UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MSN Pharmaceuticals, Inc. and MSN Laboratories Private Limited,

Petitioners,

v.

Breckenridge Pharmaceutical, Inc.,

Patent Owner.

Case No.: IPR2025-01107

U.S. Patent No. 11,013,729

DECLARATION OF MAUREEN D. DONOVAN, PH.D.

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I. BACKGROUND AND QUALIFICATIONS

1. I am a Professor in the Department of Pharmaceutical Sciences and Experimental Therapeutics at the University of Iowa.

2. I received my Bachelor of Science in Pharmacy from the University of Minnesota, College of Pharmacy (1983) and my Ph.D. from the University of Michigan, College of Pharmacy, Horace H. Rackham School of Graduate Studies (1989).

3. I began my academic career in 1989 at the University of Iowa and have held several positions in the College of Pharmacy including appointments as an Assistant Professor (1989-1996), Associate Professor (1996-2008), Professor (2008-Present), Head of the Division of Pharmaceutics and Translational Therapeutics (2008-2013), and Associate Dean for Undergraduate Education (2013-2019). Additionally, I was a Visiting Professor at the Tongji School of Pharmacy, Tongji Medical University, Wuhan, China from 2011-2020.

4. I am a member of the Environmental Health Sciences Research Center and Nanoscience and Nanotechnology Institute at the University of Iowa, as well as the American Association of Pharmaceutical Scientists, American Association of Colleges of Pharmacy, American Chemical Society and American Society for Pharmacology and Experimental Therapeutics.

5. Throughout my over 35 years as a faculty member, I have taught undergraduate, professional and graduate students about principles of drug delivery and advanced of drug delivery system design including approaches to utilize alternative routes of administration such as the nasal, pulmonary, vaginal and transdermal sites for drug administration. I have investigated comparisons between drug absorption in the GI and respiratory tracts, and I have investigated and developed extended-release formulations for GI administration and have also investigated some of those systems for their potential for inhalation abuse. I have also taught and performed research in other areas of pharmaceutics, including drug solubility, equilibria processes, pre-formulation and formulation approaches for pharmaceutical product development, and extemporaneous compounding.

6. I have published over 150 articles, book chapters, abstracts and patents in the area of pharmaceutics, drug formulation, drug absorption, drug delivery, and materials characterization and have given numerous invited national and international presentations at universities and scientific conferences. I am also frequently asked to provide seminars and consulting services to both large and small pharmaceutical companies.

7. I have supervised over 60 PharmD, MS, PhD, post-doctoral and visiting scholars in my laboratories. Many of my MS and PhD students are employed by small and large pharmaceutical companies, regulatory agencies or hold academic

positions and are active in the development and evaluation of new drug products or delivery systems.

8. My research program has been funded by the NIH, NCI, and FDA. I have also engaged in numerous joint investigations sponsored by pharmaceutical companies to assist with formulation development, absorption evaluation, and druggability assessment. My research team has developed formulations and evaluated drug absorption following topical delivery and delivery to the corneal, conjunctival, nasal, buccal, gastrointestinal and vaginal mucosae.

9. I have served on numerous grant review panels, including for various divisions of the NIH and NSF, and served as chair of the NIH Study Section: Small Business: Drug Discovery for Aging, Neuropsychiatric, and Neurologic Disorders for three terms (various official panel names). I served a 3-year term as an appointed member of the FDA Pharmaceutical Science and Clinical Pharmacology Advisory Panel and formerly served as a temporary member of that panel and for the FDA Anesthetic and Analgesic Drug Products Advisory Committee.

10. I served on the Editorial Board for American Chemical Society's Molecular Pharmaceutics (2013-2018), and the Journal of Pharmaceutical Innovation (2010).

11. Based on my education, practical training, teaching, research, editorial work, patents, consulting, and industrial experience, I consider myself an expert in the area of pharmaceutics and formulation sciences.

12. Additionally, information regarding my qualifications, experience, and publications is collected in my *curriculum vitae* (Exhibit 1006).

II. ASSIGNMENT, COMPENSATION, AND MATERIALS CONSIDERED

13. I was retained in this case by counsel for Petitioners in this proceeding before the United States Patent and Trademark Office regarding U.S. Patent No. 11,013,729 ("the '729 patent") (Ex. 1001). I am being compensated for my time at my normal rate of $500.00 per hour for consulting work and preparation of declarations, and $750 per hour for activities involving testimony, including preparation and travel time if working. My compensation is in no way dependent on the outcome of this proceeding.

14. I understand that the '729 patent is titled "Oral Pharmaceutical Compositions of Dabigatran Etexilate," and has been assigned to Breckenridge Pharmaceutical, Inc. I have been asked to provide expert opinions regarding the validity of claims 1-18 of the '729 patent. These claims are generally directed to compositions, or processes for preparing compositions, for the oral administration of dabigatran etexilate having "two distinct types of particles" wherein the first type

of particles comprise dabigatran etexilate in the form of a free base or a pharmaceutically acceptable salt or polymorph and "is free from organic and inorganic acids", and the second type of particles comprise at least one pharmaceutically acceptable organic acid, "is coated with a protective coating layer," and "is free from dabigatran etexilate."

15. In formulating the opinions in this declaration, I have relied upon my decades of experience, training, and knowledge. In addition, I considered the materials cited in this declaration and those listed in Appendix A.

16. My opinions have also been shaped by my understanding of how person of ordinary skill in the art ("POSA," as described in Section III.A below) would have understood the claims and the specification of the '729 patent at the time of the alleged invention.

III. LEGAL PRINCIPLES

17. I am not a lawyer. Petitioners' counsel explained the following legal principles to me, and I have considered these principles while forming the opinions set forth in this declaration.

A. The Person of Ordinary Skill in the Art

18. I understand that a patent should be viewed from the perspective of a POSA. I understand that a POSA is a hypothetical person considered to be a person of ordinary creativity having normal skills and knowledge in the field to which the

claims relate at the time of the filing of the earliest patent application. I understand that several factors may be considered to determine the level of skill in the art, including the following: (1) the types of problems encountered in the art; (2) prior art solutions to those problems; (3) the rapidity with which innovations are made in the field; (4) the sophistication of the technology at issue; and (5) the level of education of active workers in the field. I understand that a POSA is presumed to be familiar with all relevant and publicly available prior art as of the priority date.

19. Considering the '729 patent, the education level and experience of workers in the field relating to the '729 patent, and the problems and solutions in that field, and drawing from my own experience, it is my opinion that a POSA with respect to the '729 patent would have an advanced degree (i.e., a doctorate or masters' degree) in pharmaceutical sciences or a related discipline and at least 3-7 years of experience formulating and/or characterizing pharmaceutical dosage forms.

20. I am an expert but understand the knowledge and practice of a POSA because I have interacted with numerous individuals who would have fallen within the definition of a POSA set forth above, particularly through my professional experience, including teaching and research discussed above. Thus, whenever I state "my opinion" in this declaration, it is an opinion from a POSA's viewpoint at the relevant date, which I understand from counsel is February 21, 2012. I also have had at least the qualifications of a POSA since before 2012.

B. Obviousness

21. I understand that a patent is invalid if it claims subject matter that is not novel or nonobvious. I understand that for a claim to be novel and nonobvious, the combination of elements recited in the claim cannot be described in prior patents and/or printed publications. This type of previously known information, which also includes previously known methods, is commonly referred to as prior art.

22. I understand that a patent claim may be invalid if it would have been obvious to a POSA. To establish obviousness, I understand that it must be demonstrated that a POSA would have been motivated to combine the teachings in the prior art to achieve the claimed invention, and that the POSA would have had a reasonable expectation of success in doing so. I understand that it is not necessary to have each and every limitation in a single prior art reference—rather, references can be combined if it would have been obvious for a POSA to do so. I understand that the operative question is whether it would have been obvious for a POSA, with full knowledge of the prior art at the time of the alleged invention, to make the claimed invention, without using hindsight.

23. Petitioners' counsel has informed me that the following four factors are considered when determining whether a patent claim is obvious: (1) the scope and content of the prior art; (2) the differences between the prior art and the claim; (3)

the level of ordinary skill in the art; and (4) any objective indicia tending to prove nonobviousness.

24. I also understand that the following inquiries may be relevant to whether a patent claim is obvious: (1) whether the claimed invention was the predictable result of using prior art elements according to their known function(s); (2) whether the claimed invention provides an obvious solution to a known problem in the relevant field; (3) whether the prior art teaches the desirability of combining elements in the claimed invention; and (4) whether there was a reasonable expectation of success from the combination that may be found in the teachings of the prior art references themselves, in the nature of the need or problem in the field that was addressed by the patent, in the knowledge of POSAs, as well as in the common sense or the level of creativity exhibited by POSAs.

25. I have been informed that there need not be an express or explicit suggestion to combine references. I understand that when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a POSA has good reason to pursue the known options within his or her technical grasp. I understand that if pursuing those known options leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Petitioners' counsel also informed me that I may consider the inferences and creative steps that a POSA would employ.

26. I understand that objective evidence relevant to the issue of obviousness, such as commercial success, long-felt but unmet need, failure of others, and unexpected results, may also be considered. I understand that such evidence may be provided by the Patent Owner at any point during the patent application's prosecution at the USPTO. In addition, I understand that the Patent Owner may raise such objective evidence during this proceeding. I reserve the right to address any issues related to objective evidence should Patent Owner or its expert(s) assert them as evidence of nonobviousness.

C. Objective Indicia

27. I understand that the fact finder may consider several objective indicia (also referred to as secondary considerations), such as whether the claimed invention exhibited unexpected results, solved a problem for which there was a long felt but unresolved need, solved a problem where others had failed, and whether there was skepticism in the industry for the claimed invention, and whether the claimed invention resulted in commercial success.

28. Petitioners' counsel has also informed me that any alleged secondary considerations must have a nexus to the claimed invention. That is, the secondary considerations must be the result of one or more novel features of the claimed invention. I further understand that, unless a nexus exists between the alleged

secondary considerations and the claimed invention, the alleged secondary consideration will not support any assertion of non-obviousness.

29. I further understand that the Patent Owner bears the burden of presenting sufficient evidence of any alleged secondary consideration, as well as proof of nexus between the alleged secondary consideration and the claimed feature(s), and that the evidence presented must be commensurate with the scope of each asserted claim. That is, when the scope of the claim is broad and encompasses many embodiments, evidence of secondary considerations for a single embodiment may not be sufficient to show that the secondary consideration is applicable to the entire range of embodiments covered by the claim.

30. Petitioners' counsel has informed me that a reference that does not criticize, discredit, or otherwise discourage investigation into the claimed invention does not teach away from the claimed invention. I also understand that a reference's disclosure of preferred embodiments does not teach away from embodiments not included in the preferred list as it merely expresses a general preference for alternatives but does not criticize, discredit, or otherwise discourage investigation into the embodiments not included in the preferred list. I further understand that a prior art reference that does not specifically refer to an element of the claimed invention does not, *per se*, teach away from the claimed invention.

31. I understand that evidence of unexpected results must establish that there is a difference between the results obtained with the claimed invention and those of the closest prior art, and that the difference would not have been expected by a POSA at the time of the invention. I understand that any alleged unexpected results must be reasonably commensurate in scope with the invention as claimed, and that the results must be unexpected in terms of differences in the kind of effect, rather than a difference in the degree of effect.

IV. THE '729 PATENT

32. The '729 patent is titled "Oral Pharmaceutical Compositions of Dabigatran Etexilate."

33. I understand that the '729 patent issued from U.S. Application No. 14/379,613, that entered national phase in the United States on August 19, 2014, and was filed as PCT Appl. No. PCT/EP2013/053426 on February 21, 2013, and claims priority to an Indian patent application No. 461/MUM/2012, filed on February 21, 2012. I have been informed that for the purposes of my declaration, I should assume that the priority date for the '729 patent is February 21, 2012.

34. The '729 patent relates to oral solid formulations of dabigatran etexilate composition containing the thrombin inhibitor dabigatran etexilate with a

pharmaceutically acceptable organic acid, wherein the dabigatran etexilate and acid are in separate particles and the acid-containing particles have a protective coating.[1]

A. The "BACKGROUND OF THE INVENTION" Section

35. The '729 patent explains "[d]abigatran is a potent, reversible, univalent direct thrombin inhibitor. It reduces the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation."[2]

36. The '729 patent further explains "[d]abigatran is currently available as dabigatran etexilate mesylate (DEM) under the brand name Pradaxa® from Boehringer Ingelheim as immediate release oral capsules of 75 mg and 110 mg (in Europe) and 75 mg and 150 mg strengths (in the United States) to be administered twice daily."[3]

37. The '729 patent provides, among other things, the following information about dabigatran etexilate mesylate:

- Its aqueous solubility is "strongly pH dependent with rather high solubility in acidic media and very poor solubility in neutral and basic media;"[4]

[1] *See*, *e.g.*, Ex. 1001, Abstract, Col. 1:5-9, Col. 2:62 – Col. 3:2.

[2] *Id.*, Col. 1:57-59.

[3] *Id.*, Col. 2:4-9.

[4] *Id.*, Col. 2:14-17.

- It is a "BCS Class II drug, indicating poor aqueous solubility but good membrane permeability"[5]
- It is "acid sensitive"[6]

38. The '729 patent then describes certain known pharmaceutical compositions of dabigatran etexilate mesylate, including those described in U.S. Patent Application 2006/0183779A1 (Ex. 1007, "Brauns").[7]

B. The Examples In the '729 Patent

39. The '729 patent includes three Examples.

40. Example 1, titled "Oral Capsule Formulation of Dabigatran Etexilate Mesylate," describes a procedure for, and a composition of, tartaric acid pellets coated with hydroxypropyl methylcellulose (HPMC); a procedure for, and a composition of dabigatran etexilate mesylate granules; and a procedure for, and a composition of dabigatran etexilate mesylate oral capsule.[8]

41. Example 2, titled "Oral Capsule Formulation of Dabigatran Etexilate Mesylate," describes a procedure for, and a composition of, tartaric acid pellets, a procedure for, and a composition of dabigatran etexilate mesylate granules coated

[5] *Id.*, Col. 2:20-22.

[6] *Id.*, Col. 2:4-9.

[7] *Id.*, Col. 2:30-44.

[8] *Id.*, Col. 11:32 – Col. 12:67.

with polyvinyl pyrrolidone and talc, and a procedure for, and a composition of dabigatran etexilate mesylate oral capsule.[9]

42. Example 3, titled "Comparative Evaluation of Two Formulation Approaches for Dabigatran Etexilate Mesylate," compares the dissolution profiles of two different dabigatran etexilate mesylate formulations: "formulation A," containing "two types of particles/pellets," dabigatran etexilate mesylate pellets and coated tartaric acid pellets, prepared according to the procedure set forth in Example 3, [10] and "formulation B," "having one type of particles/pellets having both dabigatran etexilate mesylate and [tartaric] acid," "prepared according to the teachings of WO 03/074056, and in particular, Example 1."[11]

43. The '729 patent then provides the following chart for the dissolution profiles of "Formulation A" and "Formulation B," "in 0.01N HCl pH 2 media at 100 rpm USP type I (basket):"[12]

[9] *Id.*, Col. 13:1 – Col. 14:27.

[10] *Id.*, Col. 14:46 – Col. 15:40.

[11] *Id.*, Col. 14:41-45.

[12] *Id.*, Col. 15:41-60.

	% release	
Time (minutes)	Formulation A (two types of particles/pellets)	Formulation B (one type of particles/pellets)
10	65.1	19.2
15	79.2	57
20	86.7	86.1
30	92	97
45	95.5	97.6
60	96.8	98.5

44. I understand that Example 1 of WO 03/074056 is the same as Example 1 of US 2006/0183779 A1 ("Brauns").[13]

45. Brauns' Example 1 discloses two formulations, one with a total capsule weight of 288.3 mg and another with a total capsule weight of 576.5 mg.[14] These two formulations, however, include the same ingredients at the same wt%.[15]

46. Because the dissolution results in Example 3 of the '729 patent are reported as "% release," it does not matter which one of the two Brauns' Example 1 formulations are compared with the '729 patent formulation. Here, I have selected

[13] *See* Ex. 1002, p. 443 ("Formulation B is the formulation described in example 1 of US 2006/0183779 Al. This formulation is exactly the same one disclosed in example 1 of PCT application WO 2003/074056 which is an[] equivalent of US '779.")

[14] Ex. 1007, ¶[0039].

[15] *Id.*

Brauns' Example 1 formulation with a total capsule weight of 576.5 mg to compare with the '729 patent formulation.

47. I have prepared the chart below comparing the composition of formulation A (Example 3 in the '729 patent)[16] and formulation B (Brauns' Example 1).[17]

	Formulation A (dabigatran granules and coated tartaric acid granules)		**Formulation B (dabigatran pellets with tartaric acid core)**	
Components	mg/capsule	wt%	mg/capsule	wt%
Dabigatran etexilate mesylate	172.95	34.18	115.3	20
Tartaric acid	196.34	38.8	353.4	61.3
Talc	8.42	1.66	50.7	8.8
Hydroxypropyl cellulose	N.A.	N.A.	23.1	4
gum arabic	N.A.	N.A.	34	5.9
Hydroxypropyl methyl cellulose	5.62	1.11	N.A.	N.A.
Microcrystalline cellulose	67.05	13.25	N.A.	N.A.
Croscarmellose sodium	50	9.88	N.A.	N.A.
Lactose	5.62	1.11	N.A.	N.A.
Total	506		576.5	

[16] Ex. 1001, Col. 14:50 – Col. 15:15.

[17] Ex. 1007, ¶[0039].

48. As shown above, there are several differences between formulation A and formulation B.

49. First, there are only two excipients in common between formulation A and formulation B: tartaric acid and talc. Formulation A has the following additional excipients that are absent in formulation B: hydroxypropyl methyl cellulose, microcrystalline cellulose, croscarmellose sodium, and lactose. On the other hand, formulation B has the following excipients that are absent in formulation A: hydroxypropyl cellulose and gum arabic.

50. Additionally, the amounts and the percentages of dabigatran etexilate mesylate and tartaric acid are also different between formulation A and formulation B.

51. Therefore, any observed differences in the dissolution profiles for formulation A vs. formulation B cannot be properly attributed to the two-pellet vs. one-pellet structures of the formulations. Instead, any observed differences in the dissolution profiles may be attributable to the differences in the components, the amounts and the percentages of dabigatran etexilate mesylate and tartaric acid, and/or a combination of the above.

C. The Claims of The '729 Patent

52. The '729 patent includes 18 claims, of which claims 1, 11, and 16 are independent.[18] Claims 1-18 of the '729 patent are provided below.

> 1. A composition comprising: a mixture of at least two distinct types of particles wherein
>
> > a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic acids and inorganic acids; and
> >
> > b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.
>
> 2. The composition according to claim 1, further comprising at least one pharmaceutically acceptable excipient.
>
> 3. The composition according to claim 1, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.
>
> 4. The composition according to claim 1, comprising from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.
>
> 5. A unit dosage form prepared from the composition according to claim 1, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

[18] Ex. 1001, Col. 16:9 – Col. 18:30.

6. A process for the preparation of the composition according to claim 2, comprising the step of mixing the first type of particles and the second type of particles with the at least one pharmaceutically acceptable excipient.

7. The process of claim 6, wherein the first type of particles are prepared by granulation.

8. The process according to claim 7, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) granulating the blend of step (iii) with a binder solution to form organic acid granules;

v) coating the organic acid granules with a protective coating layer;

vi) blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

9. The process according to claim 7, comprising the steps of:

i) blending dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof and at least one pharmaceutically acceptable excipient;

ii) granulating the blend of step (i) with a binder solution to form granules of the dabigatran etexilate;

iii) blending at least one organic acid and at least one pharmaceutically acceptable excipient;

iv) extruding and spheronizing the blend of step (iii) to form organic acid pellets;

v) coating the organic acid pellets of step (iv) with a protective coating layer;

vi) blending the granules of step (ii) with the coated pellets of step (v) to form a mixture of at least two types of particles;

vii) optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient;

viii) adding a lubricant to the blend of step (vii);

ix) filling the lubricated mixture of step (viii) into suitable hard capsules.

10. The composition according to claim 2, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

11. A composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

12. The composition according to claim 11, comprising from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.

13. The composition according to claim 11, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

14. The composition according to claim 11, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.

15. A capsule unit dosage form prepared from the composition according to claim 14, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

16. A capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

17. The capsule according to claim 16 containing from 50 mg to 200 mg of dabigatran etexilate mesylate.

18. The capsule according to claim 16, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

V. CLAIM CONSTRUCTION

53. I understand that the terms in a patent claim should be given their ordinary and customary meaning as understood by a person of ordinary skill in the art in view of the patent and file history.

A. "particles"

54. Independent claims 1, 11, and 16 require "a mixture of at least two distinct types of particles." Dependent claims 6, 7, 9, 13, and 18 also recite the term "particles."

55. The '729 patent states that "[t]he term 'particle' as used herein is intended to mean any solid or semi-solid portion of a substance or a composition having defined physical boundaries. Examples of particles include, but are not limited to, powder, granules, pellets, beads, minitablets or the like."[19]

56. Thus, based on the language of the claims and the specification of the '729 patent, a POSA would have understood the term "particles" to mean "any solid or semi-solid portions of a substance or a composition having defined physical boundaries, such as powder, granules, pellets, beads, and minitablets."

B. "a protective coating layer"

57. Claims 1, 8, 9, 11, and 16 require "a protective coating layer" on the second type of particles that comprise at least one organic acid and are free from dabigatran etexilate.

58. The '729 patent states that "[t]he term 'protective coating layer' as used herein is intended to mean a layer of a polymeric or a non-polymeric material

[19] *Id.*, Col. 8:62-66.

disposed on the surface of a particle core in order to avoid direct contact of the particle core with its environment."[20]

59. I understand this phrase was added in an amendment dated Nov. 9, 2017 (responding to an Office Action dated Aug. 11, 2017), so that the claims were commensurate in scope with "the Examples presented, [wherein] the acid containing particles are coated but the active agent containing particles are not coated."[21]

60. I also understand that the Patent Owner made further statements related to the term "protective coating layer." For example, the Patent Owner argued during prosecution of the '729 patent that "[t]he insulating layer [of Brauns] just acts as a protective layer between the acid core and active substance layer on storage, but once in the stomach it permits the diffusion of the acid to the active substance layer immediately."[22]

61. In view of the definition in the '729 patent the Patent Owner's statements during prosecution, a POSA would have understood the term "a protective coating layer" to mean "a coating layer that prevents the organic acid from contacting dabigatran etexilate until after the composition is administered."

[20] Ex. 1001, Col. 5:39-43.

[21] Ex. 1002, pp. 349-51.

[22] Ex. 1002, p. 137 (Reply Br. dated Apr. 15, 2020).

C. "consisting of"

62. Claims 11 and 16 require a "composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient."

63. I understand that the transitional phrase "consisting of" is a term of art in patent law that has a well-established meaning, which is, creating a very strong presumption that that claim element is "closed" and therefore excludes any elements, steps, or ingredients not specified in the claim.

64. Thus, a POSA would have understood that the composition of claims 11 and 16 is closed to ingredients other than the "two distinct types of particles and at least one pharmaceutically acceptable excipient."

VI. TECHNOLOGY BACKGROUND

65. In this section, I present a brief overview of several key technologies that were known before February 2012 and relate to the issues discussed in this declaration. This section is not intended to be technically comprehensive, but rather provides a foundation for better understanding the field of the '729 patent and the prior art.

A. Dabigatran Etexilate

66. By February 2012, dabigatran etexilate was known as a small molecule direct thrombin[23] inhibitor prodrug that is orally administered and is rapidly absorbed and converted to the active form, dabigatran.[24]

67. It was known that dabigatran etexilate "is very lipophilic"[25] in its neutral form.[26]

68. Additionally, it was known that dabigatran etexilate has two weakly basic functional groups with pKa values of 4.0±0.1 and 6.7±0.1.[27] Below, I have copied the chemical structure of dabigatran etexilate provided in Brauns.[28]

[23] Thrombin "catalyzes the conversion of fibrinogen to fibrin, leading to thrombus formation. In pathological conditions, thrombus formation can result in thrombotic complications, which comprise deep-vein thrombosis (DVT), myocardial infarction, cerebrovascular disease and peripheral arterial disease." Ex. 1015, pp. 1-2.

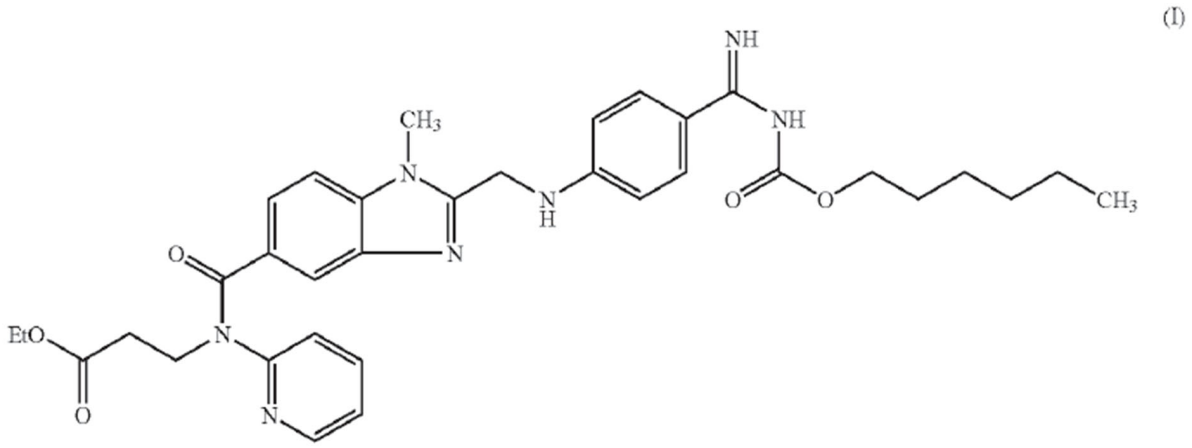
[24] Ex. 1015, Abstract, p. 2.

[25] Lipophilic and hydrophobic are often used interchangeably and describe the same property: the tendency to dissolve or interact with fatty or oily substances, and to repel water.

[26] Ex. 1018, p. 94.

[27] *Id*.

[28] Ex. 1007, ¶[0003].



69. Further, dabigatran etexilate's solubility in water was known to be "strongly pH dependent with rather high solubility in acidic media (>50 mg/mL in 0.1 N HCl) and very poor solubility in neutral and basic media (0.003 mg/mL at pH 7.4)."[29]

70. In early phase I clinical trials in healthy volunteers, dabigatran etexilate was administered in tartaric acid solution or as tablets.[30]

71. After FDA approval in October 2010, Boehringer Ingelheim marketed dabigatran etexilate as capsules for oral use under the brand name PRADAXA®.[31]

72. The PRADAXA® capsules contain 75 mg or 150 mg of dabigatran etexilate (i.e., 172.95 mg or 86.48 mg dabigatran etexilate mesylate), and are

[29] Ex. 1018, p. 94.; *see also* Ex. 1007, ¶[0024]; Ex. 1022, p. 4.

[30] Ex. 1015, p. 3.

[31] Ex. 1014, p. 1.

indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[32]

73. The PRADAXA® capsules also contain the following inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid, and the capsule shell is composed of carageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink.[33]

74. The capsules include pellets containing a tartaric acid core, an insulating layer coating the tartaric acid core, followed by a dabigatran etexilate layer. The tartaric acid core in the pellets generate an acidic microenvironment after the drug is taken, which increases dabigatran etexilate's dissolution and renders the extent of dissolution of dabigatran etexilate independent of variations in the gastric pH.[34]

75. Indeed, adding an acid to a weakly basic substance having low solubility in water under neutral or basic conditions was a known method to increase the substance's dissolution in water.[35]

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[32] *Id.*, pp. 4, 2.

[33] *Id.*, p. 4.

[34] Ex. 1015, p. 3; Ex. 1007, ¶¶[0011], [0035].

[35] Ex. 1010, ¶¶ [0002-0003].

76. However, dabigatran etexilate was also known to be chemically unstable and prone to polymorphic form transformations in acidic environment.[36] Thus, to increase the storage stability (durability) of the finished product, an insulating layer was included in PRADAXA® pellets between the tartaric acid core and the dabigatran etexilate layer to separate the acid from dabigatran etexilate before the drug is taken.[37]

77. The process for preparing pellets included in PRADAXA® capsules was also known. This process included the following steps: first, the tartaric acid pellets are produced by powder layering of tartaric acid dust onto tartaric acid crystals, which are then sprayed with an ethanolic suspension of hydroxypropyl methyl cellulose (HPMC) to coat the tartaric acid core with the HPMC insulating layer. Dabigatran etexilate mesylate suspension is then sprayed onto the coated cores.[38]

78. However, because in practice the tartaric acid cores produced by the powder layering process are "only quasi-spherical," it was "very difficult to avoid

[36] Ex. 1022, pp. 4-5.

[37] *Id.*, pp. 4-5; *see also id.*, p. 6 ("dabigatran etexilate is unstable in the presence of tartaric acid; therefore, an isolating layer between the tartaric acid core and API (Active Pharmaceutical Ingredient) layer has to be applied."); Ex. 1007, ¶[0013].

[38] Ex. 1022, pp. 4-6.

the formation of satellites[39] which cause defects in the isolating layer," leading to "impaired storage stability and hence durability of the finished product."[40]

B. Oral Solid Dosage Forms

79. "The oral route is the preferred means by which drugs are administered to humans and animals due to its convenience, simplicity and acceptability to patients."[41]

80. "Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules."[42]

81. "Capsules may be made from any suitable material such as gelatin, hydroxypropylmethylcellulose or starch. The capsules may contain one or more of tablets, powder, granules or pellets."[43]

82. Tablets and capsules usually contain other materials, often called excipients, in addition to the active ingredient (i.e., the drug substance) to help with

[39] "The so-called satellites are small particles adhering to the outside of the otherwise rounded pellets and detracting from the otherwise spherical geometry of the pellets." Ex. 1022, p. 6.

[40] Ex. 1022, p. 6.

[41] Ex. 1009, ¶[0003].

[42] Ex. 1023, p. 3.

[43] Ex. 1009, ¶[0061].

manufacturing, facilitate handling, enhance physical appearance, improve stability, and aid in the delivery of the drug after administration.[44]

83. Examples of excipients that may be included in oral solid dosage forms are diluents/fillers, binders, lubricants, glidants, and disintegrants.[45]

84. Diluents/fillers are added to oral solid dosage forms to increase the bulk of the solid dosage form or pellets. This is because the single dose of the active ingredient is typically small resulting in difficulties in providing reproducible, accurate doses as a single material.[46]

85. Binders (or granulators) are included in solid oral dosage forms because of their cohesive qualities that bind powdered materials together and because they can improve the free-flowing qualities by forming granules of desired hardness and size.[47] For example, binders were incorporated into pellet formulations to bind powders and maintain the integrity of the pellets.[48]

86. Lubricants, among other things, prevent adhesion of the materials to the surface of manufacturing components, reduce interparticle friction, and may

[44] Ex. 1023, p. 32

[45] *Id*., pp. 5-8.

[46] *Id*., p. 5; *see also* Ex. 1012, p. 11 (discussing fillers).

[47] Ex. 1023, pp. 5-6.

[48] Ex. 1012, p. 10.

improve the rate of flow of the granulation.[49] Lubricants were also used to improve the flow properties of pellets by preventing sticking and assist with the capsule filling process.[50]

87. Glidants are substances that improve the flow characteristics of a powder mixture.[51]

88. Disintegrants are substances or mixtures added to an oral solid dosage form to facilitate its breakup or disintegration after administration.[52]

89. Including "excipients (e.g. diluents, lubricants and surfactants) in a capsule formulation can have a significant effect on the rate of dissolution of drugs, particularly those that are poorly soluble and hydrophobic."[53]

90. For example, as shown below, "a hydrophilic diluent (e.g. sorbitol; lactose) often serves to increase the rate of penetration of the aqueous gastrointestinal fluids into the contents of the capsule, and to aid the dispersion and subsequent dissolution of the drug in these fluids. However, the diluent should

[49] Ex. 1023, pp. 6-7.

[50] Ex. 1012, p. 11.

[51] Ex. 1023, p. 7.

[52] Ex. 1011, p. 3.

[53] *Id.*, p. 3.

exhibit no tendency to adsorb or complex with the drug, as either can impair absorption from the gastrointestinal tract."[54]

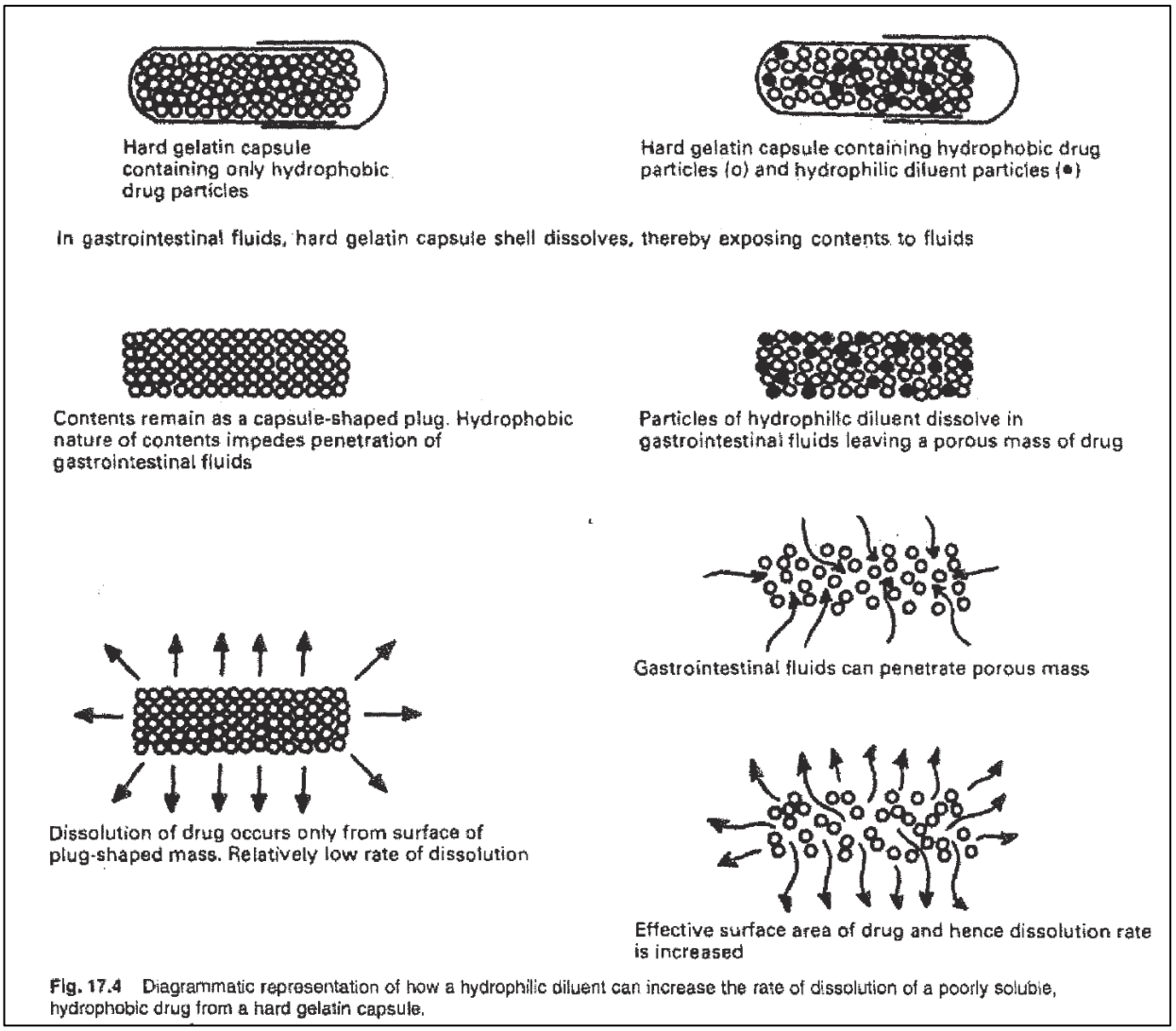


Fig. 17.4 Diagrammatic representation of how a hydrophilic diluent can increase the rate of dissolution of a poorly soluble, hydrophobic drug from a hard gelatin capsule.

91. Pellets, which are produced by a pelletization process, are "geometrically defined agglomerate[s]" that are "free-flowing, spherical or semi-

[54] *Id.*, pp. 3-4.

spherical solid units" intended mostly for oral administration, for example, when filled into hard capsules along with other desired excipients.[55]

92. Pellets were known to have several advantages, including improved flow and packing properties, and ease of coating.[56] As another advantage, using pellets in solid oral dosage forms provided "a convenient way" to separate incompatible substances that needed to be delivered in a single dose.[57]

93. There were different techniques available to prepare pellets, including compaction and drug layering.[58] "Of the compaction techniques used, extrusion and spheronization [wa]s the most popular method."[59]

94. The drug layering process "comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds."[60]

95. The extrusion and spheronization process, introduced in late 1960s, is a process that results in spherical granules. The process includes (a) dry mixing of the ingredients to prepare a homogenous powder dispersion; (b) wet massing using

[55] Ex. 1012, p. 2; *see also id.*, pp. 1, 16-17.
[56] *Id.*, p. 2.
[57] *Id.*, pp. 2, 16-17.
[58] *Id.*, p. 3; *see also id.* at p. 4.
[59] *Id*.
[60] *Id*., p. 4.

equipment and processes used in wet granulation; (c) extrusion, which produces rod-shaped particles of uniform diameter from the wet mass produced in step (b); (d) spheronization, which transforms the rods to spheres; (e) drying, if needed, to achieve the desired moisture content; and (f) screening, if needed, to achieve the desired size distribution.[61]

96. It was also known that pellets could be coated, for example, for taste masking or to control drug release.[62]

VII. OVERVIEW OF THE PRIOR ART

A. Brauns (Ex. 1007)

97. US 2006/0183779 A1 ("Brauns") is titled "Administration form for the oral application of 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1h-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester and the salts thereof." Brauns, filed by Boehringer Ingelheim, published on August 17, 2006.[63]

98. Brauns explains that "[t]he aim of the invention is to provide an improved formulation for oral use of the compound of formula I (which is also

[61] *Id.*, pp. 5-7.

[62] *Id.*, p. 8; *see also id.*, pp. 9-10 (describing techniques for coating pellets).

[63] Ex. 1007, p. 1.

referred to hereinafter as the "active substance")."[64] Based on the chemical structure, and the chemical name Brauns provided for the compound of formula I (the "active substance"), a POSA would have understood that a compound of formula I is dabigatran etexilate.[65]

99. Brauns explains that dabigatran etexilate was known as a prodrug of dabigatran, and that the "main indication" for dabigatran etexilate is "the post-operative prevention of deep-vein thrombosis."[66]

100. Brauns teaches that dabigatran etexilate "dissolves relatively well in water at low pH levels, whereas at pH levels above 5 in accordance with the definition of the European Pharmacopoeia it is virtually insoluble."[67] Thus, a POSA would have understood that dabigatran etexilate's solubility is pH dependent.

101. Brauns explains that "the use of pharmaceutically acceptable organic acids with a water solubility of >1 g/250 ml at 20° C., preferably >1 g/160 ml at 25° C., in solid oral preparations leads to a significantly improved formulation of" dabigatran etexilate and its pharmaceutically acceptable salts.[68]

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[64] *Id.*, ¶[0006].

[65] *Id.*, ¶[0003].

[66] *Id*.

[67] *Id.*, ¶[0024].

[68] *Id.*, ¶[0007].

102. Brauns provides a list of pharmaceutically acceptable acids that could be used: "tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid and aspartic acid including the hydrates and acid salts thereof. Particularly suitable for the purposes of this invention are tartaric acid, fumaric acid, succinic acid and citric acid."[69] The embodiments disclosed in Brauns' Examples include tartaric acid.[70]

103. Brauns teaches that "[a] preferred salt of the active substance is the mesylate (methanesulphonate)."[71]

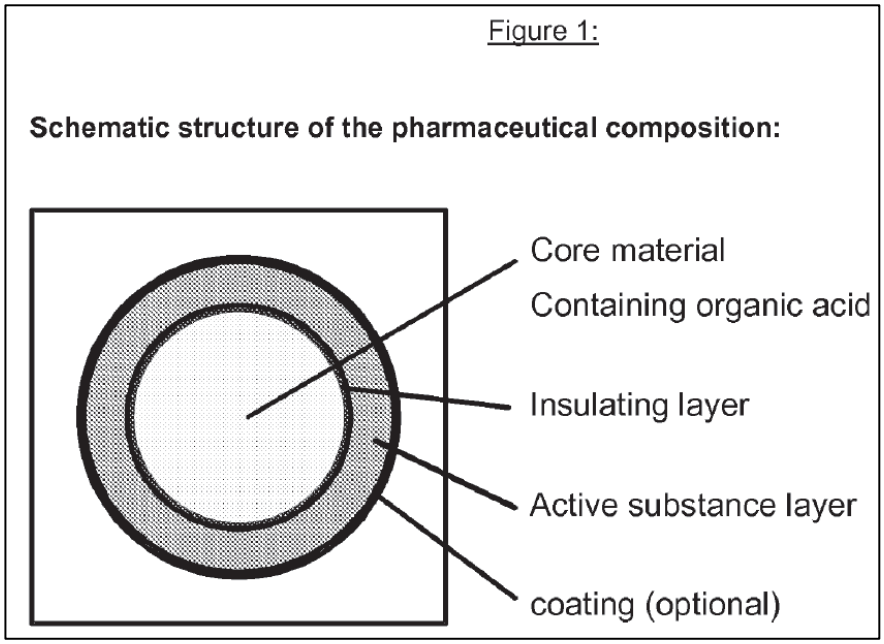
104. Brauns explains that "[a] preferred embodiment of the invention is a multiparticulate preparation in which the individual particles are constructed as in FIG. 1."[72] Brauns' Fig. 1 is provided below.

[69] *Id.*, ¶[0008].

[70] *Id.*, ¶¶[0039]-[0072] (Examples 1-2).

[71] *Id.*, ¶[0014].

[72] *Id.*, ¶[0009].



105. With respect to Fig. 1, Brauns explains that "[t]he roughly bead-shaped/spherical core region of this pellet contains/consists of the pharmaceutically acceptable organic acid. Then follows a layer, the so-called insulating layer, which separates the acid core from the layer containing the active substance. The insulating layer is in turn surrounded by the equally spherically shaped layer of active substance which may in turn be enclosed in a coating which increases the abrasion resistance and shelf life of the pellets."[73]

106. Brauns explains that the "insulating layer" is a "a water-soluble, pharmaceutically acceptable polymer," such as "gum arabic or a partially or totally synthetic polymer selected from among the hydroxypropylcelluloses,

[73] *Id.*, ¶[0010].

hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, polyvinylpyrrolidone, the copolymers of N-vinylpyrrolidone and vinyl acetate, or combinations of these polymers. Gum arabic or a hydroxypropylmethylcellulose is preferably used."[74]

107. Brauns teaches that the "insulating layer" can be applied to the acid core "by conventional methods, e.g. by applying an aqueous dispersion of the water-soluble, pharmaceutically acceptable polymer, optionally with the addition of plasticisers, separating agents and/or pigments, in a fluidised bed, in coating pans or in conventional film coating apparatus."[75]

108. Brauns provides additional details regarding the composition of the disclosed pellets. For example, Brauns teaches that the acid core can also include a "suitable binder," if the acid core is prepared by "a pan build-up process."[76] Alternatively, if the acid core is prepared by "extrusion or spheronisation," then microcrystalline cellulose can be added to the core.[77]

109. Brauns teaches that "[t]he content of the pharmaceutically acceptable organic acid is usually between 30 and 100% in the core material, corresponding to

[74] *Id.*, ¶[0013].
[75] *Id.*, ¶[0018].
[76] *Id.*, ¶[0012].
[77] *Id*.

an amount of between 20 and 90%, preferably between 20 and 80% in the finished pellet (i.e. in the pharmaceutical composition)."[78] Brauns' Examples 1 and 2 disclose formulations comprising 61.3% and 38.5% tartaric acid, respectively.[79]

110. Brauns teaches that the active substance layer includes dabigatran etexilate or a pharmaceutically acceptable salt of dabigatran etexilate, such its mesylate salt, "binders and optionally separating agents."[80]

111. As Brauns explains, "[t]he addition of separating agents such as e.g. talc or silicic acid serves to prevent the particles from aggregating during the process."[81]

112. Brauns also provides a list of suitable binders, such as "hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, copolymers of N-vinylpyrrolidone and vinyl acetate or combinations of these polymers. Preferably, hydroxypropylcellulose or copolymers of N-vinylpyrrolidone and vinyl acetate are used."[82]

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[78] *Id*.

[79] *Id*., ¶¶[0039] (Example 1), [0055] (Example 2).

[80] *Id.*, ¶[0014].

[81] *Id*.

[82] *Id*.

113. Brauns teaches that "[t]he active substance content is 5 to 60%, preferably 10 to 50% of the pharmaceutical composition."[83] Brauns' Examples 1 and 2 disclose formulations comprising 20% and 40% dabigatran etexilate mesylate, respectively.[84]

114. Brauns also teaches the dose for the oral use of "25 to 300 mg" of dabigatran etexilate per capsule, "preferably 50 to 200 mg, most preferably 75 to 150 mg of [dabigatran etexilate], in each case once or twice a day."[85]

115. Brauns teaches "[t]he preferred ratio of acid to active substance is about 0.9: 1 to about 4:1, most preferably between about 1:1 and 3:1. Preferably, at least one equivalent of acid is used per mol of" dabigatran etexilate.[86]

116. Brauns also teaches an "optional outermost layer ,which serves to reduce any increased abrasion during packing into capsules and/or to increase the shelf life, consists of pharmaceutically conventional film-forming agents, plasticisers and optionally pigments."[87]

[83] *Id*.

[84] *Id*., ¶¶[0039] (Example 1), [0055] (Example 2).

[85] *Id*., ¶[0036].

[86] *Id*., ¶[0037].

[87] *Id*., ¶[0015].

117. Brauns also explains the advantages of the disclosed formulation. For example, one advantage is " the spatial separation of the organic acid and active substance by the insulating layer. A further advantage of the construction of the pellets as described above is the fact that the organic acid does not go into solution until after the preparation has been taken and then produces an acid microclimate in which the active substance can dissolve."[88]

118. Based on this, a POSA would have understood that the Brauns' formulation provides a solution to the problem posed by the conflicting chemical properties of dabigatran etexilate, that is, dabigatran etexilate needs an acidic environment to dissolve in water, yet it is also chemically unstable in acidic environment.

119. A POSA would have further understood that the solution provided by Brauns' formulation was to spatially separate the acid from dabigatran etexilate before the drug is taken, which is achieved by the inclusion of the "insulating layer," while allowing the acid to go into the solution after the drug has been taken to produce an acidic environment in which dabigatran etexilate can dissolve.

120. Indeed, Brauns explains that the "insulating layer" between the active substance layer and the acid core was added "[t]o increase the durability of the

[88] *Id.*, ¶[0011].

finished product."[89] A POSA would have understood this teaching to mean that the "insulating layer" improves the storage stability of Brauns' finished product.

121. Brauns also teaches that "[i]n preliminary tests on test subjects with conventional tablets containing [dabigatran etexilate,] it had been established that highly variable plasma levels occurred, with individual cases of malabsorption."[90]

122. Brauns discloses results of clinical trials in which "the pharmaceutical compositions according to Examples 1 and 2 were tested for their bioavailability by comparison with a conventional tablet."[91]

123. Brauns further explains that, because dabigatran etexilate's solubility was known to be pH dependent, "the volunteers in one branch of the clinical trials were given pantoprazole, which serves to produce an elevated gastric pH."[92]

124. Brauns discloses that for individuals taking the formulation prepared according to Brauns' Example 1 (containing 50 mg of dabigatran etexilate), "[t]he relative bioavailability after pre-treatment with pantoprazole was 94% on average compared with administration without any pre-treatment."[93]

[89] *Id.*, ¶[0013].
[90] *Id.*, ¶[0023].
[91] *Id.*, ¶[0025].
[92] *Id.*, ¶[0024].
[93] *Id.*, ¶[0027].

125. In comparison, "the relative bioavailability (based on the area under the plasma concentration/time curve) of a tablet containing 50 mg of active substance, developed and produced according to the prior art and containing no water-soluble organic acid [provided in Table I], after corresponding pre-treatment with pantoprazole, is 18%."[94]

126. Brauns concluded using its multilayered pellet formulation "improved the relative bioavailability" of dabigatran etexilate "by about a factor of 5."[95]

127. Brauns also discloses results from clinical trials comparing formulations prepared according to Brauns' Example 2, compared with formulations "produced according to the prior art and containing no water-soluble organic acid," provided in Table II.[96]

128. For individuals taking formulations prepared according to Brauns' Example 2, "[t]he relative bioavailability after pre-treatment with pantoprazole was 76% on average compared with administration without any pre-treatment."[97]

[94] *Id.*, ¶[0028].

[95] *Id.*, ¶[0029].

[96] *Id.*, ¶¶[0030], [0034].

[97] *Id.*, ¶[0032].

129. On the other hand, individuals taking the prior art formulation with no water-soluble organic acid, the relative bioavailability after pre-treatment with pantoprazole was 18%.[98]

130. Brauns concluded that the relative bioavailability of dabigatran etexilate was "improved by about a factor of 4 by using" Brauns' multilayered pellet formulation.[99]

131. Based on these clinical data, Brauns concluded that " another advantage" of the disclosed formulation containing tartaric acid was that the formulation "ensures adequate bioavailability of the active substance, better than that of a conventional pharmaceutical preparation [containing no acid] and largely independent of the gastric pH;" and that the disclosed formulation containing tartaric acid "reduces fluctuations in the bioavailability of the active substance and it prevents malabsorption."[100]

132. Relatedly, Brauns describes another advantage of the disclosed formulation containing tartaric acid "is the fact that it is suitable for all patients, i.e.

[98] *Id.*, ¶[0033].

[99] *Id.*, ¶[0034].

[100] *Id.*, ¶[0035].

including those in whom the gastric pH is increased by normal physiological variability, by disease or by co-medication with drugs which raise the gastric pH."[101]

133. I understand that by February 2012, the patent application published as Brauns was under examination by the Patent Office. I understand that on December 14, 2010, Boehringer Ingelheim received a Notice of Allowance for the claims pending at the time, including claim 1, copied below.[102] I understand that no office action was issued regarding the pending claims allowed in December 2010 until June 2013.[103]

> Claim 1 (currently amended): A pharmaceutical composition for oral administration comprising:
> (a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 mL at 20° C; and
> (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material, wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof.

[101] *Id*.

[102] Ex. 1008, pp. 52-59 (Notice of Allowance, dated December 14, 2010), p. 127-131 (Listing of Claims, dated May 12, 2009).

[103] *Id.*, pp. 1-23 (Non-final Rejection, dated June 20, 2013).

134. Therefore, before February 2012, a POSA would have understood that the Patent Office had allowed claims related to compositions comprising a multilayer structure with an organic acid core and a dabigatran etexilate layer.

B. Leane (Ex. 1009)

135. US 2006/0115525 A1 ("Leane") is titled "Pharmaceutical compositions." Leane was published on June 1, 2006.[104]

136. Leane relates to "solid compositions for oral administration comprising (i) a drug compound, (ii) chitosan or a derivative thereof or a salt of chitosan or salt of a derivative of chitosan; and (iii) an organic acid."[105]

137. It was known that chitosan, "a bioadhesive polymer derived from the acetylation of chitin [comprising] glucosamine and N-acetylglucosamine units,"[106] can be used to increase the transmucosal absorption of drug compounds.[107]

138. Leane explains that "[f]or successful enhancement of absorption of a drug compound it is postulated that high local concentrations of the drug compound and an absorption enhancing compound are required. This in turn requires a dosage form from which the absorption enhancing compound and drug compound dissolve

[104] Ex. 1009, p. 1.

[105] *Id*., ¶[0005].

[106] *Id*., ¶¶[0005], [0030].

[107] *Id*., ¶[0006].

rapidly and simultaneously."[108] However, as Leane explains, preparing "a solid chitosan containing composition that meets these requirements represents a significant challenge."[109]

139. This is because, as Leane explains, chitosan has a pH dependent solubility.[110] In particular, chitosan is "a weak base (pKa 6.5) and an acidic environment is needed to convert its glucosamine units into the uncoiled and positively charged water-soluble form. At neutral and basic pH values, chitosan loses its charge and precipitates from solution, thus losing its potential bioadhesive and absorption enhancing properties."[111]

140. Leane further explains that "[t]he pH of the human small intestine ranges from 5 at the jejunum to in excess of 7.5 in parts of the colon."[112] Leane, thus concludes that "there are areas of the intestine in which chitosan is soluble and areas in which it is insoluble."[113]

141. At the low pH levels, Leane explains that "chitosan will readily hydrate and ionise. Adjacent chitosan particles will adhere to each other with the result that

[108] *Id*., ¶[0011].
[109] *Id*.
[110] *Id*., ¶[0012].
[111] *Id*.
[112] *Id*., ¶[0013].
[113] *Id*.

the surface of the dosage form forms a hydrated gelled layer which inhibits water penetration into the core of the dosage form. As a result, the chitosan will dissolve only slowly from the surface of the dosage form."[114]

142. Leane explains that they were able to produce "a solid pharmaceutical composition for oral administration from which dissolved chitosan and dissolved drug are rapidly and simultaneously liberated over the pH range found in the intestine so that the chitosan can act to improve the intestinal absorption of the drug compound" "by incorporating an organic acid into the solid pharmaceutical preparation."[115]

143. Leane teaches that the weight ratio of acid:chitosan "is preferably in the range 10:1 to 1:1, more preferably in the range 8:1 to 1:1 and most preferably in the range 6:1 to 1:1."[116]

144. Leane teaches that "[a]ny suitable organic acid may be used in the present invention," such as "lactic, glutamic, succinic, tartaric, citric, fumaric and propionic acid."[117]

[114] *Id*. ¶[0013].
[115] *Id*. ¶[0016].
[116] *Id*. ¶[0049].
[117] *Id*. ¶[0037].

145. Leane further teaches that "most preferably at least 90% of the acid is present in the form of an agglomerate."[118]

146. Leane defines the term agglomerate as "an association of particles, for example acid particles," "such as individual particles of acid engineered to a specific size."[119] More particularly, Leane explains that "[t]he agglomerate of the organic acid may be in the form of a granule, pellet, tablet or acid particle engineered to a specific size. The granules, pellets or tablets can be produced by any suitable technique known to those skilled in the art. Suitable techniques include wet granulation, dry granulation (slugging), extrusion/spheronisation, fluid bed granulation, spray drying, spray congealing, coating onto an inert seed such as a sugar seed, compression and moulding."[120]

147. Based on Leane's teachings, it is my opinion that a POSA would understand that the term "agglomerate" as used in Leane falls within the scope of the term "particles" in the '729 patent claims as understood by a POSA.[121]

148. Leane explains that the rate of dissolution of the acid agglomerate can be adjusted in two different ways. First, as Leane explains, "[t]he skilled person will

[118] *Id*. ¶[0038].

[119] *Id*. ¶[0039].

[120] *Id*. ¶[0042].

[121] *See* Section V.A above.

appreciate that by adjusting the degree of agglomeration it is possible to adjust the rate of acid dissolution," which is the result of adjusting "the surface area:weight ratio of the acid."[122] Leane teaches that "[t]ypically, the level of acid agglomeration should be such that the chitosan particles in the dosage form are able to separate and disperse before becoming hydrated, thus allowing rapid disintegration of the dosage form."[123]

149. Second, "the acid agglomerate may also be coated in order to modify its dissolution properties, for example to provide a short delay in dissolution to allow the chitosan component of the dosage form to disperse before coming into contact with dissolved acid. Coatings that can achieve this effect include those that are water soluble, those that are insoluble but water permeable and those that are soluble at the pH encountered in the small intestine."[124]

150. Based on these teachings, a POSA would have understood Leane to teach a solution to the problem posed by the conflicting chemical properties of chitosan, an active excipient with an important role in improving the absorption of the active ingredient, where chitosan needs an acidic environment to dissolve in water, yet in acidic environment, it forms a hydrated gelled layer which inhibits

[122] Ex. 1009, ¶[0042].

[123] *Id*.

[124] *Id*. ¶[0042].

water penetration into the core of the dosage form, which then slows further chitosan dissolution.

151. A POSA would have understood Leane's solution to include coated acid agglomerates in the solid oral dosage form containing chitosan, thus spatially separating the acid from chitosan. A POSA would have understood this solution would have allowed the acid to dissolve at a controlled rate, which would in turn affect chitosan's dissolution and gel formation.

152. The drug compound in Leane's teaching is a polar or high molecular weight compound while the acid-sensitive component is the active excipient, chitosan. Leane teaches the following different embodiments: (i) the drug compound is mixed with chitosan and acid agglomerates; (ii) the drug compound is incorporated into acid agglomerates, which are then mixed with chitosan; (iii) the drug compound is formed into agglomerates, which are then mixed with acid agglomerates, and chitosan; and (iv) the drug compound with chitosan are formed into agglomerates, which are then mixed with acid agglomerates.[125] In each embodiment, the acid agglomerates are separated from the acid-sensitive component, chitosan.

[125] *Id*. ¶¶[0055]-[0059].

153. Leane teaches the above mixtures can be shaped into tablets, using standard procedures, or put into capsules.[126]

154. Leane teaches that the disclosed compositions may include "other pharmaceutically acceptable ingredients such as" "diluents," "binders," "glidants," "surfactants," "lubricants," "colorants and flavourings or other agents generally used in solid pharmaceutical preparations and well known to those skilled in the art."[127]

155. Example 1 of Leane describes preparing chitosan tablets containing chitosan and mannitol and a dissolution test to measure chitosan's dissolution rate from the tablets.[128] The results showed that "although chitosan had rapidly been released from the tablets, it did not dissolve."[129]

156. Example 2 describes preparing pellets (or agglomerates) containing succinic acid (an organic acid) and sodium salicylate (a drug substance).[130]

157. Example 3 describes preparing pellets containing succinic acid and sodium salicylate that were coated with hydroxypropyl methylcellulose (HPMC).[131]

[126] *Id*. ¶[0060]; *see also id.* ¶[0061].
[127] *Id*. ¶[0062].
[128] *Id*. ¶¶[0075]-[0079].
[129] *Id*. ¶[0079].
[130] *Id*. ¶[0080].
[131] *Id*. ¶¶[0081]-[0082].

158. Example 4 describes preparing hard gelatin capsules containing chitosan, succinic acid powder, and sodium salicylate powder.[132]

159. Examples 5 and 6 describe preparing hard gelatin capsules containing chitosan and uncoated succinic acid/sodium salicylate pellets from Example 2 (Example 5), or coated succinic acid/sodium salicylate pellets from Example 3 (Example 6).[133]

160. Example 7 describes comparing dissolution of chitosan from hard gelatin capsules prepared in Examples 4-6 at pH 7.2 and pH 5.6.[134] The results are depicted in FIG. 1 (pH 7.2) and FIG. 3 (pH 5.6).

[132] *Id*. ¶[0083].

[133] *Id*. ¶¶[0084]-[0085].

[134] *Id*. ¶¶[0086]-[0089].

Figure 1. Dissolution of chitosan from capsule formulations at pH 7.2 (mean. n=3)

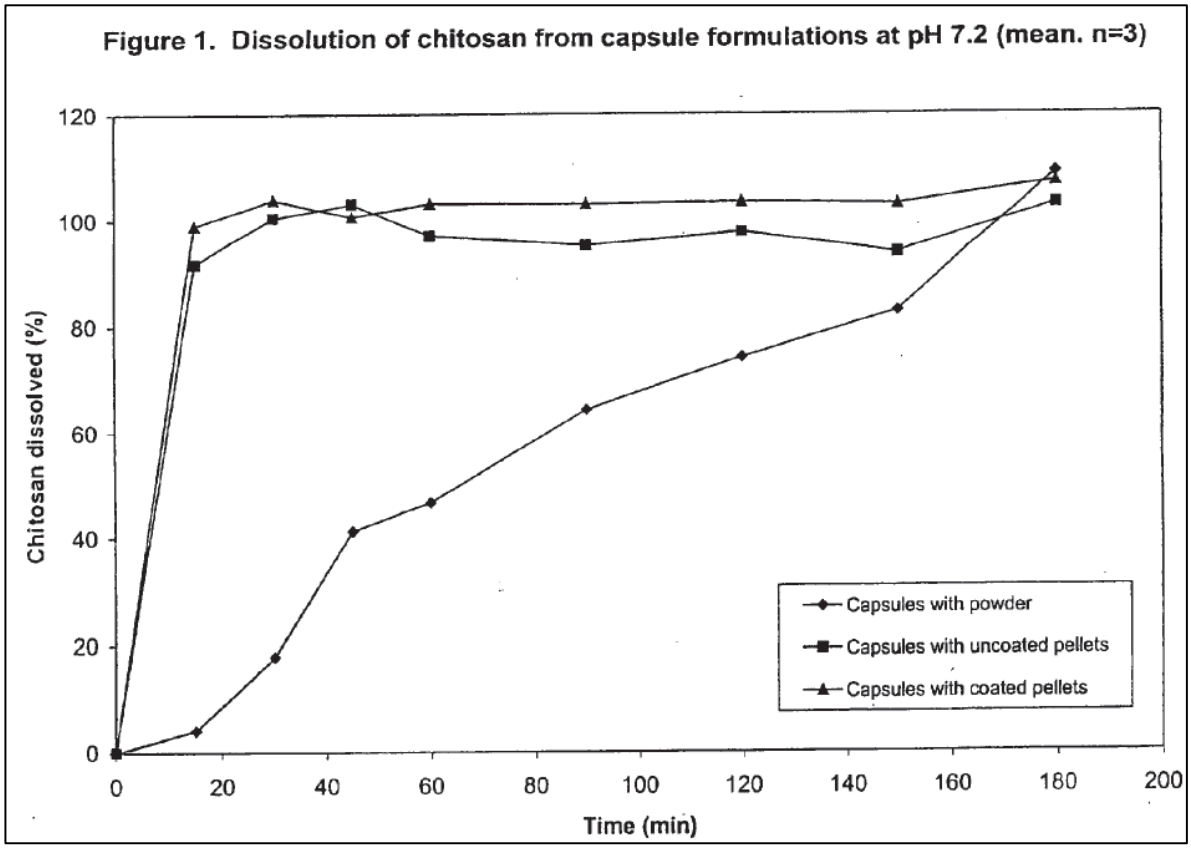
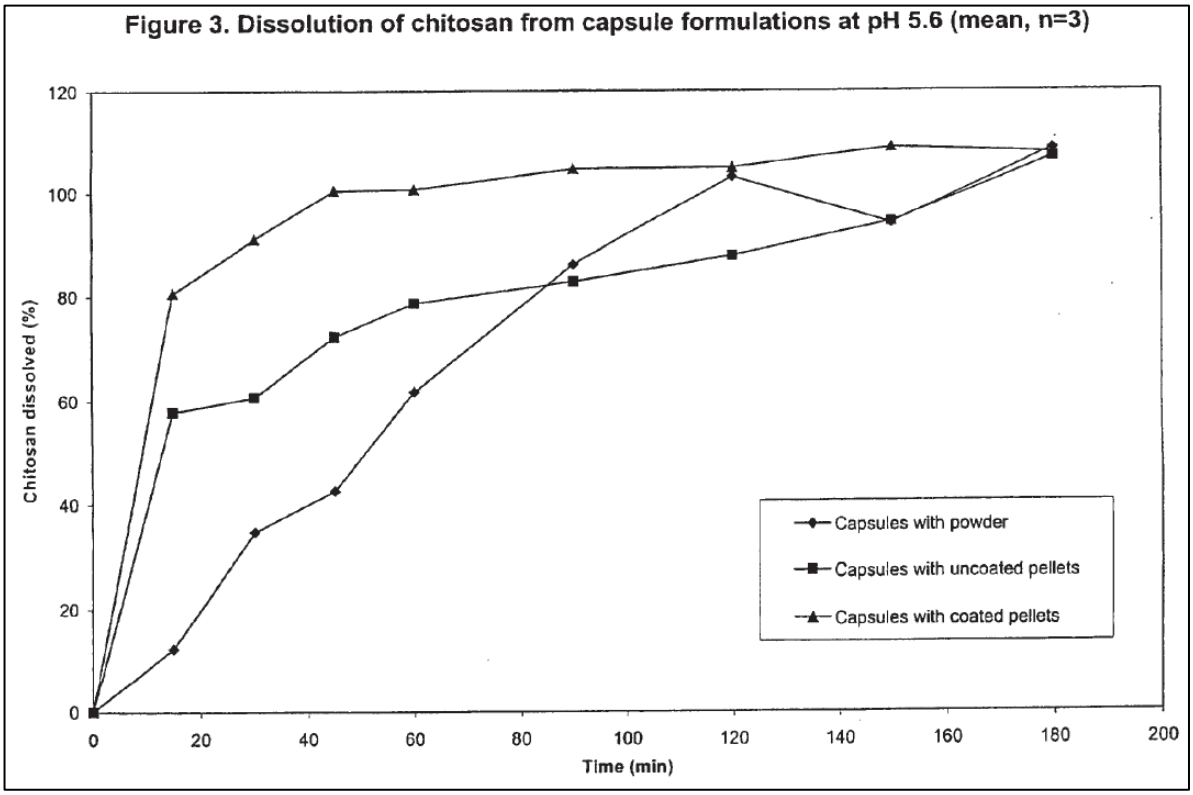


Figure 3. Dissolution of chitosan from capsule formulations at pH 5.6 (mean, n=3)



161. As shown in FIG. 1 and FIG. 3, over the initial 90 min, chitosan was more rapidly dissolved from capsules containing both coated and uncoated succinic acid/sodium salicylate pellets compared to capsules containing succinic acid/sodium salicylate powder at both pH levels.

162. As shown in FIG. 3, at pH 5.6, chitosan dissolved more rapidly from capsules with coated succinic acid/sodium salicylate pellets compared to capsules with uncoated succinic acid/sodium salicylate pellets. A POSA would have understood that the local presence/dissolution of the agglomerated acid pellets is responsible for the dissolution of chitosan while limiting excess gel formation at lower pH conditions.

C. Sugimoto (Ex. 1010)

163. US 2004/0109890 A1 ("Sugimoto") is titled "Pharmaceutical compositions." Sugimoto was published on June 10, 2004.[135]

164. Sugimoto relates to intraorally rapidly disintegrating tablets containing (i) a drug being hardly water-soluble under neutral or alkaline conditions and being highly water-soluble under acidic conditions yet presenting unpleasant taste, (ii) a water-soluble acidic substance, in which at least (i) or (ii) are coated with a water-soluble coating agent that is insoluble in alcoholic solvent.[136]

[135] Ex. 1010, p. 1.

[136] *Id.*, Abstract; *see also id.*, ¶¶[0001], [0013].

165. Sugimoto teaches that the disclosed tablet "rapidly disintegrates in the oral cavity without presenting unpleasant taste, shows rapid release and absorption of the medicinal substance in the digestive tract, and can achieve early onset of efficacy."[137]

166. Sugimoto explains that the acid is included in the formulation "to increase the solubility of the medicinal substance [that is hardly water-soluble under neutral or alkaline conditions and is highly water-soluble under an acidic conditions] especially when administered to a subject who is suffering from anacidity or wishes to use the preparation immediately after eating."[138]

167. Sugimoto teaches that "[p]referred examples" of acids that could be used in the disclosed compositions include "organic acids specifically fumaric acid, tartaric acid, succinic acid, malic acid, ascorbic acid and aspartic acid."[139]

168. Sugimoto further explains coating either the drug substance or the water-soluble acid, or both, with a water-soluble coating agent would prevent contact between the drug substance and the water soluble acid, "which is responsible to unpleasant taste, is avoidable throughout the manufacturing processes" until after

[137] *Id.*, ¶¶[0008], [0013].

[138] *Id.*, ¶[0024].

[139] *Id.*, ¶[0026].

the composition passes the oral cavity, and thus the drug substance would not present unpleasant taste in the oral cavity.[140]

169. Sugimoto also teaches that another advantage of the disclosed composition is that "after ingestion," it allows the drug substance to dissolve rapidly "at the upper part of the digestive tract" independent of the pH level.[141]

170. Based on these teachings a POSA would have understood that Sugimoto provides a solution to address the conflicting properties of drug substances that need an acidic environment to dissolve but also have unpleasant taste in the mouth when they dissolve too rapidly while in the mouth rather than in the remaining portions of the GI tract.

171. A POSA would have understood Sugimoto to teach spatially separating the acid from the drug substance and coating either or both to avoid contact between the acid and the drug substance until the composition reaches the stomach, where the acid comes into contact with the drug and increases the drug's dissolution rate independent of the stomach's pH.

172. Sugimoto also discloses how to prepare the disclosed compositions. For example, Sugimoto teaches that when one of the acids and the drug substance is

[140] *Id.*, ¶¶[0024]-[0025].

[141] *Id.*, ¶[0025].

coated, first the uncoated ingredient (e.g., the drug substance, which is referred to as ingredient (i)) and the saccharide (ingredient (ii)) are mixed, then the mixture is granulated while adding the binding agent (ingredient (iii)), after which the granules are dried, if necessary, followed by mixing the coated acid (ingredient (ii)).[142]

173. Sugimoto explains that "granulation can be carried out by any one of conventional granulation techniques such as wet granulation, layering granulation or dry granulation."[143]

174. Sugimoto also teaches coating of the acid and/or the drug substance "by granulating said ingredient (i) [i.e., the drug substance] or (ii) [the acid] while adding an aqueous solution or aqueous alcohol solution of a water-soluble coating agent being insoluble in alcoholic solvent, thereby coating the surface of granules of ingredient (i) and/or (ii) with the water-soluble coating agent and, if necessary, spraying an aqueous solution of said water-soluble coating agent being insoluble in alcoholic solvent."[144]

175. Thus, a POSA would have understood that Sugimoto's coated or uncoated granules of the acid and the drug substance fall within the scope of the term

[142] *Id.*, ¶¶[0077]-[0078].

[143] *Id.*, ¶[0080]; *see also id.* ¶¶[0081] (discussing wet granulation), [0082] (discussing layering granulation), [0083] (discussing dry granulation).

[144] *Id.*, ¶[0084].

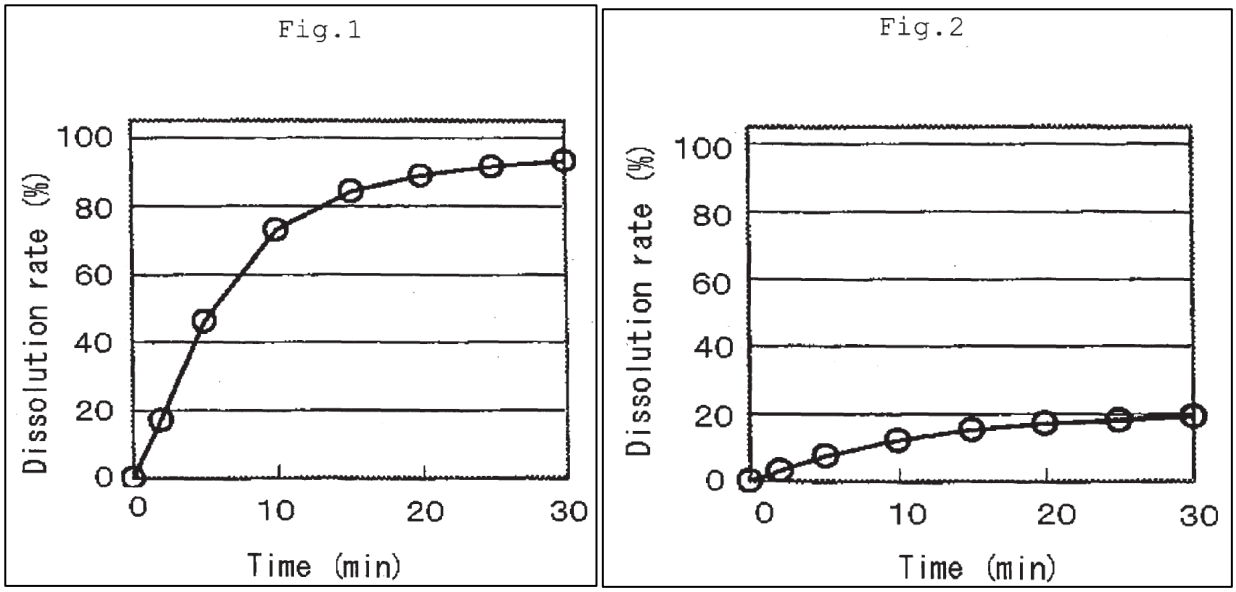
"particles" used in the '729 patent claims, as the term "particles" is understood by the POSA.

176. Example 1 describes preparing two different coated granules: (1) granules containing a drug substance and mannitol prepared using a fluidized-bed granulator, using PVP (polyvinylpyrrolidone), and (2) fumaric acid granules prepared using a fluidized-bed granulator, which were coated with HPMC. These two different granules were then mixed along with saccharide powder, followed by addition of other ingredients, compression into tablets, and preparation of intraorally disintegrating tablets.[145]

177. Reference Example 6 describes preparing intraorally disintegrating tablets similar to Example 1, except the tablets in Reference Example 6 did not include coated granules of fumaric acid.[146]

178. Experiment 5 describes measuring drug dissolution rate in water from the intraorally disintegrating tablets prepared in Example 1 and Reference Example 6.[147] The results are shown in FIGS. 1 (Example 1) and 2 (Reference Example 6).

[145] *Id.*, ¶¶[0131]-[0135].
[146] *Id.*, ¶¶[0161]-[0163].
[147] *Id.*, ¶¶[0178]-[0182].

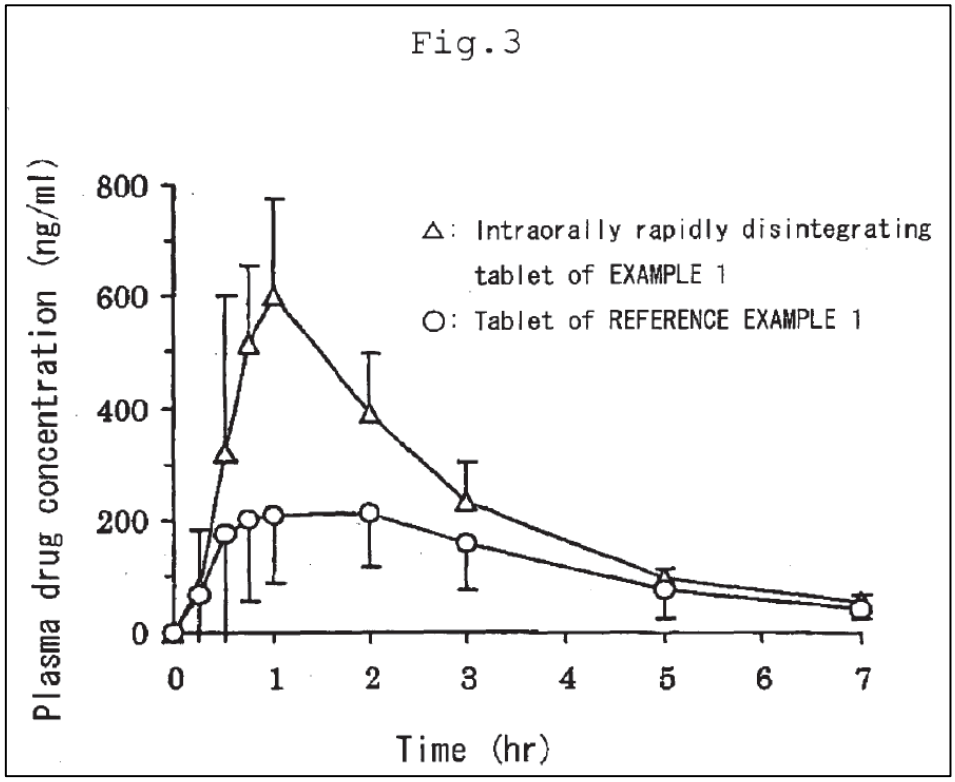


179. The results showed "a high dissolution rate in short time" for the drug in the intraorally disintegrating tablets of Example 1 (which included coated fumaric granules), while the tablets of Reference Example 6 (which did not include fumaric granules) "exhibit very poor dissolution profile."[148]

180. Experiment 6 describes measuring the drug concentration in dogs' blood after administering a tablet of Example 1 or Reference Example 6.[149] The results are shown in FIG. 3.

[148] *Id.*, ¶[0182].

[149] *Id.*, ¶¶[0183]-[0186]. Figure 3 legend includes a typo. A POSA would have understood that the "Tablet of REFERENCE EXAMPLE 1" should instead read "Tablet of REFERENCE EXAMPLE 6." *See id.*, ¶[0012].



181. The results showed "high blood drug concentration within a short time" and "high bioavailability" for the intraorally disintegrating tablets of Example 1 (which included coated fumaric granules), while the tablets of Reference Example 6 (which did not include fumaric granules) "could present only very low blood drug concentration and failed to show sufficient bioavailability."[150]

VIII. MOTIVATION TO COMBINE THE PRIOR ART

182. As discussed further below in Sections IX and X, it is my opinion that claims 1-18 of the '729 patent are rendered obvious by Brauns in view of Leane as well as Brauns in view of Sugimoto.

[150] *Id.*, ¶[0186].

183. In this section, I explain my opinions regarding a POSA's motivation to combine the teachings of Brauns with Leane or Sugimoto. I will also explain that a POSA would have had a reasonable expectation of successfully preparing a composition comprising "two distinct types of particles" wherein the first type of particles comprise dabigatran etexilate mesylate and "is free from organic and inorganic acids", and the second type of particles comprise tartaric acid, "is coated with a protective coating layer," and "is free from dabigatran etexilate," as required in claims 1-18 of the '729 patent.

184. As I discussed above, Brauns discloses improved formulation for oral administration of dabigatran etexilate comprising an organic acid (e.g., tartaric acid) prepared as multilayer pellets with an organic acid core, a layer containing dabigatran etexilate, and an insulating layer separating the organic acid from dabigatran etexilate.[151]

185. Brauns teaches including an organic acid in the dosage form provides the following advantages: (i) "ensures adequate bioavailability of the active substance, better than that of a conventional pharmaceutical preparation [containing no acid] and largely independent of the gastric pH;" (ii) "reduces fluctuations in the bioavailability of the active substance and it prevents malabsorption;" and (iii)

[151] *See* above Section VII.A.

making the formulation "suitable for all patients, i.e. including those in whom the gastric pH is increased by normal physiological variability, by disease or by co-medication with drugs which raise the gastric pH." [152]

186. Brauns also teaches that the insulating layer spatially separates the organic acid and the active substance until after the formulation is taken, which increases the stability of the final dosage form.[153]

187. Based on these teachings, a POSA would have understood that the Brauns' formulation provides a solution to the problem posed by the conflicting chemical properties of dabigatran etexilate, that is, dabigatran etexilate needs an acidic environment to dissolve in water, yet it is also chemically unstable in acidic environment. A POSA would have further understood that the solution provided by Brauns' formulation was to spatially separate the acid from dabigatran etexilate before the drug is taken, achieved by the inclusion of the "insulating layer," while allowing the acid to go into the solution after the drug has been taken to produce an acidic environment in which dabigatran can dissolve.

188. However, by February 2012, a POSA would have understood that the Patent Office had allowed claims in Brauns, a Boehringer Ingelheim patent

[152] Ex. 1007, ¶[0035].

[153] *Id.*, ¶[0013].

application, in which the allowed claims covered the Brauns' multilayer structure comprising a multilayer structure with an organic acid core and a dabigatran etexilate layer.[154]

189. Thus, a POSA would have been motivated to design a dabigatran etexilate oral dosage form that retained the advantageous properties of the Brauns' preparation but differed structurally from the multilayer pellets of Brauns, to design around Boehringer Ingelheim's pending claims that had been allowed by the Patent Office at that time.

190. Additionally, a POSA would have been motivated to look for alternative ways for spatially separating the organic acid from dabigatran etexilate than Brauns' multilayer structure because, in practice, it was difficult to prepare an intact insulating layer, which was required for storage stability and durability of the finished product.[155]

191. As I discussed above, the prior art taught an alternative structure for separating chemically incompatible substances that needed to be delivered in a

[154] Ex. 1008, pp. 52-59 (Notice of Allowance, dated December 14, 2010), p. 127-131 (Listing of Claims, dated May 12, 2009), pp. 1-23 (Non-final Rejection, dated June 20, 2013).

[155] Ex. 1022, p. 5.

single dose.[156] In particular, using distinct pellets was known as a "convenient" structure for this purpose.[157]

192. Thus, a POSA would have been motivated to prepare a composition comprising two distinct particles (pellets), one comprising dabigatran etexilate and another comprising an organic acid (such as tartaric acid), with a reasonable expectation that the organic acid would improve the dissolution of dabigatran etexilate after administration while being spatially separated from the chemically incompatible dabigatran etexilate before administration.

193. This motivation and reasonable expectation of success was further supported by the prior art's disclosure of successful implementation of two-particle systems in similar situations.

194. For example, as I discussed above, Leane teaches a solution to the problem posed by the conflicting chemical properties of chitosan, i.e., chitosan needs an acidic environment to dissolve in water, yet in acidic environment, it forms a hydrated gelled layer which inhibits water penetration into the core of the dosage form, which then slows further chitosan dissolution. A POSA would have understood Leane's solution to include coated acid agglomerates in the solid oral

[156] Ex. 1012, pp. 2, 16-17.

[157] *Id.*, p. 2.

dosage form containing chitosan, thus spatially separating the acid from chitosan. A POSA would have understood this solution would have allowed the acid to dissolve at a controlled rate, which would in turn increase chitosan's dissolution by limiting gel formation.[158]

195. Further, a POSA would have recognized that one of Leane's preferred embodiments was a capsule formulation containing coated organic acid particles separated from chitosan that provided faster chitosan dissolution compared to capsules where organic acid was not separated from chitosan.[159]

196. As another example, as I discussed above, Sugimoto provides a solution to address the conflicting properties of drug substances that need acidic environments to dissolve but also have unpleasant taste in the mouth. A POSA would have understood Sugimoto to teach spatially separating the acid from the drug substance and coating the acid and/or the drug substance to avoid contact between the acid and the drug substance until the composition reaches the stomach, after which the acid comes into contact with the drug and increases the dissolution of the drug substance independent of the stomach's pH.[160]

[158] *See* above Section VII.B.

[159] Ex. 1009, ¶¶[0085]-[0089] (Examples 6-7).

[160] *See* above Section VII.C.

197. Therefore, it is my opinion that a POSA would have been motivated to combine the teachings of Brauns with Leane, or with Sugimoto, with a reasonable expectation of successfully preparing a composition comprising two particles, one comprising dabigatran etexilate and another comprising a coated organic acid.

IX. GROUND 1: BRAUNS IN VIEW OF LEANE RENDER OBVIOUS CLAIMS 1-18 OF THE '729 PATENT

198. In my opinion, there are no inventive differences between the prior art and the subject matter claimed in claims 1-18 of the '729patent. The elements of the claimed subject matter are disclosed in Brauns and/or Leane or are rendered obvious in view of their teachings. As discussed above, a POSA would have followed clear motivation in the art to prepare the claimed compositions/capsules with a reasonable expectation of success in doing so. Therefore, in light of the teachings of Brauns and Leane, and the knowledge of those of skill in the art, each of claims 1-18 of the '729 patent would have been obvious over Brauns in view of Leane.

A. Independent Claim 1

1. "A composition comprising: a mixture of at least two distinct types of particles"

199. It is my opinion that Leane discloses "a composition comprising a mixture of two distinct types of particles."[161]

[161] Ex. 1009, ¶¶[0038]-[0040], [0058]-[0059].

200. For example, Leane teaches embodiments including those in which the drug compound is formed into agglomerates, which are then mixed with acid agglomerates, and chitosan; and those in which the drug compound with chitosan are formed into agglomerates, which are then mixed with acid agglomerates.[162]

201. As discussed above, a POSA would have understood the term "agglomerates" as used in Leane to fall within the scope of the term "particles" as used in claims of the '729 patent.[163]

2. "wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof"

202. Brauns discloses pellets that contain dabigatran etexilate mesylate, which is a pharmaceutically acceptable salt of dabigatran etexilate.[164] A POSA would have understood that the term "pellets" as used in Brauns falls within the scope of "particles" as used in claims of the '729 patent.[165] Thus, a POSA would have understood that Brauns discloses particles that contain dabigatran etexilate mesylate.

[162] *Id*. ¶¶[0058]-[0059].

[163] *See* above ¶¶146-147.

[164] *See* Ex. 1007, ¶¶[0003], [0050]-[0053].

[165] *See* above Section V.A.

3. "wherein the first type of particles is free from organic acids and inorganic acids; and"

203. It is my opinion that the combination of Brauns in view of Leane renders obvious this element, which require that the "the first type of particles is free from organic acids and inorganic acids."

204. First, Leane teaches embodiments including those in which the drug compound is formed into agglomerates, which are then mixed with acid agglomerates, and chitosan; and those in which the drug compound with chitosan are formed into agglomerates, which are then mixed with acid agglomerates.[166] As discussed above, Leane's "agglomerates" falls within the scope of the term "particles." Thus, a POSA would have understood that Leane teaches particles containing a drug compound and/or an active excipient (e.g. chitosan, the substance with pH-dependent solubility) that do not include an acid.

205. Further, as discussed above in Section VI.A, dabigatran etexilate was known to be prone to chemical degradation and polymorphic form transformation in acidic environment. This would have motivated a POSA to prepare dabigatran etexilate particles that do not contain any organic or inorganic acid to prevent dabigatran etexilate's chemical degradation and polymorphic form transformation during manufacturing or in the final dosage form.

[166] Ex. 1009, ¶¶[0058]-[0059].

4. "b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate."

206. Brauns discloses particles (pellets) that contain tartaric acid (a pharmaceutically acceptable organic acid), which are coated with an insulating layer.[167] Brauns teaches that the insulating layer prevents contact between the acid and dabigatran etexilate (an acid sensitive drug substance) until after the composition is administered, thus increasing the "durability of the finished product" before the drug is taken, while allowing the organic acid to create an acidic microclimate to dissolve the active substance after the drug is taken.[168]

207. As I discussed in Section V.B, a POSA would have understood the term "a protective coating layer" in the '729 patent claims to mean "a coating layer that prevents the organic acid from contacting dabigatran etexilate until after the composition is administered."

208. As I discussed above, a POSA would have understood that the term "pellets" as used in Brauns falls within the scope of "particles" as used in claims of the '729 patent. Further, Brauns discloses that the acid core is coated with an

[167] *See* Ex. 1007, ¶¶[0039]-[0049].

[168] *Id.*, ¶¶[0011],[0013].

insulating layer that prevents the organic acid from coming into contact with dabigatran etexilate until after the preparation has been taken.[169]

209. Thus, a POSA would have understood that Brauns discloses "particles" comprising at least one pharmaceutically acceptable acid that is coated with a "protective coating layer."

210. Leane similarly discloses agglomerates of a pharmaceutically acceptable organic acid (i.e., succinic acid), which are coated with a coating layer.[170] Leane teaches coating the acid agglomerates advantageously improves chitosan dissolution by controlling the rate at which the acid comes into contact with chitosan after the composition is administered.[171] Thus, a POSA would have understood the coating layer disclosed in Leane to be a "protective coating layer."

211. As discussed above, Leane's "agglomerates" falls within the scope of the term "particles." Thus, a POSA would have understood that Leane discloses "particles" comprising at least one pharmaceutically acceptable acid that is coated with a "protective coating layer."

212. The other requirement of this element that "the second type of particles … is free from dabigatran etexilate" is rendered obvious by Leane, which discloses

[169] *See* Section VII.A.

[170] *See* Ex. 1009, ¶¶[0080]-[0082].

[171] *Id.,* ¶[0044].

coated acid-containing agglomerates that are free from chitosan (i.e., the pH-dependent material that the acid is present to solubilize).[172] Leane also discloses embodiments including those in which the drug compound is formed into agglomerates, which are then mixed with acid agglomerates, and chitosan; and those in which the drug compound with chitosan are formed into agglomerates, which are then mixed with acid agglomerates.[173] Thus, Leane discloses organic acid particles that are free from the drug compound and/or chitosan.

213. Further, as discussed above in Section VI.A, dabigatran etexilate was known to be prone to chemical degradation and polymorphic form transformation in acidic environment. Thus, a POSA would have been motivated to use Leane's teachings to prepare organic acid particles free from dabigatran etexilate with a reasonable expectation of success.

214. For the above reasons, it is my opinion that the combination of Brauns in view of Leane renders obvious claim 1 of the '729 patent.

[172] *Id.*, ¶¶[0080]-[0082].

[173] *Id*. ¶¶[0058]-[0059].

B. Independent Claims 11 and 16, and Dependent Claims 2, 10, and 14

1. Claims 11 and 16

215. The only differences between independent claim 1 and independent claims 11 and 16 is that whereas claim 1 requires "[a] ***composition comprising***: a mixture of at least two distinct types of particles," claim 11 requires "[a] ***composition consisting of*** a mixture of two distinct types of particles ***and at least one pharmaceutically acceptable excipient***," and claim 16 requires "[a] ***capsule containing a pharmaceutical composition consisting of*** a mixture of two distinct types of particles ***and at least one pharmaceutically acceptable excipient***." The remaining limitations of claims 11 and 16 are identical to those of claim 1 and are obvious for the same reasons as discussed above in Section IX.A.

216. It is my opinion that claims 11 and 16, which require ***a composition consisting*** of two distinct types of particles ***and at least one pharmaceutically acceptable excipient*** are obvious over Brauns in view of Leane.

217. First, Leane discloses an embodiment consisting of two distinct types of particles in which the active excipient, chitosan (the material having pH-dependent solubility), and the drug substance are present in the first particles and an organic acid is present in the second particles.[174]

[174] Ex. 1009, ¶[0059].

218. Leane also teaches that the disclosed compositions may also contain at least one pharmaceutically acceptable excipient, such as a diluent, disintegrant, surfactant, lubricant, etc., "generally used in solid pharmaceutical preparations and well known to those skilled in the art."[175]

219. Further, as discussed above in Section VI.B, it was well-known that a pharmaceutically acceptable excipient, such as a glidant, lubricant, and diluent/filler, may be added in solid oral dosage forms, such as capsules.

220. Regarding claim 16 that recites "[a] capsule," both Brauns and Leane disclose capsule dosage forms that contain pellets.[176] Thus, it would have been obvious to formulate the composition of claim 1 in a capsule.

221. Thus, claims 11 and 16 are obvious over Brauns in view of Leane.

2. Claim 2

222. Claim 2 depends from claim 1 and requires that the composition further comprises "at least one pharmaceutically acceptable excipient." For the same reasons discussed above with respect to independent claims 11 and 16, *see* Section IX.B.1, claim 2 is invalid as obvious over Brauns in view of Leane.

[175] *Id.*, ¶[0062].

[176] Ex. 1007, ¶¶[0054], [0072]; Ex. 1009, ¶¶[0084]-[0085].

3. Claims 10 and 14

223. Claims 10 and 14 depend from claims 2 and 11, respectively, and require that "the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof."

224. As discussed above, Leane teaches that the disclosed compositions may contain at least one pharmaceutically acceptable excipient, such as a diluent, disintegrant, surfactant, lubricant, etc., "generally used in solid pharmaceutical preparations and well known to those skilled in the art."[177]

225. Further, as discussed above in Section VI.B, it was well known that a pharmaceutically acceptable excipient, such as a glidant, lubricant, and diluent/filler, may be added in solid oral dosage forms.

226. Thus, claims 10 and 14 are obvious over Brauns in view of Leane.

C. Dependent Claims 3, 5, 12, 15 and 17

227. Claims 3 and 12 depend from claims 1 and 11, respectively, and require that the compositions contain "from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate." And claims 5, 15, and 17 depend from claims 1,

[177] Ex. 1009, ¶[0062].

14, and 16, respectively, and require that the compositions contain "from 50 mg to 200 mg of dabigatran etexilate mesylate."

228. Brauns discloses that "the active substance [i.e., dabigatran etexilate] content is 5 to 60%, preferably 10 to 50% of the pharmaceutical composition."[178] Brauns also discloses that the "preferred salt" of dabigatran etexilate is "the mesylate (methanesolphonate)" and dabigatran etexilate mesylate is present in Brauns' exemplary embodiments in amounts of 57.7 mg and 115.3 mg.[179]

229. It would have been obvious to a POSA to use dabigatran etexilate mesylate in the ranges and amounts disclosed by Brauns, which overlap with the claimed ranges, in a two-pellet composition as disclosed by Leane for all the reasons discussed above.[180]

230. I understand that because Brauns discloses overlapping ranges and amounts for dabigatran etexilate, the burden would shift to the Patent Owner to show that the overlapping range would not have been obvious because the prior art taught away from the claimed range, the claimed range produces new and unexpected results, or the claimed range is critical to the alleged invention. I have not seen any

[178] Ex. 1007, ¶[0014].

[179] *Id.*, ¶¶ [0039], [0055] (Examples 1-2).

[180] *See, e.g.,* Section VIII.

evidence that could show the claimed range would not have been obvious. I reserve the right to respond to any such evidence presented by the Patent Owner.

231. Therefore, it is my opinion that a combination of Brauns in view of Leane renders obvious claims 3, 5, 12, 15, and 17 of the '729 patent.

D. Dependent Claim 4

232. Claim 4 depends from claim 1 and requires that the composition comprises "from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid."

233. Brauns discloses that the organic acid is present in a concentration of "between 20 and 90%, preferably between 20 and 80% in the finished pellet (i.e., in the pharmaceutical composition)."[181] Further, Braun's exemplary embodiments disclose pellet compositions that contain 61.3% and 38.5% by weight of tartaric acid.[182]

234. Leane discloses that "[t]he amount of acid is chosen in order to provide rapid dissolution of the chitosan present in the composition. The weight ratio of acid:chitosan … in the composition of the invention is preferably in the range 10: 1 to 1: 1, more preferably in the range 8: 1 to 1: 1 and most preferably in the range 6:

[181] Ex. 1007, ¶[0012].

[182] *Id.*, ¶¶[0039], [0055] (Examples 1-2).

1 to 1: 1."[183] Further, Leane's exemplary embodiments disclose a capsule containing an organic acid in the form of coated pellets where the organic acid is 45% w/w of the composition prior to coating and ~ 40% after coating.[184]

235. Thus, both Brauns and Leane teach compositions comprising organic acid at wt% that overlap with the range required by claim 4.

236. As stated above, I understand that because Brauns and Leane disclose overlapping ranges for the claimed acid, the burden would shift to the Patent Owner to show that the overlapping range would not have been obvious because the prior art taught away from the claimed range, the claimed range produces new and unexpected results, or the claimed range is critical to the alleged invention. I have not seen any evidence that could show the claimed range would not have been obvious. I reserve the right to respond to any such evidence presented by the Patent Owner.

237. Thus, it is my opinion that claim 4 is obvious over Brauns in view of Leane.

E. Dependent Claims 6-9

238. Claim 6 depends from claim 2 and is directed to "[a] process … comprising the step of mixing the first type of particles and the second type of

[183] Ex. 1009, ¶[0049].

[184] *Id.*, ¶¶[0080]-[0082], [0085] (Examples 2, 3, and 6).

particles with the at least one pharmaceutically acceptable excipient." Claim 7 depends from claim 6 and specifies that "the first type of particles are prepared by granulation." Claim 8 depends from claim 7 and specifies additional process steps. Claim 9 also depends from claim 7 and requires a process that is the same in all respects to claim 8 except for step iv.

1. Claims 6 and 7

239. It is my opinion that claim 6 is obvious over Brauns in view of Leane for the same reasons I discussed with respect to claims 11 and 16.[185]

240. Regarding claim 7, which requires the first type of particles are prepared by granulation, Leane discloses, the agglomerates can be in the form of a granule, pellet, tablet, or particle prepared using a wide range of methods including wet or dry granulation or fluid bed granulation.[186] Thus, it would have been obvious to a POSA to prepare particles containing dabigatran etexilate by granulation as required in claim 7. Therefore, it is my opinion that claim 7 is obvious over Brauns in view of Leane.

2. Claim 8

241. Claim 8 depends from claim 7 and recites additional process steps.

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[185] *See* Section IX.B.1.

[186] Ex. 1009, ¶[0042]; *see also id.*, ¶[0080] (disclosing the use of wet granulation to prepare acid-containing agglomerates).

242. In steps i)-ii), dabigatran etexilate is first blended with at least one pharmaceutically acceptable excipient and then the blend of step i) is granulated with a binder solution to form granulates of dabigatran etexilate. And in steps iii)-iv), at least one organic acid is first blended with at least one pharmaceutically acceptable excipient and then the blend of step iii) is granulated with a binder solution to form organic acid-containing granules.

243. As discussed above, Leane discloses that agglomerates can be in the form of a granule, pellet, tablet, or particle prepared a wide range of methods including wet or dry granulation or fluid bed granulation.[187] Leane also discloses the use of wet granulation to form acid-containing agglomerates in which a binder is mixed with an organic acid and drug and then water is added to form a granulate.[188]

244. Further, it was well known that binders could be incorporated into pellet formulations to bind powders and maintain the integrity of the pellets.[189]

245. Leane teaches embodiments including those in which the drug compound is formed into agglomerates, which are then mixed with acid

[187] Ex. 1009, ¶[0042].

[188] *Id*., ¶[0080].

[189] *See* above Section VI.B.

agglomerates, and chitosan; and those in which the drug compound with chitosan are formed into agglomerates, which are then mixed with acid agglomerates.[190]

246. Thus, a POSA would have found it obvious in view of Brauns and Leane to use a granulation method to form granules of dabigatran etexilate and a binder and/or granules of an organic acid and a binder.

247. Step v) of claim 8 requires "coating the organic acid granules with a protective coating layer."

248. As discussed above, Brauns discloses that organic acid cores are coated with an "insulating layer, which separates the acid core from the layer containing the active substance," and that the insulating layer falls within the scope of the "protective coating layer."[191]

249. Leane also discloses coating the organic acid-containing pellets with a water-soluble polymer layer, which controls the rate at which the acid comes into contact with chitosan after the administration.[192] Thus, a POSA would have understood that the water-soluble polymer layer in Leane falls within the scope of the "protective coating layer."

[190] *Id*. ¶¶[0058]-[0059].

[191] *See* Section IX.A.4.

[192] Ex. 1009, ¶¶[0044]-[0047], [0081]-[0082].

250. Further, coating of pellets was routinely done, for example, to modify dissolution properties, control drug release rates, or for taste-masking.[193]

251. Thus, it would have been obvious to a POSA to apply a protective coating layer to the organic acid-containing pellets in view of Brauns and Leane.

252. Step vi) of claim 8 requires "blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules."

253. Leane teaches blending the coated acid granules with other ingredients before weighing them into hard gelatin capsules.[194] As discussed above, Leane teaches embodiments including those in which the drug compound is formed into agglomerates, which are then mixed with acid agglomerates, and chitosan; and those in which the drug compound with chitosan are formed into agglomerates, which are then mixed with acid agglomerates.[195]

254. Thus, it would have been obvious to a POSA to blend the two types of granules to form a mixture in view of Brauns and Leane.

255. Step vii) of claim 8 requires "optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable

[193] *See* Section VI.B.

[194] Ex. 1009, ¶[0084].

[195] *Id*. ¶¶[0058]-[0059].

excipient." And step viii) of claim 8 requires "adding a lubricant to the blend of step (vii)."

256. Leane teaches that the disclosed compositions may contain at least one pharmaceutically acceptable excipient, such as a diluent, disintegrant, surfactant, lubricant, etc., "generally used in solid pharmaceutical preparations and well known to those skilled in the art."[196]

257. Further, as discussed above, it was within the knowledge of a POSA to combine pellet compositions with a diluent, glidant, and/or lubricant.[197]

258. Thus, it would have been obvious to a POSA to add at least one pharmaceutically acceptable excipient, such as a lubricant, to the blend of granules.

259. Step ix) of claim 8 requires "filling the lubricated mixture of step (viii) into suitable hard capsules."

260. Both Brauns and Leane disclose dosage forms of hard capsules.[198]

261. The use of hard capsules for pelleted compositions was also well known.[199]

[196] Ex. 1009, ¶[0062].

[197] *See* Section VI.B.

[198] Ex. 1007, ¶¶[0021], [0054], [0072]; Ex. 1009, ¶¶[0061], [0084]-[0085].

[199] *See* Section VI.B.

262. Thus, it would have been obvious to a POSA to use the pellet compositions to fill a hard capsule.

263. For all the reasons discussed above, it is my opinion that claim 8 is obvious over Brauns in view of Leane.

3. Claim 9

264. Claim 9 requires a process that is the same in all respects to claim 8 except that step iv) of claim 9 requires "extruding and spheronizing the blend of step (iii) to form organic acid pellets."

265. Leane discloses extrusion and spheronization of a wet granulate to form acid-containing agglomerates.[200]

266. Further, extrusion/spheronization was one of the most popular methods for preparing pellets.[201]

267. Thus, it would have been obvious to a POSA to use extrusion and spheronization to form granules of an organic acid and a binder.

268. Thus, in view of the above, and the reasons discussed above with respect to claim 8, claim 9 is obvious over Brauns in view of Leane.

[200] Ex. 1009, ¶[0080].

[201] *See* Section VI.B.

F. Dependent Claims 13 and 18

269. Claims 13 and 18 depend from claims 11 and 16, respectively, and further require that "the first type of particles comprise at least one pharmaceutically acceptable excipient."

270. As noted above, the first type of particles contain dabigatran etexilate, and a POSA would have found it obvious to prepare pellets that contain an active pharmaceutical ingredient such as dabigatran etexilate in combination with a pharmaceutically acceptable excipient such as a binder or diluent. For example, Brauns discloses the formation of a dabigatran etexilate layer that contains a binder.[202]

271. Leane also discloses that the agglomerate compositions "may also contain other pharmaceutically acceptable ingredients" such as diluents and binders.[203]

272. The use of binders to prepare pellets, such as drug-containing pellets, was also well known.[204]

273. Thus, it is my opinion that claims 13 and 18 are obvious over Brauns in view of Leane.

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[202] Ex. 1007, ¶¶[0019], [0050]-[0051], [0066]-[0068].

[203] *See* Ex. 1009, ¶[0062].

[204] *See* Section VI.B.

G. Objective Indicia of Nonobviousness Do Not Overcome the Strong Showing of Obviousness

274. I understand that during prosecution of the '729 patent, the applicant submitted three declarations alleging unexpected results: (i) the Gandhi declaration, dated December 17, 2015[205]; (ii) the Tyebji declaration, dated May 5, 2016;[206] and (iii) the Xu declaration, dated May 5, 2016.[207] As discussed below, the results described in these declarations are not surprising or unexpected to a POSA. Thus, these declarations do not overcome the strong case of obviousness discussed here.

1. The Gandhi Declaration

275. The Gandhi declaration describes results of stability studies comparing the stability of compositions comprising dabigatran etexilate particles and coated acid particles (according to the '729 patent) and compositions without said coating.[208] The results showed that the compositions comprising dabigatran etexilate particles and coated acid particles were more stable than those without the coating.[209]

276. First, both Leane and Sugimoto disclose compositions comprising acid-containing pellets having a protective coating layer that prevents contact with the

[205] Ex. 1002, pp. 447-450.

[206] *Id.*, pp. 442-445.

[207] *Id.*, pp. 439-441.

[208] *Id.*, p. 448 at ¶5.

[209] *Id.*, pp. 448-49 at ¶¶5-6.

material having pH-dependent solubility until after the composition has been administered.[210] Thus, the concept of coating acid particles in pharmaceutical compositions to control the timing and/or the rate at which the acid comes into contact with a material having pH-dependent solubility was not new or inventive.

277. Further, as discussed above in Section, III.C, I understand that evidence of unexpected results must establish that there is a difference between the results obtained with the claimed invention and those of the closest prior art, and that the difference would not have been expected by a POSA at the time of the invention.

278. The Gandhi declaration fails to compare the claimed composition of the '729 patent to the closest prior art, i.e., Brauns. As discussed above, Brauns discloses dabigatran etexilate compositions comprising pellets with a coated acid core.[211]

279. Further, the data disclosed in the Gandhi declaration would not have been surprising or unexpected in view of the Brauns' teachings and a POSA's knowledge. For example, Brauns teaches that the coating was added to the acid core "[t]o increase the durability of the finished product."[212] Further, it was known that

[210] Ex. 1009, ¶¶[0038]-[0048], [0081]-[0082]; Ex. 1010, ¶¶[0013], [0024], [0029], [0131]-[0132].

[211] *See* Section VII.A.

[212] Ex. 1007, ¶[0013].

dabigatran etexilate is chemically unstable and prone to polymorphic form transformations in acidic environment.[213] Thus, it would not have been surprising or unexpected to a POSA that a composition comprising dabigatran etexilate particles and coated acid particles were more stable than those without the coating.

2. The Tyebji Declaration

280. The Tyebji declaration describes "Comparative Evaluation of Two Formulation Approaches for Dabigatran Etexilate Mesylate:"

- "Formulation A is according to the present invention and has two types of particles/pellets (one of them comprising dabigatran etexilate mesylate and the other one comprising a coated organic acid)"
- "Formulation B is the formulation described in example 1 of US 2006/0183779 A1 [Brauns]," which "is also the one which has been tested in example 3 of the present invention."[214]

281. Thus, the Tyebji declaration describes the results provided in Example 3 of the '729 patent.

282. I discussed Example 3 of the '729 patent above in Section IV.B, where I presented a chart comparing the composition of formulation A and formulation B. I have copied the chart here as well. The chart shows several differences between

[213] Ex. 1022, pp. 4-5.

[214] Ex. 1002, p. 443.

formulation A and formulation B in terms of the type and the wt% of the excipients such as tartaric acid, as well as the amounts and the percentages of dabigatran etexilate mesylate.

	Formulation A (dabigatran granules and coated tartaric acid granules)		**Formulation B (dabigatran pellets with tartaric acid core)**	
Components	mg/capsule	wt%	mg/capsule	wt%
Dabigatran etexilate mesylate	172.95	34.18	115.3	20
Tartaric acid	196.34	38.8	353.4	61.3
Talc	8.42	1.66	50.7	8.8
Hydroxypropyl cellulose	N.A.	N.A.	23.1	4
gum arabic	N.A.	N.A.	34	5.9
Hydroxypropyl methyl cellulose	5.62	1.11	N.A.	N.A.
Microcrystalline cellulose	67.05	13.25	N.A.	N.A.
Croscarmellose sodium	50	9.88	N.A.	N.A.
Lactose	5.62	1.11	N.A.	N.A.
Total	506		576.5	

283. Therefore, any observed differences in the dissolution profiles for formulation A vs. formulation B cannot be properly attributed to the two-pellet vs. one-pellet structures of the formulations. Instead, any observed differences in the dissolution profiles may be attributable to the differences in type and the wt% of the excipients such as tartaric acid, the amounts and the percentages of dabigatran etexilate mesylate, and/or a combination of the above.

284. In any event, given the above differences, a POSA would not have found it surprising or unexpected to observe different dissolution profiles for Formulation A compared to Formulation B.

285. Further, the data in Example 3 of the '729 patent and the Tyebji declaration show that the only time points at which Formulation A provides faster dissolution are at 10 and 15 minutes. By 20 minutes and at all following time points, the dissolution rates of the two dosage forms are similar. Below I have copied the data provided in Example 3 of the '729 patent.[215]

	% release	
Time (minutes)	Formulation A (two types of particles/pellets)	Formulation B (one type of particles/pellets)
10	65.1	19.2
15	79.2	57
20	86.7	86.1
30	92	97
45	95.5	97.6
60	96.8	98.5

286. The different % release at 10- and 15-minutes time point would not have been surprising or unexpected to a POSA. The pellets in Brauns' Formulation B include three layers separating the media from the tartaric acid core, whereas the

[215] Ex. 1001, Col. 15:41-60; *see also* Ex. 1002, pp. 444-445.

coated acid particles in Formulation A only include one layer separating the tartaric acid from the media. Therefore, it would not have been surprising or unexpected to observe it would take a few minutes longer for the tartaric acid in Formulation B to be released into the media compared to Formulation A. Thus, given that it was known that tartaric acid enhances dabigatran etexilate's solubility, it would not have been surprising or unexpected to observe a faster dissolution rate at 10- and 15-minutes time points for Formulation A compared to Formulation B.

3. The Xu Declaration

287. The Xu declaration describes "In-vivo bioequivalence study of formulation of the present invention having two types of particles/pellets (Formulation A) and formulation having one type of particles/pellets (Formulation B)."[216]

288. I understand that "Formulations A and B" in the Xu Declaration are the same formulations describes in Example 3 of the '729 patent.[217]

[216] Ex. 1002, p. 440.

[217] *Id*.

289. The Xu Declaration provides the results of fasting and fed studies in two charts that are barely legible.[218] The Xu Declaration concludes that the two formulations "exhibit[ed] the same bioavailability."[219]

290. Taking the conclusion at face value, it would not have been unexpected to observe the same bioavailability between Formulations A and B.

291. The FDA Guidance regarding Dissolution Testing of Immediate Release Solid Oral Dosage Forms teaches that "[t]he mean T50% gastric residence (emptying) time is 15-20 minutes under fasting conditions. Based on this information, a conservative conclusion is that a drug product undergoing 85% dissolution in 15 minutes under mild dissolution test conditions in 0.1N HCl behaves like a solution."[220] In other words, "the bioavailability of the drug is not limited by dissolution."[221]

292. Thus, it would have been reasonable for a POSA to conclude that the bioavailability of a drug product is not limited by its dissolution if it undergoes 85% dissolution in 15-20 minutes under mild dissolution test conditions in 0.1N HCl, the

[218] *Id*.

[219] *Id*.

[220] Ex. 1016, p. 6.

[221] *Id*.

same conditions used for measuring the dissolution of Formulations A and B in the '729 patent.

293. As shown in the dissolution profiles in the '729 patent, Formulations A and B reach approximately 85% dissolution by 20 minutes. Therefore, a POSA would have reasonably expected that the bioavailability of dabigatran etexilate would not be limited by its dissolution rate. Thus, a POSA would have reasonably expected that any difference between the dissolution rates of Formulations A and B would not affect the bioavailability of dabigatran etexilate. Thus, it would not have been surprising or unexpected to observe that Formulations A and B showed the same bioavailability.

X. GROUND 2: BRAUNS IN VIEW OF SUGIMOTO RENDER OBVIOUS CLAIMS 1-18 OF THE '729 PATENT

294. In my opinion, there are no inventive differences between the prior art and the subject matter claimed in claims 1-18 of the '729 patent. The elements of the claimed subject matter are disclosed in Brauns and/or Sugimoto or are rendered obvious in view of their teachings. As discussed above, a POSA would have followed clear motivation in the art to prepare the claimed compositions/capsules with a reasonable expectation of success in doing so. Therefore, in light of the teachings of Brauns and Sugimoto, and the knowledge of those of skill in the art,

each of claims 1-18 of the ’729 patent would have been obvious over Brauns in view of Sugimoto.

A. Independent Claim 1

1. “A composition comprising: a mixture of at least two distinct types of particles”

295. It is my opinion that Sugimoto discloses “a composition comprising a mixture of two distinct types of particles.” For example, Sugimoto discloses uncoated granules comprising a drug substance as well as coated granules comprising an acid.[222] Sugimoto also discloses a mixture of coated granules comprising an active ingredient and coated granules comprising an acid.[223]

296. As discussed above, it is my opinion that the “granules” disclosed in Sugimoto fall within the scope of the term “particles,” as a POSA would have understood this term in the ’729 patent.[224]

297. Thus, Sugimoto discloses “a composition comprising a mixture of two distinct types of particles.”.

[222] Ex. 1010, ¶¶[0024], [0078], [0084].

[223] *Id.*, [0131]-[0133] (Example 1); *see also id.*, ¶¶[0136]-[0150] (Examples 2-5).

[224] *See* above Section VII.C.

2. "wherein a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof"

298. Brauns discloses particles or pellets that contain dabigatran etexilate mesylate, which is a pharmaceutically acceptable salt of dabigatran etexilate.[225]

299. Further, Sugimoto discloses a composition having two types of particles, wherein the first particles contain a drug substance[226] that is "hardly water-soluble under neutral or alkaline conditions and being highly water-soluble under acidic conditions yet presenting unpleasant taste under acidic conditions."[227] Thus, a POSA would have understood that the drug substance disclosed in Sugimoto has a similar pH-dependent solubility compared to dabigatran etexilate.

3. "wherein the first type of particles is free from organic acids and inorganic acids; and"

300. It is my opinion that this element would have been obvious to a POSA over Brauns in view of Sugimoto. In particular, Sugimoto discloses that the drug substance and acid should be kept separated from one another to avoid contact between the drug substance and the acid until the composition reaches the stomach,

[225] Ex. 1007, ¶¶[0003], [0050]-[0053].

[226] The chemical structure of the drug substance exemplified in Sugimoto's Examples shows that the drug substance is in the form of a free base. Ex. 1010, ¶[0131].

[227] Ex. 1010, ¶¶[0013], [0131].

and discloses the preparation of drug-containing granules that are free from any acids.[228]

301. Further, dabigatran etexilate was known to be prone to chemical degradation and polymorphic form transformation in acidic environment.[229]

302. Thus, a POSA would have been motivated, with a reasonable expectation of success, to prepare dabigatran etexilate particles free from organic acids and inorganic acids.

4. "b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate."

303. Brauns discloses particles (pellets) that contain tartaric acid (a pharmaceutically acceptable organic acid), which are coated with an insulating layer.[230] Brauns teaches that the insulating layer prevents contact between the acid and dabigatran etexilate (an acid sensitive drug substance) until after the composition is administered, thus increasing the "durability of the finished product" before the drug is taken, while allowing the organic acid to create an acidic microclimate to dissolve the active substance after the drug is taken.[231]

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[228] *Id.*, ¶¶[0013], [0024], [0131].

[229] *See* above Section VI.A.

[230] *See* Ex. 1007, ¶¶[0039]-[0049].

[231] *Id.*, ¶¶[0011],[0013].

304. As I discussed in Section V.B, a POSA would have understood the term "a protective coating layer" in the '729 patent claims to mean "a coating layer that prevents the organic acid from contacting dabigatran etexilate until after the composition is administered."

305. As I discussed above, a POSA would have understood that the term "pellets" as used in Brauns falls within the scope of "particles" as used in claims of the '729 patent. Further, Brauns discloses that the acid core is coated with an insulating layer that prevents the organic acid from coming into contact with dabigatran etexilate until after the preparation has been taken.[232]

306. Thus, a POSA would have understood that Brauns discloses "particles" comprising at least one pharmaceutically acceptable acid that is coated with a "protective coating layer."

307. Further, Sugimoto discloses granules of a pharmaceutically acceptable organic acid (i.e., fumaric acid), which are coated with a coating layer that prevents contact between the acidic pH soluble drug substance and the acid until the composition reaches the stomach.[233]

[232] *See* Section VII.A.

[233] Ex. 1010, ¶¶[0024]-[0025], [0132].

308. As discussed above, it is my opinion that the "granules" disclosed in Sugimoto fall within the scope of the term "particles," as a POSA would have understood this term in the '729 patent.[234]

309. Further, Sugimoto teaches that the coating layer added to the acid granules prevent contact between the acid and the drug substance "throughout the manufacturing process," and while the composition is "go[ing] through the oral cavity."[235] Thus, a POSA would have understood that the coating layer in Sugimoto prevents contact between the acid and the drug substance until after the administration.

310. Thus, a POSA would have understood the coating layer in Sugimoto falls within the scope of the "protective coating layer," as this term in the '729 patent would have been understood by a POSA.

311. The additional requirement that "the second type of particles … is free from dabigatran etexilate" is rendered obvious by Sugimoto, which discloses coated acid-containing granules that are free from a drug substance having pH-dependent solubility.[236]

[234] *See* above Section VII.C.

[235] Ex. 1010, ¶¶[0024]-[0025], [0132].

[236] Ex. 1010, ¶¶[0013], [0024]-[0025, [0132].

312. Further, as discussed above in Section VI.A, dabigatran etexilate was known to be prone to chemical degradation and polymorphic form transformation in acidic environment. Thus, a POSA would have been motivated to use Sugimoto's teachings to prepare organic acid particles free from dabigatran etexilate with a reasonable expectation of success.

313. Accordingly, the combination of Brauns in view of Sugimoto renders obvious each limitation of claim 1 of the '729 patent.

B. Independent Claims 11 and 16, and Dependent Claims 2, 10, and 14

1. Claims 11 and 16

314. The only differences between independent claim 1 and independent claims 11 and 16 is that whereas claim 1 requires "[a] ***composition comprising***: a mixture of at least two distinct types of particles," claim 11 requires "[a] ***composition consisting of*** a mixture of two distinct types of particles ***and at least one pharmaceutically acceptable excipient***," and claim 16 requires "[a] ***capsule containing a pharmaceutical composition consisting of*** a mixture of two distinct types of particles ***and at least one pharmaceutically acceptable excipient***." The remaining limitations of claims 11 and 16 are identical to those of claim 1 and are obvious for the same reasons as discussed above in Section X.A.

315. It is my opinion that claims 11 and 16, which require ***a composition consisting*** of two distinct types of particles ***and at least one pharmaceutically acceptable excipient*** are obvious over Brauns in view of Sugimoto.

316. First, Sugimoto discloses an embodiment consisting of two distinct types of particles in which a drug having pH-dependent solubility similar to dabigatran etexilate is in the first particles and an organic acid is present in the second particles.[237]

317. Second, Sugimoto also teaches that the disclosed compositions contain at least one pharmaceutically acceptable excipient, such as a binding agent.[238]

318. Further, as discussed above in Section VI.B, it was well-known that a pharmaceutically acceptable excipient, such as a glidant, lubricant, and diluent/filler, may be added in solid oral dosage forms, such as capsules.

319. Regarding claim 16 that recites "[a] capsule," Brauns discloses capsule dosage forms that contain pellets.[239] Thus, it would have been obvious to formulate the composition of claim 1 in a capsule.

320. In sum, it is my opinion that , claims 11 and 16 are obvious over Brauns in view of Sugimoto.

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[237] *Id.*, ¶¶[0013], [0024]-[0025], [0131]-[0132].

[238] *Id.*, ¶[0024].

[239] Ex. 1007, ¶¶[0054], [0072].

2. Claim 2

321. Claim 2 depends from claim 1 and requires that the composition further comprises "at least one pharmaceutically acceptable excipient." For the same reasons discussed above with respect to independent claims 11 and 16, *see* Section X.B.1, claim 2 is invalid as obvious over Brauns in view of Sugimoto.

3. Claims 10 and 14

322. Claims 10 and 14 depend from claims 2 and 11, respectively, and require that "the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof."

323. Sugimoto discloses using binders when preparing granules.[240] As another example, Sugimoto discloses using "a water-soluble binding agent."[241]

324. Further, as discussed above in Section VI.B, it was well known that a pharmaceutically acceptable excipient, such as a glidant, lubricant, and diluent/filler, may be added in solid oral dosage forms.

325. Thus, claims 10 and 14 are obvious over Brauns in view of Sugimoto.

[240] Ex. 1010, ¶[0081].

[241] *Id.*, ¶[0024].

C. Dependent Claims 3, 5, 12, 15 and 17

326. Claims 3 and 12 depend from claims 1 and 11, respectively, and require that the compositions contain "from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate." And claims 5, 15, and 17 depend from claims 1, 14, and 16, respectively, and require that the compositions contain "from 50 mg to 200 mg of dabigatran etexilate mesylate."

327. Brauns discloses that "the active substance [i.e., dabigatran etexilate] content is 5 to 60%, preferably 10 to 50% of the pharmaceutical composition."[242] Brauns also discloses composition that the "preferred salt" of dabigatran etexilate is "the mesylate (methanesolphonate)" and dabigatran etexilate mesylate is present in Brauns' exemplary embodiments in amounts of 57.7 mg and 115.3 mg.[243]

328. It would have been obvious to a POSA to use dabigatran etexilate mesylate in the amounts disclosed by Brauns, which overlap with the claimed amounts, in a two-pellet composition as disclosed by Sugimoto for all the reasons discussed above.[244]

329. I understand that because Brauns discloses overlapping ranges and amounts for dabigatran etexilate, the burden would shift to the Patent Owner to show

[242] Ex. 1007, ¶[0014].

[243] *Id.*, ¶¶ [0039], [0055] (Examples 1-2).

[244] *See, e.g.,* Section VIII.

that the overlapping range would not have been obvious because the prior art taught away from the claimed range, the claimed range produces new and unexpected results, the claimed range is critical to the alleged invention. I have not seen any evidence that could show the claimed range would not have been obvious. I reserve the right to respond to any such evidence presented by the Patent Owner.

330. Therefore, it is my opinion that a combination of Brauns in view of Sugimoto renders obvious claims 3, 5, 12, 15, and 17 of the '729 patent.

D. Dependent Claim 4

331. Claim 4 depends from claim 1 and requires that the composition comprises "from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid."

332. Brauns discloses that the organic acid is present in a concentration of "between 20 and 90%, preferably between 20 and 80% in the finished pellet (i.e., in the pharmaceutical composition)."[245] Further, Braun's exemplary embodiments disclose pellet compositions that contain 61.3% and 38.5% by weight of tartaric acid.[246]

[245] Ex. 1007, ¶[0012].

[246] *Id.*, ¶¶[0039], [0055] (Examples 1-2).

333. Further, Sugimoto discloses a composition in which the organic acid in the form of coated pellets is ~6.7% w/w.[247]

334. Thus, both Brauns and Sugimoto teach compositions comprising organic acid at wt% that overlap with the amount required by claim 4.

335. As stated above, I understand that because Brauns and Sugimoto disclose overlapping ranges for the claimed acid, the burden would shift to the Patent Owner to show that the overlapping range would not have been obvious because the prior art taught away from the claimed range, the claimed range produces new and unexpected results, the claimed range is critical to the alleged invention. I have not seen any evidence that could show the claimed range would not have been obvious. I reserve the right to respond to any such evidence presented by the Patent Owner.

336. Thus, it is my opinion that claim 4 is obvious over Brauns in view of Sugimoto.

E. Dependent Claims 6-9

337. Claim 6 depends from claim 2 and is directed to "[a] process … comprising the step of mixing the first type of particles and the second type of particles with the at least one pharmaceutically acceptable excipient." Claim 7 depends from claim 6 and specifies that "the first type of particles are prepared by

[247] Ex. 1010, ¶¶[0131]-[0133] (Example 1).

granulation." Claim 8 depends from claim 7 and specifies additional process steps. Claim 9 also depends from claim 7 and requires a process that is the same in all respects to claim 8 except for step iv.

1. Claims 6-7

338. It is my opinion that claim 6 is obvious over Brauns in view of Sugimoto for the same reasons I discussed with respect to claims 11 and 16.[248]

339. Regarding claim 7, which requires the first type of particles are prepared by granulation, Sugimoto discloses the use of wet granulation methods to form the drug- and acid-containing granules.[249] Thus, it would have been obvious to a POSA to prepare particles containing dabigatran etexilate by granulation as required in claim 7. Therefore, it is my opinion that claim 7 is obvious over Brauns in view of Sugimoto.

2. Claim 8

340. Claim 8 depends from claim 7 and recites additional process steps.

341. In steps i)-ii), dabigatran etexilate is first blended with at least one pharmaceutically acceptable excipient and then the blend of step i) is granulated with a binder solution to form granulates of dabigatran etexilate. And in steps iii)-iv), at least one organic acid is first blended with at least one pharmaceutically acceptable

[248] *See* Section IX.B.1.

[249] Ex. 1010, ¶¶[0131]-[0132], [0136], [0140], [0148]-[0149].

excipient and then the blend of step iii) is granulated with a binder solution to form organic acid-containing granules.

342. Sugimoto discloses the use of wet granulation to form the drug- and acid-containing granules.[250]

343. For example, Sugimoto teaches that the ingredients are granulated after they are mixed, that mixing can be performed "with any of conventional methods known in the field of pharmaceuticals."[251]

344. Sugimoto discloses mixing the drug substance with a water-soluble saccharide, such as mannitol, before preparing granules comprising the drug substance.[252]

345. Sugimoto discloses using a binder during the granulation process.[253] Sugimoto exemplifies polyvinylpyrrolidone (PVP) as a binding agent.[254]

346. Further, incorporating binders into pellet formulations to bind powders and maintain the integrity of the pellets was well known.[255]

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[250] *Id*.

[251] *Id*., ¶[0076].

[252] *Id*., ¶¶[0028], [0078], [0131].

[253] *Id*., ¶[0081].

[254] *Id*., ¶[0131].

[255] *See* above Section VI.B.

347. Additionally, adding pharmaceutically acceptable excipients, such as fillers or lubricants, before preparing pellets or granules was well known in the art.[256]

348. Thus, a POSA would have found it obvious in view of Brauns and Sugimoto to use a wet granulation method to form granules of dabigatran etexilate and a binder and/or granules of an organic acid and a binder.

349. Step v) of claim 8 requires "coating the organic acid granules with a protective coating layer."

350. As discussed above, Brauns discloses that organic acid cores are coated with an "insulating layer, which separates the acid core from the layer containing the active substance," and that the insulating layer falls within the scope of the "protective coating layer."[257]

351. Sugimoto also discloses coating the organic acid-containing granules with a water-soluble coating layer to prevent contact between the acid and the drug substance "throughout the manufacturing process," and while the composition is "go[ing] through the oral cavity."[258] Thus, a POSA would have understood that the coating layer in Sugimoto prevents contact between the acid and the drug substance until after the administration.

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[256] *Id.*

[257] *See* Section IX.A.4.

[258] Ex. 1010, ¶¶[0024]-[0025], [0132].

352. Further, coating of pellets was routinely done, for example, to modify dissolution properties, control drug release rates, or for taste-masking.[259]

353. Thus, it would have been obvious to a POSA to apply a protective coating layer to the organic acid-containing pellets in view of Brauns and Sugimoto.

354. Step vi) of claim 8 requires "blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules."

355. Sugimoto teaches blending the coated acid granules with the granules comprising the drug substance.[260] Thus, it would have been obvious to a POSA to blend the two types of granules to form a mixture in view of Brauns and Sugimoto.

356. Step vii) of claim 8 requires "optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient." And step viii) of claim 8 requires "adding a lubricant to the blend of step (vii)."

357. Sugimoto discloses blending drug- and acid-containing granules with a pharmaceutically acceptable excipient, including a lubricant.[261]

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[259] *See* Section VI.B.

[260] Ex. 1010, ¶¶[0133], [0137], [0141], [0145], [0150].

[261] Ex. 1010, ¶¶[0133]-[0134], [0137]-[0138], [0141]-[0142], [0145]-[0146], [0150]-[0150].

358. Further, as discussed above, it was within the knowledge of a POSA to combine pellet compositions with a diluent, glidant, and/or lubricant.[262]

359. Thus, it would have been obvious to a POSA to add at least one pharmaceutically acceptable excipient, such as a lubricant, to the blend of granules.

360. Step ix) of claim 8 requires "filling the lubricated mixture of step (viii) into suitable hard capsules."

361. Brauns discloses hard capsule dosage forms.[263]

362. Further, the use of hard capsules for pelleted compositions was also well known.[264]

363. Thus, it would have been obvious to a POSA to use the pellet compositions to fill a capsule.

364. For all the reasons discussed above, it is my opinion that claim 8 is obvious over Brauns in view of Sugimoto.

3. Claim 9

365. Claim 9 requires a process that is the same in all respects to claim 8 except that step iv) of claim 9 requires "extruding and spheronizing the blend of step (iii) to form organic acid pellets."

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[262] *See* Section VI.B.

[263] Ex. 1007, ¶¶[0021], [0054], [0072].

[264] *See* Section VI.B.

366. Brauns discloses forming pellets by "extrusion/spheronization."[265]

367. Further, extrusion/spheronization was one of the most popular methods for preparing pellets.[266]

368. Thus, it would have been obvious to a POSA to use extrusion and spheronization to form granules of an organic acid and a binder.

369. Thus, in view of the above, and the reasons discussed above with respect to claim 8, claim 9 is obvious over Brauns in view of Sugimoto.

F. Dependent Claims 13 and 18

370. Claims 13 and 18 depend from claims 11 and 16, respectively, and further require that "the first type of particles comprise at least one pharmaceutically acceptable excipient."

371. As noted above, the first type of particles contain dabigatran etexilate, and a POSA would have found it obvious to prepare pellets that contain an active pharmaceutical ingredient such as dabigatran etexilate in combination with a pharmaceutically acceptable excipient such as a binder or diluent. For example, Brauns discloses the formation of a dabigatran etexilate layer that contains a binder.[267]

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[265] Ex. 1007, ¶¶[0012], [0017].

[266] *See* Section VI.B.

[267] Ex. 1007, ¶¶[0019], [0050]-[0051], [0066]-[0068].

372. Sugimoto also discloses drug substance-containing granules that include an excipient.[268]

373. The use of binders to prepare pellets, such as drug-containing pellets, was also well known.[269]

374. Thus, it is my opinion that claims 13 and 18 are obvious over Brauns in view of Sugimoto.

G. Objective Indicia of Nonobviousness Do Not Overcome the Strong Showing of Obviousness

375. For the same reasons discussed above in Section IX.G, it is my opinion that the results described in the three declarations submitted during the prosecution of the '729 patent are not surprising or unexpected to a POSA. Thus, these declarations do not overcome the strong case of obviousness discussed here.

XI. SUPPLEMENTATION AND REBUTTAL

376. I may also testify in rebuttal to testimony or opinions offered by other witnesses. I reserve my right to supplement or amend this report in light of any additional information or documents, in response to any critique of my declaration or alternative opinions advanced by or on behalf of the Patent Owner.

[268] Ex. 1010, ¶[0131].

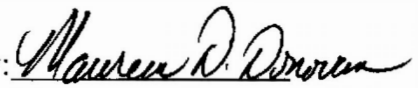
[269] *See* Section VI.B.

XII. CONCLUSIONS

377. For the reasons discussed above, it is my opinion that Brauns in view of Leane, and Brauns in view of Sugimoto render obvious claims 1-18 of the '729 Patent.

378. I declare that all statements made herein to my knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: June 6, 2025

By: 
Maureen D. Donovan, Ph.D

Appendix A – Materials Considered

Exhibit	Description
1001	U.S. Patent No. 11,013,729
1002	File History of U.S. Appl. No. 14/379,613
1003	File History of U.S. Appl. No. 17/241,793
1004	File History of U.S. Appl. No. 18/356,642
1005	Declaration of Maureen D. Donovan, Ph.D.
1006	Curriculum Vitae of Maureen D. Donovan, Ph.D.
1007	U.S. Patent Publication No. 2006/0183779 ("Brauns")
1008	File History of U.S. Appl. No. 11/381,890
1009	U.S. Patent Publication No. 2006/0115525 ("Leane")
1010	U.S. Patent Publication No. 2004/0109890 ("Sugimoto")
1011	*Pharmaceutics: The Science of Dosage Form Design*, M.E. Aulton, Ed. (2d. edition 2002) pp. 247-48 ("Aulton")
1012	K. Lavanya *et al*. "Pelletization Technology: A Quick Review," *Int'l J. Pharm. Sci. & Res. 2*(6):1337-55 (June 2011) ("Lavanya")
1013	Reserved
1014	FDA Approved Label for Pradaxa (October 2010)
1015	J. Stangier, "Clinical Pharmacokinetics and Pharmacodynamics of the Oral Direct Thrombin Inhibitor Dabigatran Etexilate," *Clin. Pharmacokinet. 47*(5):285-95 (2008) ("Stangier")
1016	FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms (August 1997)
1017	FDA Dissolution Methods for Dabigatran Etexilate Mesylate (09/22/2011)
1018	Australian Public Assessment Report for Dabigatran etexilate mesylate (May 2011)
1019	FDA Paragraph IV Patent Certifications (06/15/2020)
1020	USPTO Assignments for U.S. Appl. No. 14/379,613
1021	U.S. Patent Publication No. 2008/0069891 ("Habib")
1022	International Patent App. Pub. No. WO 2012/001156 A2 ("Krka")
1023	Remington, The Science and Practice of Pharmacy, 21st Ed., Chapter 45, Oral Solid Dosage Forms (2006) ("Remington")
1024	Steward Memorandum, Interim Processes for PTAB Workload Management (March 26, 2025)