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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JEFFERY JON SEYER, AMY LEE CONDER, ANGELA PEARCE TAYLOR, and BONNY RENÉ SHAW[1]

Appeal 2018-000122
Application 12/819,760[2]
Technology Center 1600

Before RICHARD M. LEBOVITZ, TAWEN CHANG, and RYAN H. FLAX, *Administrative Patent Judges*.

PER CURIAM

DECISION ON APPEAL

The claims in this appeal are directed to a pharmaceutical composition comprising sodium ibuprofen dihydrate and mannitol. The Examiner rejected the claims under 35 U.S.C. § 103 as obvious. Pursuant to 35 U.S.C. § 134, Appellants appeal the Examiner's determination that the claims are unpatentable. We have jurisdiction for the appeal under 35 U.S.C. § 6(b). The Examiner's decision is affirmed.

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[1] The Appeal Brief ("Br." entered July 1, 2017) lists Wyeth, LLC, as the Real Party in Interest. Br. 3.
[2] "The '760 Application."

STATEMENT OF THE CASE

"Solid dosage forms of ibuprofen are well known." Spec. 1:25. According to the Specification, however, "poor tablet compression, stability and disintegration remain critical formulation issues." *Id.* at 1:25–27. Further according to the Specification, the present invention is advantageous because

> it allows for the formation of [sodium ibuprofen] tablet/caplet cores having a maximum daily sodium content for a patient of less than 140 mg/day . . . and further provides . . . cores and corresponding coated . . . cores exhibiting improved physical stability, high tablet/caplet hardness· and high . . . core strength, coupled and balanced with excellent dissolution and bioavailability characteristics.

Id. at 1:9–19.

Claims 1–4 and 9–12 stand rejected by the Examiner under 35 U.S.C. § 103(a) as obvious in view of Gruber et al. (U.S. Patent Application Pub. No. 2008/0020042 A1, published Jan. 24, 2008) ("Gruber"). Ans. 3; Final Act. 3.

Claims 1 and 4 are representative and are reproduced below (indentations added for emphasis):

> 1. A pharmaceutical composition for commercial manufacture and use in pain relief and/or fever reduction in humans comprising a core, said core comprising sodium ibuprofen dihydrate, mannitol, and at least one lubricant;
>
> wherein the sodium content of said pharmaceutical composition is below 140 mg per 1200 mg of free ibuprofen;
>
> wherein the disintegration time of said core is no greater than 5.48 minutes;
>
> wherein the friability measurement of a batch of said core is no greater than 0.55%; and

wherein the pharmaceutical composition has a hardness greater than 80 N.

4. A pharmaceutical composition for commercial manufacture and use in pain relief and/or fever reduction in humans comprising a coated core, said core containing sodium ibuprofen dihydrate, mannitol,

at least one disintegrant comprising microcrystalline cellulose in an amount greater than 0.1 %, and at least one lubricant;

said coated core having a sodium content of less than 23 mg;

wherein the disintegration time of said core is no greater than 5.48 minutes;

wherein the friability measurement of a batch of said core is no greater than 0.55%; and

wherein the pharmaceutical composition has a hardness greater than 80 N.

REJECTION

The Examiner found that Gruber discloses a core comprising sodium ibuprofen dihydrate and mannitol, which are also recited in claims 1, 3, and 4.[3] Final Act. 3. The Examiner also found that Gruber teaches that its core may comprise calcium carbonate or tricalcium phosphate, which are disintegrants, and microcrystalline cellulose and sodium dodecylsulfate, which are lubricants. *Id.* at 3–4. The Examiner further found that Gruber teaches compositions having a hardness and disintegration time within the scope of the claims. *Id.* at 4.

[3] Claim 3 is similar to claims 1 and 4, reproduced above, except that the sodium content is described as the "composition having a ratio of sodium ibuprofen dihydrate to total sodium content of about 11:1 by weight." Br. 16–17 (Claims App.).

The Examiner found that Gruber does not "explicitly disclose that the pharmaceutical composition has a ratio of sodium ibuprofen to total sodium of about 11:1," as required by claim 3, or "a friability of no greater than 0.55%," as required by all the claims. *Id.* Nevertheless, the Examiner concluded that "[i]t would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to employ the teachings of Gruber . . . to devise Applicant's presently claimed pharmaceutical composition." *Id.* at 5.

With respect to the claimed sodium content, the Examiner noted that "the weight ratio of sodium ibuprofen dihydrate as a whole to sodium in 'sodium ibuprofen dihydrate' itself is . . . about 11:1" and found that "it is common knowledge that the long established trend since at least the late 1960s is to provide 'low sodium' or 'reduced sodium' products for human consumption to minimize the generally perceived hazards associated with too much sodium intake, and to boost potassium intake." *Id.* The Examiner further found that Gruber also discloses utilizing alkali bicarbonates. *Id.* The Examiner determined that it would have been obvious to one of ordinary skill "to employ sodium ibuprofen dihydrate with an alkaline bicarbonate agent, wherein the alkali is not sodium (e.g. is calcium or potassium)" to minimize sodium intake and, thereby, meet the claimed sodium content. *Id.*

With respect to the friability limitation, the Examiner found that, because Gruber suggests compositions having "the same requisite constituent elements in the same amounts" as the claimed compositions, the properties of the compositions must also be the same and "it follows that the

pertinent Gruber composition will have a corresponding friability, if actually measured, of no greater than 0.55%." *Id.* at 6.

DISCUSSION

Appellants do not separately argue the claims. We therefore limit our analysis to claims 1, 3, and 4 as representative. Unless otherwise noted, we adopt the Examiner's findings of fact and reasoning regarding the Examiner's rejection of claims 1, 3, and 4 under pre-AIA 35 U.S.C. § 103(a) (Final Act. 3–10; Ans. 3–16) and agree that these claims are obvious over Gruber. Only those arguments timely made by Appellants in the Appeal Brief (no Reply Brief was submitted) have been considered; arguments not so presented in the Brief are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived."). We highlight the following findings of fact for emphasis.

Findings of Fact

1. Gruber teaches an ibuprofen tablet comprising a tablet core and, if desired, a coat, wherein

> the tablet core, based on the weight of the tablet core, consists of 50 to 100% by weight sodium ibuprofen hydrate and 50 to 0% by weight auxiliary material component and contains no lubricant and no disintegrant, and wherein the sodium ibuprofen hydrate has a water content of 8 to 16% by weight, preferably 11 to 16% by weight, possesses a sufficient hardness, is comparably small and leads to a particularly rapid increase in blood level and thereby to an accelerated onset of analgesic effect.

Gruber Abstract; *see also id.* ¶ 36–40.

2. Gruber teaches that the tablets of its invention can contain for example "about 128 mg to 1024 mg of sodium ibuprofen hydrate (corresponding to 100 mg to 801 mg ibuprofen), in which dosages in the range of about 256 mg to 768 mg, in particular about 256 mg to 512 mg, are generally preferred." *Id.* ¶ 50.

3. Gruber teaches that "the ability of sodium ibuprofen to be tabletized heavily depends on its water content and, contrary to current opinion, it is possible to produce tablets with sufficient hardness and short disintegration times, that contain comparatively little or no auxiliary material." *Id.* ¶ 18.

4. Gruber teaches that

> [i]t is quite common, that the sodium ibuprofen dehydrate [sic] is delivered from the manufacturer with a water content not corresponding to the dihydrate, as the water of crystallization is easily lost upon drying at 40–50° C. and the substance easily changes into the monohydrate form by drying. This fact illustrates the importance of a precise control of the water content, and it may also explain why the dependence of the ability to be tabletized on the water content has not been discovered in the art.

Id. ¶ 25. Gruber teaches that "[a]ttention should . . . be paid during production to ensure that the water content of the sodium ibuprofen hydrate lies in the [suggested] ranges." *Id.* ¶ 52.

5. Gruber teaches that, "[a]ccording to a preferred embodiment, the tablet core can essentially consist of sodium ibuprofen hydrate and be essentially free of auxiliary materials, i.e. it can contain preferably less than 0.1% by weight or especially preferably no auxiliary materials." *Id.* ¶ 37. Gruber teaches, however, that in this embodiment "the water content of the sodium ibuprofen hydrate should be preferably about 11 to 16% by weight, a

water content of about 12.5 to 15% by weight, in particular about 13 to 14% by weight, being especially preferred." *Id.*

6. Gruber teaches that the elimination of lubricant and disintegrant and the reduction or elimination of further auxiliary materials in the tablet formulation of its invention is to "enable[] a significant decrease of the tablet weight and size." *Id.* ¶ 31.

7. Gruber suggests that where the water content of the sodium ibuprofen hydrate is lower, "a comparatively high auxiliary material proportion is in general indicated." *Id.* ¶ 49; *see also id.* ¶ 26.

8. Gruber teaches that its tablet "do not contain significant quantities (i.e., less than 0.1% by weight) of lubricant in the tablet core, and . . . are advantageously completely free of inner lubricants." *Id.* ¶ 28.

9. Gruber teaches that its tablets "expediently do not contain significant quantities (i.e. less than 0.1% by weight) of disintegrants . . . such as . . . microcrystalline cellulose . . . and advantageously they are completely free of such materials." *Id.* ¶ 29.

10. Gruber teaches that "[t]he distintegration times of the tablets of this invention are generally significantly below 10 minutes, typically in the range from about 2 to 7 minutes." *Id.* ¶ 30.

11. Gruber teaches that its tablets should have a tablet hardness (measured by means of a Schleuniger Hardness Tester) of preferably at least about 30 N, especially preferably at least about 40 N." *Id.* ¶ 37; *see also id.* at Table 1 (providing examples of tablets having hardness values greater than 80 N (examples 12, 26, 29, 34, 42, 43, and 47–49)).

12. Gruber teaches that "[p]referably suitable as the auxiliary material component in the tablet core are fillers and/or basic auxiliary

materials. Furthermore, if desired, the tablet core can contain a low quantity of surfactant." *Id.* ¶ 41.

13. Gruber teaches that examples of preferably suitable basic auxiliary materials include calcium carbonate and tricalcium phosphate. *Id.* ¶ 42. Gruber teaches that "the proportion of the basic auxiliary materials in the tablet core may, if present, preferably be about 5 to 30% by weight, in particular about 6 to 25% by weight, based on the weight of the tablet core." *Id.* ¶ 43.

14. Gruber teaches mannitol as an example of a preferably suitable filler for its tablets. *Id.* ¶ 44. Gruber teaches that "[t]he proportion of the filler in the tablet core can, if present, preferably amount to about 1 to 25% by weight, in particular about 3 to 20% by weight and typically about 5 to 15% by weight, based on the weight of the tablet core." *Id.* ¶ 45.

15. Although Gruber teaches that "[t]he addition of a surfactant is . . . generally not required," Gruber also teaches that, "[i]f desired, the tablet mixture can also contain a surfactant such as sodium dodecylsulfate as auxiliary material" in an amount "in general not over about 2% by weight and . . . typically . . . 0.1 to 2% by weight, for example about 1% by weight, based on the weight of the tablet core." *Id.* ¶ 48.

16. The Examiner finds, and Appellants have not disputed, that sodium dodecylsulfate is also known as sodium lauryl sulfate. Final Act. 4.

17. Gruber teaches examples of compositions comprising 53.0% sodium ibuprofen hydrate, 12.7% water, 20.0% povidone K25, 5.0% mannitol, and 22.0% $NaHCO_3$ (Examples 47 and 48), which Gruber teaches as having tablet hardness of 115 and 105 N respectively and disintegration time of 7.2 and 7.8 minutes respectively. *Id.* at Table 1. Gruber also teaches

that its examples 9–20, 22, 23, 26–36, 41, 44, 45 and 47–50 showed "good to very good tablet properties (hardness, disintegration time, friability, look of the tablet surface), in particular those of the Examples 12, 15–20, 22, 23, 29, 34, 47 and 48 resulting in practically perfect tablets." *Id.* ¶ 69.

18. The Specification teaches that microcrystalline cellulose (MCC) and sodium lauryl sulfate are lubricants. Spec. 6:29.

19. The Specification teaches that disintegrants may comprise "microcrystalline cellulose (MCC) plus one or more of . . . metal carbonate . . . , or calcium phosphate." *Id.* at 6:33–7:5.

20. The Specification teaches that, by law, a warning must appear on the label of over the counter drug products intended for oral ingestion "if the amount of sodium present in the labeled maximum daily dose of the product is more than 140 milligrams." *Id.* at 7:17–25.

Appellants contend that the Examiner improperly failed to consider the Declaration of Expert Jeffery Jon Seyer under 37 C.F.R. § 1.132 ("Seyer Declaration"), filed on October 16, 2014. Br. 8–9. Appellants contend that the Examiner has not established that Gruber suggests a sodium ibuprofen dihydrate core having the claimed friability. *Id.* at 10. Appellants contend that Gruber teaches away from compositions with disintegrants and lubricants. *Id.* at 13. Finally, Appellants contend that a skilled artisan would not have had reason to combine the various disclosures of Gruber with a reasonable expectation of arriving at the claimed invention. *Id.* at 11, 13–14. We address these arguments below.

When considered together with the evidence of obviousness, the Seyer Declaration does not show the claims to be non-obvious

Appellants contend that the Examiner did not provide a substantive response to the Seyer Declaration. Br. 9. Appellants state that the Seyer Declaration "provided Applicants' rebuttal evidence to the Examiner's reading of Gruber and of the Examiner's finding of obviousness." Br. 8. Appellants state that the Seyer Declaration shows "the technological challenges experienced by the Applicants and their developmental efforts which led to the invention." *Id.* The Declaration also provides "experimental test data," which Appellants contend demonstrate "manufacturing and stability problems with prior art tablets as represented" by Gruber and further shows "how the tablets prepared in accordance with the present invention showed superior results" and "was commercially successful in the marketplace." *Id.* at 8–9.

The Examiner Properly Considered the Seyer Declaration

As discussed by the Examiner (Ans. 6–7), the Declaration was addressed in the Office Action mailed January 26, 2015. Thus, we are not persuaded by Appellants' contention that the Examiner failed to provide a substantive response to the Seyer Declaration.

Gruber addressed the problem of formulating sodium ibuprofen

Dr. Seyer identified problems with formulating sodium ibuprofen and sodium ibuprofen dihydrate, stating that, because of these problems, efforts at developing a commercially viable formulation were discontinued. Seyer Decl. ¶¶ 8–13. Dr. Seyer stated that sodium ibuprofen dihydrate "presents a

known challenge as it is difficult to granulate and has markedly poor compression properties." *Id*. ¶ 8. *See also id*. ¶ 11 (stating that "[s]odium ibuprofen is a poorly compressible material that is difficult to work with").

Gruber similarly mentions difficulties with formulating sodium ibuprofen. Gruber ¶ 15. However, Gruber explained how these difficulties could be addressed using sodium ibuprofen hydrate:

> Surprisingly it was found that the ability of sodium ibuprofen to be tabletized heavily depends on its water content and, contrary to current opinion, it is possible to produce tablets with sufficient hardness and short disintegration times, that contain comparatively little or no auxiliary material, if a sodium ibuprofen hydrate is used with a water content of 8 to 16% by weight, preferably 11 to 16% by weight and the water content is precisely controlled.

Gruber ¶ 18.

While Dr. Seyer identifies problems with formulating sodium ibuprofen, he omitted the fact that Gruber acknowledged this difficulty and disclosed using *sodium ibuprofen hydrate* to address it. All the rejected claims require sodium ibuprofen hydrate, the form of sodium ibuprofen that Gruber expressly teaches has "useful compression and disintegration properties." Gruber ¶ 18. Dr. Seyer states that sodium ibuprofen "is a poorly compressible material" (Seyer Decl. ¶ 11), but Gruber recognized this problem and solved it using sodium ibuprofen hydrate. Dr. Seyer's discussion about the difficulties of compressing sodium ibuprofen is, therefore, unpersuasive because he and his co-inventors utilized the same solution described in the prior art by Gruber.

Likewise, Dr. Seyer's discussion about the difficulties of working with sodium ibuprofen *dihydrate* is not persuasive because it does not

address Gruber's suggestion that manufacturing issues with sodium ibuprofen dihydrate may be due to loss of water content due to drying, and that by controlling water content and thereby reducing the need for auxiliary materials a significant decrease of tablet size and weight may be achieved. FF3, FF4, FF6.

Use of MCC in claimed invention is obvious

Dr. Seyer stated that his team was aware of publications suggesting sodium ibuprofen combinations that did not include MCC "because that material was thought to result in poorly compressible combinations . . . and could also potentially retard dissolution." Seyer Decl. ¶ 10. Dr. Seyer states that "researchers such as Peter Gruber have taught against using MCC is [sic, in] Sodium Ibuprofen formulations." *Id.* ¶ 13. We address Gruber's disclosure below.

Gruber first explains that lubricants are not necessary to make its tablets comprising sodium ibuprofen hydrate, and may even make the tablet worse:

> In fact it was found that addition of classic lubricants such as magnesium stearate even increases the danger that the final mixture sticks to the surface of the punch. Moreover, the customary lubricants are hydrophobic and would decrease the compressibility and the disintegration properties. Therefore, the tablet formulations of this invention expediently do not contain significant quantities (i.e. less than 0.1 % by weight) of lubricant in the tablet core, and they are advantageously completely free of inner lubricants.

Gruber ¶ 28.

Gruber further explains that "it turned out as a consequence of the absence of inner lubricants, that it is also no longer required to add a

disintegrant to the tablet mix," allowing the proportion of auxiliary materials to "be further reduced or even completely eliminated." Gruber ¶ 29. MCC is a disintegrant. Gruber teaches:

> The water solubility of the sodium ibuprofen hydrate is actually so great, that the disintegration of the tablet cannot be improved through the addition of customary disintegrants or combinations of fillers such as microcrystalline cellulose with disintegrants. Therefore, the tablet formulations of this invention expediently do not contain significant quantities (i.e. less than 0.1 % by weight) of disintegrants or fillers with disintegrant properties, such as crosslinked polyvinylpyrrolidones, magnesium aluminium silicates, *microcrystalline cellulose*, starches, sodium carboxymethylcellulose starches etc., and advantageously they are completely free of such materials.

Id. (emphasis added.)

Thus, the basis for Gruber's reason for teaching that MCC is not necessary in its tablets is because the water solubility of sodium ibuprofen hydrate is "so great" that additional disintegrants, such as MCC, are not needed.

On the other hand, Gruber teaches that insignificant quantities of less than 0.1% of a disintegrant may be present. Gruber ¶ 29 (reproduced above). Claim 4 recites a pharmaceutical composition comprising "at least one disintegrant comprising microcrystalline cellulose in an amount greater than 0.1%." While the two ranges do not overlap, they "are so close that *prima facie* one skilled in the art would have expected them to have the same properties," shifting the burden to the applicant to show they are different and thus should not be considered obvious from the prior art composition. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985); *see also In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("We have . . . held that a prima facie case of obviousness exists when the

claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties."). Appellants have not met this burden.

Moreover, as the Examiner points out, the broadest reasonable interpretation of the claim limitation "at least one disintegrant comprising MCC in an amount greater than 0.1%" is that the total amount of disintegrants in the composition, including MCC, be greater than 0.1% – i.e., the amount of MCC by itself need not be greater than 0.1%. Final Act. 7. As the Examiner also points out, Gruber teaches that its compositions may comprise other ingredients, e.g., calcium carbonate, and the Specification teaches that the disintegrants of the invention may comprise MCC plus a metal carbonate. *Id.*; *see also* FF13, FF19. Given that Gruber teaches that its composition may include less than 0.1% MCC and also suggest inclusion of a metal carbonate such as calcium carbonate, Gruber suggests at least one disintegrant comprising MCC in an amount greater than 0.1%.

We, therefore, agree with the Examiner's finding that disintegrant limitation in claim 4 is met by Gruber's disclosures.

With regard to Dr. Seyer's arguments about MCC having negative properties and Gruber teaching away from its use (Seyer Decl. ¶ 13), Gruber teaches that Examples 24 and 25 show that "tablet formulations, which additionally contain microcrystalline cellulose, talc and, if applicable, the disintegrant material Kollidon CL, are worse than comparable examples without these additions." Gruber ¶ 71. Gruber specifically states that "tablet hardness is not improved through these additions, and the disintegration time is about 9 minutes." *Id.* However, Gruber does not solely attribute this

result to MCC because talc is also present, and even if Gruber did, the amount of MCC in these tablets is 10.5% (Gruber 7, Table 1), which is more than 100-fold more than the claimed lower limit of above 0.1%. Appellants have not established that a skilled artisan would, based on such result with 10.5% MCC and talc, predict that values as low as about 0.1% MCC would have the same worsening effect.

Neither Gruber nor the Seyer Declaration suggests that the prior art unequivocally teaches away from using MCC. Gruber teaches prior art in its background section which used MCC in ibuprofen formulations. Gruber ¶¶ 10, 12. Dr. Seyer acknowledged in his Declaration that MCC is "commonly used as a binder/filler in tablet formations" and "[i]ncluding MCC often results in hard, durable tablets suitable for large scale commercial manufacture." Seyer Decl. ¶ 13. Therefore, Dr. Seyer admits that MCC was known to be beneficial in tablets, consistent with Gruber's disclosure, providing an additional reason to have included it in a tablet.

Use of mannitol in claimed invention is obvious

Dr. Seyer also states that "mannitol in a formulation usually results in a low hardness, friable tablet that breaks apart easily when chewing." Seyer Decl. ¶ 12. However, Gruber teaches three formulations comprising sodium ibuprofen dihydrate and mannitol with hardness values of 76 N, 115 N, and 105 N, respectively (Examples 45, 47, and 48 in Table 1 of Gruber ¶ 66), the latter two of which meet the claimed hardness limitation of 80N. Thus, Dr. Seyer's statement about mannitol leading to "low hardness" is not supported by the evidence before us.

Furthermore, Gruber discloses that mannitol is a preferred filler (Final Act. 10; FF14) and states that such fillers "improve the compressibility" of the tablet (Gruber ¶ 44), providing an express reason to have incorporated it in a tablet.

Seyer Declaration does not evidence secondary considerations commensurate with the scope of the claims

Dr. Seyer described in his Declaration testing the combination of mannitol and MCC, and each of these ingredients by itself. Seyer Decl. ¶ 16. In paragraphs 17 and 18 of his Declaration, he describes "how [the inventors] ho[m]ed in [on their] best formulation of using combinations of mannitol with MCC to achieve excellent manufacturing characteristics despite MCC being discounted by other established experts such as Peter Gruber." Seyer Decl. ¶ 15.

To begin, as noted by the Examiner, the results achieved in the Seyer Declaration are accomplished with specific amounts of mannitol and MCC. Ans. 7–9; Seyer Decl. ¶¶ 16–17 (Tables 1 & 6). The claims are unlimited as to specific amounts. Seyer's experiments also describe *placing* the mannitol and MCC in either 1) the granulation or 2) the compression mix prior to carrying out the compression process. In Table 1, MCC is in the compression mix and mannitol is in the granulation of Formula 1. In Table 6, MCC is in the compression mix, but the mannitol is in both the granulation and compression mix. Dr. Seyer describes this "placement" of MCC and mannitol components as a "new idea." Seyer Decl. ¶ 17. Dr. Seyer stated "by carefully choosing the right blend and the placement in the formula, we were able to formula very good tablets that have not been achievable by others and that could be easily commercialized." *Id.* ¶ 18.2.

However, the claims are neither limited to how the formulation is manufactured nor to whether the mannitol and MCC are placed in the granulation, compression mix, or both. Claim 1 does not even require the presence of MCC. Thus, to the extent that Dr. Seyer's experiments are intended as evidence of secondary considerations,[4] they are not commensurate with the full scope of the claim because, while the claim is limited to specific hardness, friability, and disintegration characteristics, it is not limited to the specific amounts of each ingredient or the manufacturing process utilized to achieve such values. *See In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005).

Moreover, Appellants did not establish a nexus between the evidence and the claimed pharmaceutical composition. "A nexus between the merits of the claimed invention and the evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision." *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1575 (Fed. Cir. 1984); *Hearing Components, Inc. v. Shure*

[4] Factual considerations that underlie the obviousness inquiry include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, praise, and unexpected results. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Secondary considerations are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[] independent evidence of nonobviousness . . . [and] enable[] the court to avert the trap of hindsight." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (internal quotation marks and citations omitted).

Inc., 600 F.3d 1357, 1374 (Fed. Cir. 2010). In this case, the merits of the invention described in Dr. Seyer's Declaration is a composition comprising specific amounts of each of the claimed ingredients made by a specific manufacturing process, none of which are recited in the claims. Thus, the recited characteristics and "new idea" relied upon by Appellants were conferred by specific features that are not recited in the claims. Therefore, Appellants have not established a nexus between what is actually claimed and the properties recited in the claims and described in Dr. Seyer's Declaration.

Finally, Dr. Seyer stated that the product described in his Declaration "has been tremendously successful in the U.S. marketplace for a year and a half with no equivalent products fielded by competitors." Seyer Decl. ¶ 18.2. However, no evidence of the stated commercial success has been provided, such as "significant sales in a relevant market." *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311–1312 (Fed. Cir. 2006). Thus, there is insufficient information to determine whether the product described in Dr. Seyer's Declaration was commercially successful.

Comparisons to Gruber's compositions in Seyer Declaration does not show claims are non-obvious

Appellants state that "[t]wo of the closest Gruber formulations were tested to show their inferior quality and characteristics." Br. 9. Appellants state that such results "further demonstrat[e] that Gruber's approach and disclosure would not have taught one of skill in the art to make the claimed formulations." *Id.* at 10. In particular, the Seyer Declaration states that Dr. Seyer tested the tablets made according to the formulation in Examples 42 and 47 of Gruber and found that the friability of these tablets were outside

the claimed amount of "no greater than 0.55%" and that Gruber's Examples 42 and 47 "would not be . . . commercially viable formula[s]." Seyer Decl. ¶¶ 19.1–19.3.

The evidence is not sufficiently persuasive. As an initial matter, "[A]ll disclosures of the prior art, including nonpreferred embodiments, must be considered." *In re Lamberti*, 545 F.2d 747, 280 (CCPA 1976). Thus, the fact that certain examples in Gruber may not meet the friability limitation of the claims does not show that Gruber's disclosures fail to render the claimed composition obvious.

We further note that, while the Seyer Declaration sets out the raw material formula used to make the tablets of Gruber's Examples 42 and 47, the declaration fails to state the water content of the sodium ibuprofen dihydrate. Seyer Decl. ¶¶ 19.2–19.3. In light of Gruber's explicit disclosures regarding the importance of water content in the ability of sodium ibuprofen to be tabletized and the need to ensure that water content of the sodium ibuprofen hydrate lies in the suggested ranges, the Seyer Declaration has not provided sufficient evidence for us to evaluate whether the tested formulations are, in fact, identical to the formulations of Gruber's Examples 42 and 47. FF3, FF4.

In addition, the Seyer Declaration states that Gruber's formulas were "compressed . . . using 10.5 mm round tooling so as to compare to the manufacturing process" in the instant application. Seyer Decl. ¶ 19.2. Gruber, however, states that its formulations were "compressed on a rotary press with 16 presses at an average hourly output of 40[,]000-60[,]000 tablets." Gruber ¶ 65. It is thus unclear whether Dr. Seyer in fact used identical manufacturing procedure as that described in Gruber. To the extent

the compression tools were indeed different, Appellants did not establish that departing from Gruber's manufacturing process by using the 10.5 mm rounding tool would have had no effect on the tablet's subsequent friability value. Seyer Decl. ¶ 19.3.

Assuming that the formulations tested in the Seyer Declaration are identical to the formulations of Gruber's Examples 42 and 47 and made by the same process, and to the extent the experimental data in Seyer's Declaration is intended to show evidence of unexpected results, we are not persuaded. We have already explained that the experimental data contained in the Seyer Declaration is not commensurate with the scope of the claims and have not shown sufficient nexus between the claim limitations and any expected results. Furthermore, we are not persuaded that the Seyer Declaration has compared the claimed compositions to the closest prior art.

For example, Gruber's Example 42 does not comprise either mannitol (as in claims 1, 3, and 4) or MCC (as in claim 4). Thus, Example 42 is not the "closest Gruber formulation" because it lacks mannitol, which is required by all the claims, and MCC, which is required by claim 4. In contrast, Example 45 of Gruber, which was not tested by Dr. Seyer, appears closer than Example 42 to the claimed composition because it contains mannitol. Example 42 is also characterized by Gruber as "sticky," and is not among the list of tablets said to have good friability or to be "practically perfect," while Example 45 is described as having good to very good tablet properties (hardness, distintegration time, friability, look of the tablet surface)." Gruber ¶ 69. Accordingly, one of ordinary skill in the art would not have expected Example 42 to have good friability, but instead would have expected it to be inferior.

We note that Dr. Seyer also did not test Example 48, which has the same ingredients and amounts as Example 47, but is made by a different manufacturing process. The Seyer Declaration states that Example 48 was not tested because it has the same ingredients as Example 47 and lower hardness. Seyer Decl. n. 1. As Dr. Seyer acknowledges, however, Examples 48 and 49 are manufactured differently. *Id.* In particular, the tablets in Gruber were produced by combining materials A (i.e., auxiliary material(s) in the granulate) and material B (i.e., tabletization auxiliary material(s)). Gruber ¶¶ 64, 65. The $NaHCO_3$ is placed in material B in Example 47 and in material A in Example 48. Gruber ¶ 66 (Table 1). To the extent Appellants argue that *placement* of the tablet ingredients in the granulation and compression mix affected the properties of the resulting tablet, *see*, *e.g.*, Seyer Decl. ¶ 18.2, Dr. Seyer has not established that Example 48, with the $NaHCO_3$ *placed in a different auxiliary material* than in Example 47, would have a friability outside the claimed range.

Dr. Seyer's apparent purpose was to show that Gruber's formulations comprising mannitol, and having a hardness within the scope of the claims, do not meet the claimed friability limitation. Assuming this to be the case, such a result would still not show that it would not be obvious for a skilled artisan to arrive at the claimed compositions, for the reasons discussed above. Moreover, as explained above, Dr. Seyer did not test Examples 48 and 45,[5] both of which also contained mannitol, and it is unclear whether the

[5] Gruber's Example 45 has a reported hardness of 76 N, which is slightly lower than the claimed value of greater than 80 N. Gruber Table 8. However, as shown in Gruber Figure 1, it is known that tablet hardness may be increased at least to some extent by increasing the compressive force. Gruber Fig. 1.

identical manufacturing process was used. Therefore, Dr. Seyer did not even persuasively establish that the recited friability was not achieved or achievable by Gruber with a formulation comprising mannitol.

The Examiner has established a prima facie case of obviousness with respect to the friability limitation

Appellants contend that the Examiner has not shown that Gruber's tablets meet the limitation regarding friability (no greater than 0.55%). Br. 10. Appellants emphasize that Gruber "does not disclose the friability of any of the disclosed tablets." *Id.* We are not persuaded.

As discussed above, Gruber suggests a composition comprising all of the claimed ingredients, even if it does not provide an example of a composition comprising all of these ingredients. "Where . . . the claimed and prior art products are identical or substantially identical . . . the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products." *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977) (citations and footnote omitted).

Appellants contend that "[i]t is factually incorrect that Gruber's disclosed compositions are the same as those claims being appealed." Br. 10. Appellants do not explain what is factually incorrect about the Examiner's finding in this regard. To the extent that Appellants' argument is that none of the examples disclosed in Gruber contain all of the

ingredients required by the claims, we note that "all disclosures of the prior art, including nonpreferred embodiments, must be considered." *In re Lamberti*, 545 F.2d 747, 280 (CCPA 1976). Appellants' focus on only Gruber's examples is thus misguided.

Neither are we persuaded by Appellants' arguments relying on the Seyer Declaration, i.e., that "representative samples from Gruber showed much poorer friability measurements." Br. 10. In addition to the issues we noted above with respect to the testing described in the Seyer Declaration, none of the Gruber examples tested in the Seyer Declaration contain all of the ingredients recited in the claims, even though such a composition is suggested by Gruber's disclosures. Thus, the fact that they allegedly showed "much poorer friability measurements" does not suffice to meet the burden articulated in *In re Best* for showing that "the prior art products do not necessarily or inherently possess the characteristics of [the] claimed product."

A skilled artisan would have had reason to manufacture tablets having the claimed sodium content.

Appellants contend that a skilled artisan would not have had "motivation to prepare a low-sodium sodium ibuprofen composition." Br. 11 (emphasis omitted).

We are not persuaded. As explained above, the Examiner found that, in making a composition suggested by Gruber, a skilled artisan would have had a reason to utilize an alkaline bicarbonate agent using an alkali other than sodium, in order to minimize sodium intake. Final Act. 5. Thus, the

Examiner found that Gruber's disclosures render the claimed sodium content prima facie obvious. *Id.*

Appellants contend that the evidence cited by the Examiner as a reason to lower the sodium content "only discusses sodium levels in the context of food and daily consumption and does not suggest reducing the sodium content of a medicine such as ibuprofen." Br. 11.

This argument is not persuasive. Based on the molar sodium content of sodium ibuprofen dihydrate, the Examiner found that the sodium content recited in the claims is "basically equivalent to stipulating that the sodium ibuprofen dihydrate is the only element in the composition that contains sodium." Final Act. 7–8. Appellants did not dispute this finding. The Examiner also found that "Gruber's examples 1–8, 10–12, 14, 21, and 33 disclose compositions in which the sodium ibuprofen dihydrate is the only element in the composition that contains sodium." *Id.* at 8. The Examiner, therefore, concluded that Gruber contemplated compositions without additional sodium. *Id.*

Gruber also discloses using alkali material other than a sodium salt, such as potassium hydrogen carbonate. Gruber ¶ 42; Final Act. 7. Thus, even if the Examiner's reasoning regarding lowering sodium content to minimize sodium intake were not persuasive, the Examiner established that Gruber described formulations which lacked additional sodium and contemplated other carbonate salts.

Finally, while the evidence cited by the Examiner for lowering sodium intake may have been directed at foods, one of ordinary skill in the art is "not an automaton," but is a person of "ordinary creativity" (*KSR*, 550 U.S. at 421) and would have recognized sodium intake could be reduced

from any source, including a pharmaceutical. Indeed, this is shown by the Specification itself, which explains that "by law, a warning must appear on the label of over the counter drug products intended for oral ingestion "if the amount of sodium present in the labeled maximum daily dose of the product is more than 140 milligrams." FF20.

Gruber does not teach away from the claimed compositions comprising disintegrants and lubricants

Appellants contend that Gruber teaches away from the inclusion of lubricants and disintegrants. Br. 13. We are not persuaded.

Claims 1, 3, and 4 all recite "at least one lubricant," but does not limit how much (or little) lubricant is present. Gruber discloses that the lubricant can be present in an amount "less than 0.1% by weight" of its formulations. Gruber ¶ 28. Moreover, as the Examiner points out, Gruber teaches that its tablets may contain 0.1 to 2% sodium dodecylsulfate, also known as sodium lauryl sulfate, which the Specification acknowledges to be a lubricant. FF15, FF18. Thus, Gruber does not teach away from including the amount of lubricants required by the claims.

Claim 4, as discussed above, further comprises a disintegrant, which comprises MCC in an amount greater than 0.1%. Gruber discloses that the disintegrants can be present in an amount "less than 0.1% by weight" of its formulations. Gruber ¶ 29. As discussed above, the claimed ranges "are so close that prima facie one skilled in the art would have expected them to have the same properties," shifting the burden to Appellants to show they are different. *Titanium Metals*, 778 F.2d at 783; *see also In re Peterson*, 315 F.3d at 1329. This burden was not met.

As also discussed above, the broadest reasonable interpretation of the claim limitation "at least one disintegrant comprising MCC in an amount greater than 0.1%" is that the total amount of disintegrants in the composition, including MCC, be greater than 0.1%. The Specification teaches that the disintegrants of the invention may comprise MCC plus a metal carbonate. FF19. In addition to teaching that the composition may contain disintegrants in an amount less than 0.1%, Gruber also teaches that its compositions may comprise calcium carbonate, which is a metal carbonate, in an amount of about 6 to 25% by weight. FF13. Accordingly, Gruber does not teach away from a composition comprising "at least one disintegrant comprising MCC in an amount greater than 0.1%."

The Examiner has established a prima facie case that a skilled artisan would have had reason to combine Gruber's disclosures to arrive at the claimed invention, with a reasonable expectation of success

Appellants contend that the Examiner erred in concluding

> that one of ordinary skill in the art would have a reasonable expectation that the resulting tablet would exhibit the optimal rate of disintegration and maximum hardness, and been motivated to make the claimed invention, AND would have been able to make the claimed invention by attempting routine variations of the cited prior disclosures.

Br. 13. We are not persuaded and address each of these arguments below.

A skilled artisan would have a reasonable expectation of success in preparing the claimed tablets

As an initial matter, and as already discussed above with respect to the friability limitation, Gruber suggests a composition having all of the claimed ingredients in the claimed amounts. Thus, a skilled artisan would have a

reasonable expectation of success of preparing a tablet having the claimed ingredients. In light of the substantial similarity between the claimed composition and the composition suggested by the prior art, the burden is shifted to Appellants to show that the composition suggested by Gruber would not necessarily or inherently possess the characteristics (i.e., hardness, disintegration times, and friability) of the claimed product. *In re Best*, 562 F.2d at 1255. Appellants have not provided persuasive evidence to satisfy this burden, and to the extent such properties are inherent, they do not render the claims non-obvious even if a skilled artisan cannot "reliably predict" such properties. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) ("The discovery of a new property . . . of a previously known composition, even when that property . . . [is] unobvious from the prior art, can not impart patentability to claims to the known composition.").

Furthermore, a skilled artisan would have a reasonable expectation of being able to prepare a tablet having the claimed rate of disintegration and hardness by following Gruber's disclosures, because Gruber explicitly teaches that its tablets have disintegration times and hardness values that overlap with the claimed ranges and also teaches that several of its formulations showed "good to very good tablet properties" including friability and others of which resulted in "practically perfect tablets." FF10 (teaching tablets typically having disintegration times from about 2 to 7 minutes); FF11 (teaching that it is especially preferable that tablets have hardness of at least about 40 N and providing examples of tablets having hardness values above 80 N); FF17. "A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art," *In re Peterson*, 315 F.3d at 1329–30, and

Appellants have not provided persuasive evidence why a skilled artisan would not reasonably expect to be able to prepare a tablet having the claimed characteristics when Gruber teaches tablets having overlapping disintegration times and hardness values.

A skilled artisan would be motivated to prepare tablets having the claimed properties

As already discussed, Gruber teaches sodium ibuprofen dihydrate tablets having the claimed auxiliary ingredients as optional ingredients. Thus, Gruber's explicit disclosures serves as motivation for a skilled artisan to prepare tablets comprising claimed ingredients. Appellants have not provided persuasive evidence showing that such a composition would not necessarily or inherently possess the claimed characteristics relating to hardness, disintegration times, and friability. *In re Best*, 562 F.2d at 1255. A skilled artisan need not have the same reason as Appellants (e.g., to achieve a certain hardness, disintegration times, and/or friability) to combine the ingredients in the claimed manner. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007).

Moreover, we are not persuaded by Appellants' apparent argument that a skilled artisan would not have been motivated to prepare a tablet having the allegedly optimal hardness and disintegration times. As evidenced by Gruber, hardness and disintegration times (as well as friability) are well-known in the prior art as important tablet properties for optimization. FF17.

Appellants argue that "[t]here is . . . no suggestion of the desirability of tablets having hardness greater than 80N as Gruber is satisfied with relatively low hardnesses of about 30N or 40N" and that Gruber "does not

discuss friability at all." Br. 14. We are not persuaded. Gruber teaches that tablet hardness is especially preferred to be *at least* about 40 N, but suggests that much higher hardness values are desirable: all of the examples Gruber describes as "almost perfect" tablets have hardness values significantly above 40 N. FF11, FF17. Likewise, as already discussed and contrary to Appellants' contention, Gruber suggests that friability is an important tablet property by listing it among the properties considered in evaluating its examples. FF17.

Finally, we are not persuaded by Appellants' arguments that, because "Gruber exemplified numerous possible combinations of excipients, many or most of which are not within the presently claimed composition," that "it is only with the hindsight benefit of [Appellants'] disclosure that one of ordinary skill could pick and choose [and] discern which specific pharmaceutical elements could be selected from the prior art to recreate the claimed invention." Br. 13–14. While it is true that Gruber discloses many possible combinations of excipients, not all of which would be within the claimed composition, the claimed compositions are not non-obvious merely because Gruber made obvious compositions other than what is claimed. *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("[D]isclos[ing] a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art.")

Appellants have not shown that a skilled artisan would not have been able to arrive at the claimed invention based on Gruber's disclosures

Appellants contend that, "[a]lthough Gruber discloses a sodium ibuprofen composition, Gruber does not disclose a composition with qualities and characteristics as strong as [Appellants']" and "contains no suggestion that one could reliably predict tablet properties as claimed. Br. 14.

We note once again that, because Gruber suggests a composition having all of the claimed ingredients, the burden is shifted to Appellants to show that the suggested composition would not have the claimed hardness, disintegration times, and friability. *In re Best*, 562 F.2d at 1255. We find Appellants have not met this burden.

Appellants point to the fifty examples in Table 1 of Gruber showing "various tablets have extremely different hardnesses and disintegration times (even when prepared using similar recipes) and there is no suggestion of how to predict the properties of the resultant tablets in view of the varying manufacturing formulas provided." Br. 14. Appellants argue that there is no disclosure in Gruber how to predict the hardness and disintegration times, and that Gruber "states in para. 0027 that hardness and disintegration time are nearly independent of the compressive force used during tabletization despite the lack of a disintegrant. Accordingly, this disclosure does not provide any teaching of how to prepare or predict tablet properties." *Id.*

We are not persuaded. None of the examples in Table 1 of Gruber contains all of the claimed ingredients in the amounts suggested by Gruber (e.g., MCC, mannitol, lubricants such as sodium lauryl sulfate, calcium carbonate). Thus, they do not satisfy Appellants' *In re Best* burden for

showing that the composition rendered obvious by Gruber (i.e., a sodium ibuprofen dihydrate tablet comprising the claimed ingredients in the amounts suggested by Gruber) would not necessarily or inherently have the claimed tablet properties relating to hardness, disintegration times, and friability when manufactured in the manner taught in Gruber.

We acknowledge Appellants' argument that Gruber appears to show that compositions containing the same ingredients in the same amounts (e.g., Examples 28, 29, and 30 of Gruber) may have different hardness values, friability, and disintegration times depending on the manufacturing process. Br. 14. However, because the claims recite a range of hardness values, friability, and disintegration, and because examples 28, 29, and 30 are very different from the compositions comprising the claimed ingredients that are suggested by Gruber, we find that this evidence does not persuasively show that the tablets suggested by Gruber containing all of the claimed ingredients would not necessarily or inherently fall within the claimed ranges of hardness, friability, and disintegration times, if manufactured in the manner taught by Gruber.

Indeed, we do not agree with Appellants' argument that "Gruber does not disclose a composition with qualities and characteristics as strong as Applicants'" or that Gruber does not "provide any teaching of how to prepare or predict tablet properties." Br. 14. Some of the closer examples in Gruber to the claimed composition are Examples 45, 47, and 48, because each of these comprise mannitol. Example 45 has a disintegration time of 4.3 min, which is within the scope of claims 1, 3, and 4, although it has a hardness of 76 N which falls outside of it. However, it is so close to 80 N, it

would be reasonably expected to have the same properties. *Titanium Metals*, 778 F.2d at 783. The friability of this tablet was not tested by Dr. Seyer.

Examples 47 and 48 have hardness values of 115 N and 105 N, respectively, which are within the claim scope, but have disintegration times of 7.2 min and 7.8 min, outside the scope of the claims. However, as found by the Examiner, Figure 1 of Gruber suggests that the hardness and disintegration times within the scope of the claim could be routinely met by following Gruber's guidance. Specifically, Figure 1 of Gruber, which reveals "the hardness and the disintegration time of a tablet of this invention in relation to the compressive force used in the tabletization process" (Gruber ¶ 19), shows a compressive force that results in a tablet having a disintegration time below 5 and a hardness of 80 N, both values of which meet the corresponding values of the claim. *See* Final Act. 9 discussing the values shown in Figure 1 of Gruber.

Figure 1 is reproduced (grey shading added) below:

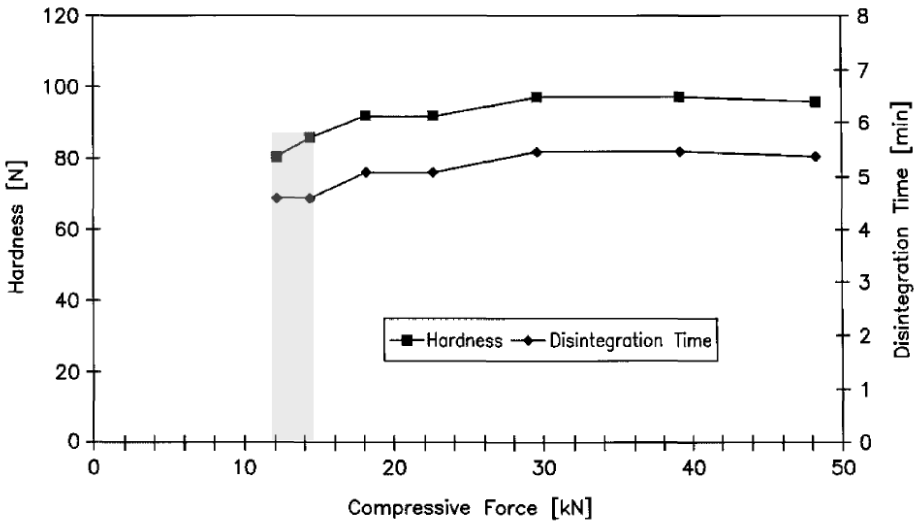

Figure 1, reproduced above, shows the compressive force to make a tablet with a hardness of about 80 N and above and a disintegration time below about 5 min (grey shading added to emphasize these values). While

these tablets do not contain mannitol (Gruber ¶ 27), Gruber attributes the hardness and short disintegration times to the water content of the sodium ibuprofen. Gruber ¶ 18 (reproduced above). It is true, as discussed by Appellants, that Gruber states that "hardness and disintegration time of the tablets of this invention are *nearly* independent of the compressive force used during tabletization" (Gruber ¶ 27) (emphasis added), yet Gruber shows there is a relationship in at least a part of the graph and Figure 1 expressly shows compressive forces that result in properties that meet the claimed limitations.

With respect to the claimed friability property, while Gruber does not disclose actual friability values, Gruber discloses that its tablets exhibit good friability. Gruber ¶ 69; Ans. 9–10. We agree with the Examiner that "Appellant cannot patent or re-patent a prior art composition merely by documenting a 'new' property of the prior art composition, even if the property is not expressly disclosed in the prior art."[6] Answer 10. Thus, because Appellants determined the friability of only one of three examples in Gruber comprising mannitol and did not test examples said to have good friability (Gruber ¶ 69), it has not been persuasively established that Gruber's examples lack the friability disclosed in the claims.

[6] It is well-established by case precedent that merely recognizing something that was inherent, but not known before, is insufficient to render an old process again patentable. *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002); *see also In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990); *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999); *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007).

SUMMARY

For the foregoing reasons, the obviousness rejection of claims 1, 3, and 4 is affirmed. Claims 2 and 9–12 were not argued separately, and fall with claims 1, 3, and 4. 37 C.F.R. § 41.37(c)(1)(iv).

TIME PERIOD

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