to about 8%, and more preferably about 0.25 to about 5%, based on the total weight of the composition. *Id.* Appellant asserts that the total amount of extra-multiparticulate material

taught by Noack is therefore 0.6 to 35%, preferably 0.95 to 25%, and more preferably 1.25 to 15%, based on the total weight of the composition and the above-described ranges. *Id.* Appellant contends that, even if the upper values were relied upon, this would give a maximum amount of 35 wt% of extra-particulate material, which is well below the minimum amount of 45 wt% matrix required by claim 1. *Id.*

We are not persuaded by Appellant's argument. Appellant argues that Noack neither teaches nor suggests the limitation of claim 1 reciting "wherein said dosage form comprises 35–45% wt of said melt-extruded particulates and 45–65% wt of said matrix, based on the total weight of the dosage form."

As an initial matter, Noack is directed to: "an *extended release* multiparticulate formulation of a therapeutic agent, wherein coated core multiparticulate particles of the therapeutic agent are overcoated with a binder-dispersing agent," i.e., "[a] matrix compris[ing] a continuous phase comprising a gel-forming agent," as recited in the claims. Noack Abstr. (emphasis added). Specifically, Noack teaches that: "The present invention relates to an extended release multiparticulate composition, comprising a plurality of particulates, each comprising: a core comprising a hydrophilic therapeutic agent and a binder, a release rate controlling polymer coating the core, and a binder-dispersing agent overcoating the polymer coating." Noack ¶ 12.

Noack teaches that:

> In the embodiment of the composition described immediately above, the at least one extra-multiparticulate material preferably comprises an extra-multiparticulate binder. The extra-particulate binder preferably imparts sufficient cohesion to the

> multiparticulates and extra-multiparticulate material being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Suitable extra-multiparticulate binders include … celluloses such as, but not limited to, methylcellulose, microcrystalline cellulose, and carmellose sodium (e.g., Tylose™);…. An extra-multiparticulate binder, if present, constitute[s] in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the composition.

Noack ¶ 44. Noack further teaches:

> In addition to a binder, the extra-multiparticulate material of the multiparticulate composition of the present invention preferably further comprises one or more pharmaceutically acceptable extra-multiparticulate lubricant.… sulfate. Such extra-multiparticulate lubricants, if present, constitute in total about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the composition.

Id. ¶ 46. And Noack additionally teaches:

> In yet another embodiment, the composition of the present invention optionally further comprises one or more pharmaceutically acceptable diluents as excipients.… like. Such diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 10% to about 80%, of the total weight of the composition.

Id. ¶ 49.

Combining the elements of the extra-multiparticulate constituents of the matrix taught by Noack, it is evident that the range of constituents encompasses the range of "45–65 % wt" of the dosage form required by claim 1.

Noack further teaches that: "The multiparticulates of the extended release tablet of the present invention preferably contain a therapeutic amount of the therapeutic agent. How much of any given therapeutic agent constitutes a therapeutic amount for a given subject is dependent inter alia on the body weight of the subject." Noack ¶ 51.

We agree with the Examiner that, because the range of extra-multiparticulate constituents of the dosage form substantially overlaps those recited in the claims, and because the ratio of active particulate to extra-multiparticulate constituents is a result-effective variable, a person of ordinary skill in the art could, by optimizing the ratio between multiparticulate therapeutic agent and extra-multiparticulate matrix, arrive at the ratios of concentrations recited in the claims. *See In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980) (holding that: "discovery of an optimum value of a result effective variable … is ordinarily within the skill of the art").

We do not disagree with Appellant that the Examples of Table 1 of Noack do not teach the claimed ratios of particulate and matrix recited in claim 1. However, as we have explained *supra*, Noack teaches ranges of constituents that overlap those of Appellant's claims on appeal. That is sufficient to establish a *prima facie* case of obviousness. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (holding that: "[i]n cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness"). Furthermore, "all disclosures of the prior art, including unpreferred embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)).

With respect to the Tamber Declaration, Dr. Tamber points to paragraphs [0010]–[0011] of Noack. Those paragraphs teach that:

> Some therapeutic agents, such as clindamycin, are particularly difficult to produce in the form of compressed tablets of multiparticulates due to the fact that they tend to behave like a monolithic tablet when multiparticulates thereof are directly compressed into tablets, failing to disintegrate within less than 30 minutes, as is preferred for multiparticulate tablets. Furthermore, the recommended dosage of some agents, such as clindamycin, is relatively large for an average adult human. In an unpublished study, oral compressed tablets produced by directly compressing multiparticulate clindamycin were found to demonstrate a sustained release rate. However, the tablets behaved like monolithic tablets, failing to disintegrate in a 24 hour dissolution test. As part of the same study, it was found that disintegration time could be reduced by the addition of extra-multiparticulate material to the formulation; but, a significant increase in tablet size was needed in order to incorporate the extra-multiparticulate material. The resulting tablet size was so large that oral administration to an average adult human would be impractical.
>
> What is needed is an oral extended release multiparticulate formulation that minimizes particulate agglomeration while promoting cohesiveness of compressed formulations of the multiparticulates. What is also needed for active agents, such as clindamycin, that require relatively high drug loading is such a multiparticulate compressed formulation that minimizes the amount of extra-multiparticulate material in the formulation.

Dr. Tamber attests that:

> In my opinion the skilled person reading these paragraphs in the context of the general teaching of Noack would not be motivated to use at least 45% matrix material because this would imply the extra-multiparticulate material in the formulation is not minimized as according to paragraphs [0010] and [0011]. Furthermore, the skilled person would not be motivated to

> formulate tablets comprising at least 45% matrix material with the multiparticulate formulations described in Table 1, as tablet weights, which are unsuitable for oral ingestion of at least 1481.7 mg (7% weight gain), 1523.2 mg (10% weight gain) and 1592.4 mg (15% weight gain) would be obtained.

Tamber Decl. ¶ 9.

We do not find Dr. Tamber's Declaration persuasive that Noack fails to teach or suggest the disputed limitation of claim 1. Paragraphs [0010] and [0011] are expressly directed to problems with the use of certain therapeutic agents, such as clindamycin (a lincomycin antibiotic), in the compositions of Noack, because "they tend to behave like a monolithic tablet when multiparticulates thereof are directly compressed into tablets." Noack ¶ 10. Neither Appellant nor Dr. Tamber adduces any evidence of record to show that the claimed "non-stretched, melt-extruded particulates comprising a drug which is an opioid agonist" with "an average diameter of 200-800 μm" and "present as a discontinuous phase in said matrix," would act in a fashion similar to clindamycin, i.e., as a "monolithic tablet when multiparticulates thereof are directly compressed into tablets." *Id.* Absent such evidence, Appellant may not take the particular teachings of paragraphs [0010] and [0011] out of their specific context in an attempt to bootstrap them into a general teaching that *all* extra-multiparticulate constituents should be minimized in *all* of the compositions taught by Noack.

As such, and in view of the express teachings of Noack in paragraphs [0044], [0046], and [0049], and quoted *supra*, we are not persuaded that a skilled artisan would be necessarily discouraged from following the teachings of Noack to arrive at a composition comprising 35–45% wt of the

melt-extruded particulates and 45–65% wt of the matrix, as required by the claims.

Similarly, we are not persuaded, and for the same reasons we have explained *supra*, by Dr. Tamber's reliance upon the examples of Table 1 of Noack. *See* Tamber Decl. ¶ 8. These are exemplary embodiments which, although instructive, do not embody the complete scope of the teachings of Noack, all of which must be considered in our obviousness analysis. *Biocraft*, 874 F.2d at 807. Moreover, the exemplary embodiments of Table 1 of Noack comprise the antibiotic clindamycin as the active agent, which, as we have also explained, is not the claimed opioid agonist. Dr. Tamber's assertion that: "[T]he skilled person would not be motivated to formulate tablets comprising at least 45% matrix material with the multiparticulate formulations described in Table 1, as tablet weights, which are unsuitable for oral ingestion" (Tamber Decl. ¶ 9) may very well be relevant to compositions in which clindamycin is the active ingredient, but Appellant provides no evidentiary support that similar results would necessarily be obtained for the claimed opioid agonist.

Issue 2

Appellant argues further that the Examiner mistakenly relied upon paragraph [0049] of Noack as teaching that that 10 to 80% diluent may be included in the compositions. App. Br. 18.

Analysis

According to Appellant, paragraph [0049] describes "yet another embodiment" of the composition of the invention optionally further

comprising one or more pharmaceutically acceptable diluents as excipients. App. Br. 17. That is, Appellant argues, paragraph [0049] describes a separate embodiment from that described in paragraphs [0043] to [0047], in which the composition of the invention further comprises extra-multiparticulate material compressibly comingled with the plurality of multiparticulates. App. Br. 17. Appellant contends that the most preferred form of the embodiment of paragraph [0043] is a compressed tablet, whereas tableting is just one possibility in the embodiment of paragraph [0049]. *Id.* Appellant contends, therefore, that there is no teaching or suggestion in Noack that the teachings of the two embodiments could or should be combined. *Id.*

Furthermore, argues Appellant, there is no teaching or suggestion in Noack that the diluents disclosed in paragraph [0049] are intended to be included in the extra-multiparticulate material (i.e., the matrix), rather than in the acive multiparticulates, of the dosage form. App. Br. 18. Appellant notes that the Examiner relies upon paragraph [0033] of Noack to support the finding that the 10–80% diluent disclosed in paragraph [0049] is intended to be included in the matrix of the dosage form. *Id.* (citing Final Act. 10). However, Appellant argues, the Examiner's reasoning ignores the overall teaching of Noack that the amount of extra-multiparticulate material in the dosage form should be minimized. *Id.* Appellant asserts that a skilled artisan would recognize this as a key feature of the dosage forms disclosed in Noack and so would not choose to include a large quantity of diluent into the matrix when incorporating the melt-extruded particulates of Hayes into an overall dosage form based on the teaching of Noack. *Id.* Appellant also

points to the paragraph 9 of the Tamber Declaration in support of their argument. *Id.*

We are not persuaded by Appellant's arguments. Paragraph [0049] of Noack expressly teaches, in relevant part, that: "In yet another embodiment, the composition of the present invention *optionally further comprises* one or more pharmaceutically acceptable diluents as *excipients*." (emphases added). The language "optionally further comprises" implies that the diluents are an optional addition to the directly preceding embodiments, all of which are concerned with the formulation of the extra-multiparticulate matrix. *See* Noack ¶¶ 37–48. Furthermore, the use of the term "excipient" in paragraph [0049] to describe the diluent indicates that the diluent is indeed considered by Noack to constitute a portion of the extra-multiparticulate matrix, and not the active multiparticulate agent.

Finally, we have already addressed Appellant's arguments and the Tamber Declaration regarding paragraphs [0010]–[0011] in the context of whether a person of ordinary skill in the art would not be motivated to combine the references to arrive at the claimed invention. We need not repeat that explanation other than to state that we find Appellant's argument no more persuasive upon repetition.

Issue 3

Appellant argues that the Examiner erred because the combined cited prior art neither teaches nor suggests making melt-extruded particulates with a diameter falling within the claimed range of 200–800 μm. App. Br. 19.

Analysis

Appellant acknowledges that the Examiner finds that Hayes cites a reference which teaches melt-extruded particulates of 0.1 to 5 mm and further finds that Noack teaches melt-extrusion and screening to provide a particle size of 250 μm. App. Br. 19. Appellant argues that there is no teaching in Hayes that it would be advantageous or beneficial to use melt-extruded particulates of the same diameter as those of the cited reference. *Id.* Appellant asserts that Hayes teaches that a diameter of 1 mm is preferred, and exemplifies particulates with diameters of 1 mm and 1.5 mm. *Id.* at 19–20. Therefore, Appellant asserts, there is no teaching in Hayes, including in the reference to the prior art citation, that would motivate the skilled person to produce a dosage form comprising melt-extruded particulates having a diameter falling within the claimed range. *Id.* at 20.

With respect to the teachings of Noack, Appellant contends that the Examiner relies upon paragraphs [0034] and [0035]. App. Br. 20. However, argues Appellant, these paragraphs disclose a wide range of particulate diameters, from 10 μm to 2 mm. Noack does not teach that any particular advantage is associated with the specific size of 250 μm and in fact teaches that "[t]he particular size range selected depends upon desired flow characteristic of the particles, content uniformity, and surface area desired." *Id.* (alteration in original) (citing Noack ¶ 35).

We are not persuaded. Appellant acknowledges that Hayes teaches that melt-extruded particulates with diameters of 0.1mm (100 μm) to 5 mm are known in the art, and which encompass the range recited in Appellant's claims. *See* Hayes ¶ 10. Appellant also acknowledges that Noack also teaches a range of particle diameters (10 μm to 2 mm) that encompasses

Appellant's claimed range of 200–800 μm. *See* Noack ¶¶ 34–35. Appellant also acknowledges that Noack expressly teaches that: "The particular particle size range selected depends upon desired flow characteristic of the particles, content uniformity, and surface area desired." *Id.* at ¶ 35. This latter teaching directly suggests to a person of ordinary skill in the art that particle diameter is a result-effective variable.

"[W]here 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." *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955). This rule is limited to cases in which the optimized variable is a "result-effective variable." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (citing *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977). As we have explained, Noack teaches that particle diameter is a result-effective variable. Noack ¶ 35. We consequently are not persuaded that it would not have been obvious to a person of ordinary skill in the art to optimize the particle diameter to Appellant's claimed range from the broader ranges taught by both Noack and Hayes.

We consequently affirm the Examiner's rejection of the claims.

B. Claims 27 and 55

Appellant argues these claims separately. App. Br. 25. Appellant argues that the combined cited prior art neither teaches nor suggests an opioid antagonist (claim 27) or that the opioid antagonist is naloxone (claim 55). *Id.*

Analysis

As an initial matter, Appellant adduces no evidence, nor makes any argument, that the combined references fail to teach or suggest the disputed limitations, beyond a bare assertion that the references do not teach them. That is insufficient. *See In re Lovin*, 652 F.3d 1349, 1357 (Fed. Cir. 2011) ("[W]e hold that the Board reasonably interpreted Rule 41.37 to require more substantive arguments in an appeal brief than a mere recitation of the claim elements and a naked assertion that the corresponding elements were not found in the prior art").

Furthermore, the Examiner expressly finds that Arkenau-Maric teaches that naloxone is a known opioid antagonist that may be used in combination with the opioid agonist oxycodone. Final Act. 5 (citing Arkenau-Maric ¶¶ 46, 25, 63). We agree. For example, Arkenau-Maric expressly teaches that: "Another known possibility for impeding abuse is to add to the dosage form antagonists of the active substance, for example naloxone or naltrexone in the case of opioids." Arkenau-Maric ¶ 8.

We consequently affirm the Examiner's rejection of these claims.

DECISION

The Examiner's rejection of claims 1, 3, 7, 11, 12, 14, 21, 22, 24–28, 30, 31, and 53–55 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. §	Basis	Affirmed	Reversed
1, 3, 7, 11, 12, 14, 21, 22, 24–28, 30, 31, 53–55	103(a)	Hayes, Noack, Arkenau-Maric	1, 3, 7, 11, 12, 14, 21, 22, 24–28, 30, 31, 53–55	
Overall Outcome			1, 3, 7, 11, 12, 14, 21, 22, 24–28, 30, 31, 53–55	