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

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

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DECISION ON APPEAL

This is an appeal\textsuperscript{1,2} under 35 U.S.C. § 134 involving claims to a method of intravaginally administering pellets, including a debranched starch and a therapeutic agent. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

\textsuperscript{1} Appellants identify the Real Party in Interest as Henkel IP & Holding GmbH (\textit{see} Br. 3).
\textsuperscript{2} We have considered and herein refer to the Specification of Apr. 24, 2012 ("Spec."); Final Office Action of Sep. 15, 2016 ("Final Act."); Appeal Brief of Feb. 16, 2017 ("Br."); and Examiner’s Answer of Jun. 1, 2017 ("Ans.").
Statement of the Case

Background

“Vaginal drug delivery is a promising route for local and systemic delivery” (Spec. ¶ 3). “There is a need for the development of a new vaginal delivery form which assures an acceptable retention time, combined with a good spreading over the vaginal epithelium” (Spec. ¶ 8). “It has been discovered that pharmaceutical pellets made using a crystalline debranched amylase resistant starch are particularly useful for the vaginal delivery of active agents” (Spec. ¶ 11). “Vaginal drug delivery using the pellets of the invention combines the advantages of the fast spreading semi-solid formulations with a better retention time” (Spec. ¶ 12). “A specific starch grade has been identified as a material suitable for use as an excipient for pellets prepared via extrusion/spheronization” (Spec. ¶ 16).

The Claims

Claims 1–5, 7, 8, 15–17, and 19–22 are on appeal. Independent claim 1 is representative and reads as follows:

1. A method of treating or preventing a condition in a patient comprising administering to a patient a composition comprising pellets, said pellets comprising at least one excipient and a therapeutic agent,

   wherein at least one excipient is a crystalline debranched amylase resistant starch comprising D-anhydroglucose units organized into double-helical crystalline chains

   wherein said crystalline debranched amylase resistant starch is greater than 50 % by total weight of the excipient,

   wherein said pellets are administered intravaginally, and
wherein the size of the pellets range from 300 to 1000 micrometer.

The Rejection

The Examiner rejected claims 1–5, 7, 8, 15–17, and 19–22 under 35 U.S.C. § 103(a) as obvious over Besemer,³ De Luigi Bruschi,⁴ and Dukic⁵ (Final Act. 4–12).

The Examiner finds that Besemer teaches “debranched starches are useful in vaginal drug delivery, and have the beneficial property of minimal disintegration” (Final Act. 5). The Examiner finds although “Besemer does not explicitly teach the debranched amylase resistant starch comprises D-glucose units organized into double-helical crystalline chains[,]” Besemer teaches a matrix material including “an essentially crystalline straight-chain” of α-1,4-anhydroglucose units (Final Act. 5–6). The Examiner finds that “Besemer suggests starch derivatives are obtained from debranching branched glucans . . . [which] would result in a debranched amylase resistant starch comprising α-1,4-anhydroglucose in a helix structure” (Final Act. 6.)

The Examiner acknowledges that “Besemer does not explicitly teach a method of treating a vaginal disorder or condition” (Final Act. 6.) The Examiner finds that De Luigi Bruschi teaches “a method of treatment of vaginal disorders, such as vulvovaginal candidiasis, comprising administering a vaginal bioadhesive controlled release matrix comprising an antifungal as a pharmaceutical active and starch derivatives such as amylose,

⁵ Dukic et al., US 2006/0246192 A1, published Nov. 2, 2006
wherein the matrix is granulated (granules are a form of pellet)” (Final Act. 7.)

The Examiner determines it would have been obvious to one of ordinary skill in the art to utilize the straight-chain debranched amylose starch comprising composition taught by Besemer in the method taught by De Luigi Bruschi, since the prior art establishes that starch derivatives such as amylose are suitable for intravaginal treatment with an antifungal and debranched straight-chain amylose is a starch derivative subject to little or no disintegration and little or no attack by a-amylase.

(Final Act. 7–8).

The Examiner acknowledges that “De Luigi Bruschi and Besemer do not explicitly teach a granule in the claimed size range or that the pellets are prepared by extrusion followed by spheronization” (Final Act. 8). The Examiner finds that Dukic teaches “the use of crystalline debranched starch in the preparation of pharmaceutical pellets by extrusion-spheronization” and “the diameter of the pellets ranges from about 0.70 to 1.40 mm” (Final Act. 8–9). The Examiner determines it would have been obvious to one of ordinary skill in the art to formulate the pellets taught by De Luigi Bruschi and Besemer utilizing the methods taught by Dukic since the prior art establish that extrusion-spheronization is a suitable method for forming pharmaceutical pellets comprising a debranched starch and an antifungal.

(Id.).

The issue with respect to this rejection is: Does the evidence of record support the Examiner’s conclusion that the combination of Besemer, De Luigi Bruschi, and Dukic renders the claims obvious?
Findings of Fact ("FF")

1. Besemer teaches “a composition for delayed release of an active substance in a target environment, the active substance being incorporated in a polysaccharide matrix” (Besemer 1:3–6).

2. Besemer teaches “that the matrix material in which the active substance is incorporated comprises an essentially crystalline, straight-chain glucan. The glucan is preferably an α-glucan and in particular an α-1,4-glucan and preferably has essentially a helix structure” (Besemer 2:8–11).

3. Besemer teaches “[t]he α-1,4-glycan can, for example, be an amylose. Amylose is a straight chain of α-1,4-anhydroglucose units” (Besemer 2:19–22).

4. Besemer teaches “administration forms which comprise such crystalline straight-chain glucans as matrix-forming material are subject to little or no disintegration and little or no attack by α-amylase” (Besemer 3:17–19).

5. Besemer teaches “[t]he composition can also be in the form of a capsule in which the matrix material containing active substance is present, for example in granular form or powder form” (Besemer 4:42–45).

6. Besemer teaches compositions “characteri[z]ed in that the matrix material comprises at least 50% by weight of a crystalline, straight-chain α-glucan having essentially a helix structure” (Besemer 9:9–16).

7. Besemer teaches “[t]he active substance can be of diverse natures. For example it can be medicaments for oral, rectal, vaginal or transdermal administration” (Besemer 4:15–17).
8. Besemer teaches “[r]elease can take place in an aqueous medium, such as the gastrointestinal tract of animals, or in plants or in the soil, but also into the air” (Besemer 4:25–27).

9. De Luigi Bruschi teaches a hydrophilic matrix “used in combination with at least one pharmaceutically acceptable active principle for manufacturing solid bioadhesive controlled release formulations for the treatment of vaginal disorders, such as vulvovaginal candidiasis” (De Luigi Bruschi Abstract).

10. De Luigi Bruschi teaches that “[u]nfortunately in the specific case of the bioadhesive controlled release vaginal delivery, the small vaginal daily secretions are not sufficient to hydrate conventional matrix tablets. This means that matrix tablets not achieving the swollen state, in practice arrest or slow down the drug diffusion process” (De Luigi Bruschi 4:4–8).

11. De Luigi Bruschi teaches that “it has been discovered that the inclusion of a disintegrant in an hydrophilic matrix made by one or more ether of cellulose and one or more polyacrylic acid derivatives, promoted a rapid achievement of the swollen state even in presence of limited quantities of vaginal secretions” (De Luigi Bruschi 5:11–14).

12. De Luigi Bruschi teaches “[d]isintegrating agents suitable to be used in the present invention can be chosen from different classes” including “starch derivatives such as amylose” (De Luigi Bruschi 7:25–31) where the composition may comprise “at least one disintegrant in amounts of 2 – 50%, with respect to the weight of the matrix” (De Luigi Bruschi 20:11–12).

13. De Luigi Bruschi teaches “[t]he controlled release properties of the vaginal tablets may be modified by the presence in the dosage form of
soluble and insoluble fillers . . . the soluble excipients can be selected from . . . amylose” (De Luigi Bruschi 8:12–20).

14. De Luigi Bruschi teaches “[a]mong the variety of drugs that can be incorporated into the controlled release bioadhesive vaginal tablets object of the present invention are the antimycotics, used in the treatment of the vulvovaginal candidiasis” (De Luigi Bruschi 9:14–16).

15. Dukic teaches “the use of crystalline debranched starch in the preparation of pharmaceutical pellets by extrusion-spheronization. Such excipients are useful in any dry dosage form, including tablets and capsules, for either immediate or sustained release” (Dukic ¶ 28).

16. Dukic teaches “[t]he active agents may be distributed inside the pellets” (Dukic ¶ 75).

17. Dukic teaches

[use of debranched starches provides a yield of greater than 80% and in one embodiment greater than 90%. Yield is intended to mean the percent of the extruded composition which resulted in usable pellets, that is pellets which are substantially spherical solid particles whose diameter size range from about 100 microns to about 3 mm. In one embodiment, the diameter of the pellets ranges from about 0.70 to 1.40 mm.

(Dukic ¶ 70).

18. Dukic teaches “[t]he active principles which may be vehiculated by the pellets of this invention include . . . antifungals” (Dukic ¶ 74).

Principles of Law

A prima facie case for obviousness require “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” KSR Int’l Co. v.
Analysis

We adopt the Examiner’s findings of fact and conclusion of law (see Final Act. 4–16, FF 1–18) and agree that the combination of Besemer, De Luigi Bruschi, and Dukic renders the claims obvious. We address Appellants’ arguments below.

Appellants contend “that Besemer only describes formulations intended to pass through the gastrointestinal system” and that “[a] skilled person would not have predicted that a formulation – only established as useful for oral administration – could be successfully used intravaginally” (Br. 6).

We do not find this argument persuasive because Besemer expressly teaches that composition may include “medicaments . . . for vaginal administration” (FF 7). Contrary to Appellants’ arguments, there is no teaching limiting Besemer to only oral compositions. Even if oral compositions are preferred, “the fact that a specific [embodiment] is taught to be preferred is not controlling, since 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).

Appellants contend that:

[I]n view of the challenges presented by vaginal drug delivery, as discussed by DeLuigi Bruschi, a skilled artisan would not have considered the teachings of Besemer, which relate to oral compositions for delayed release in the gastrointestinal tract, to be applicable to the teachings of DeLuigi Bruschi, which relates to vaginal formulations.

( Br. 7–8).
We do not find this argument persuasive. As discussed above, Besemer is not limited to oral compositions, and expressly teaches medicaments for vaginal administration (FF 7). Moreover, while De Luigi Bruschi describes the problems associated with “conventional matrix tablets” (FF 11), De Luigi Bruschi explains that “the inclusion of a disintegrant . . . promoted a rapid achievement of the swollen state even in presence of limited quantities of vaginal secretions” (FF 11). De Luigi Bruschi teaches that desirable disintegrants may include amylose (FF 12). Therefore, the ordinary artisan, interested in addressing De Luigi Bruschi’s concerns with hydration, would have had reason to include amylose based disintegrants as directly suggested by De Luigi Bruschi (FF 12). A “given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine.” Medicem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006).

In addition, the rejection relies upon the combination of Besemer, De Luigi Bruschi, and Dukie to reasonably suggest formulation of the composition into granules or pellets contained in a capsule (FF 5, 15, 16). Appellants provide no evidence that Besemer’s starch-based granules in a capsule would be subject to the concerns of De Luigi Bruschi. Finally, De Luigi Bruschi teaches amylose is a suitable excipient for intravaginal administration (FF 12, 13).

Appellants contend that “Besemer teaches a matrix material comprising at least 50% by weight of crystalline, straight chain alpha-glucan composition” and “DeLuigi Bruschi teaches to utilize large quantities, in the range of 30–90 or 40–80 wt%, of MCC [microcrystalline cellulose] . . . as the excipient matrix” (Br. 8). Appellants contend “[g]iven the importance
of using large quantities of MCC in DeLuigi Bruschi, a skill artisan would not be led to simply disregard MCC in the matrix and to minimize the use of such excipient” (id.).

We do not find this argument persuasive because “[t]he test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference . . . Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.” In re Keller, 642, F.2d 413, 425 (CCPA 1977). We note that De Luigi Bruschi teaches that amylose may be used in amounts of 2 to 50% as a disintegrant (FF 12), directly adjacent to the range of “greater than 50%” required by claim 1, and reasonably expected to share the same properties. See In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (“We have also 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.)

We find the combination of the references suggests intravaginally administering the Besemer’s formulations for treating vaginal disorders, such as vulvovaginal candidiasis, as taught by De Luigi Bruschi using compositions comprising amylose. The prior art need not suggest incorporating the De Luigi Bruschi’s formulation wholesale into Besemer’s formulation.

Appellants contend that Besemer and De Luigi Bruschi are directed to tablets, not “capsules with pellets” ( Br. 9). Appellants further contend that Dukic “is solely directed to compositions for oral delivery, and does not
teach or suggest any compositions or methods that would be suitable for vaginal delivery” (id.).

We do not find these arguments persuasive because they fail to address the combined teachings of the references. “Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.” In re Merck & Co., 800 F.2d 1091, 1097 (Fed. Cir. 1986). As discussed above, Besemer teaches “[t]he composition can also be in the form of a capsule in which the matrix material containing active substance is present, for example in granular form or powder form” (FF 5) and is not limited to tablet formulations. Moreover, the Examiner cites Dukie for extrusioning and spheronizing crystalline debranched starch pellets ranging in size from 700 to 1,400 micrometer (FF 17), not for vaginal administration. When the references are considered together, Dukie complements Besemer’s and De Luigi Bruschi’s method of intravaginally administering active agent containing formulations, by providing appropriately sized pellets including an antifungal active agent. As the Examiner points out, Dukie demonstrates that “extrusion-spheronization is a suitable method for forming pharmaceutical pellets comprising a debranched starch and an antifungal” (Ans. 19), useful “for either immediate or sustained release” (FF 15) and Besemer is interested in delayed release compositions (FF 1) for vaginal administration (FF 7).

Conclusion of Law

A preponderance of the evidence of record support the Examiner’s conclusion that the prior art renders claim 1 obvious.
SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Besemer, De Luigi Bruschi, and Dukic. Claims 2–5, 7, 8, 15–17, and 19–22 fall with claim 1.

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

AFFIRMED