

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.

Petitioner,

v.

EXELIXIS, INC.

Patent Owner.

Case No. IPR2025-00210

Patent 11,298,349

**DECLARATION OF GRAHAM BUCKTON, Ph.D., IN SUPPORT OF
PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT 11,298,349**

TABLE OF CONTENTS

	Page No.
I. BACKGROUND AND QUALIFICATIONS	1
II. MATERIALS CONSIDERED.....	5
III. LEGAL STANDARDS	5
A. Prior Art Date	5
B. Written Description and Priority	6
C. Anticipation	7
D. Obviousness.....	9
IV. THE PERSON OF ORDINARY SKILL IN THE ART	10
V. CLAIM CONSTRUCTION.....	12
VI. INTRODUCTION TO THE '349 PATENT	14
VII. TECHNICAL BACKGROUND AND STATE OF THE ART	17
A. Cabozantinib and the (L)-Malate Salt of Cabozantinib	17
B. Pharmaceutical Compositions	23
1. Fillers.....	27
2. Disintegrants	29
3. Glidants	30
4. Lubricants.....	32
VIII. GROUND 1: ANTICIPATION OF CLAIMS 1-3 BY WILSON	34

TABLE OF CONTENTS

(*cont'd*)

	Page No.
A. The Challenged Claims Are Not Entitled to an Earlier Priority Date	34
1. Exelixis’s prior statements regarding the claimed subject matter	37
2. The ’349 patent’s “priority” applications do not convey possession of claims 1-3	45
a. U.S. Provisional Application No. 61/441,520 (which is cross-referenced in the ’349 patent) does not convey possession of claims 1-3	45
b. U.S. Provisional Application No. 61/441,527 (which is cross-referenced in the ’349 patent) does not convey possession of claims 1-3	46
c. U.S. Application No. 13/984,559 (which is cross-referenced in the ’349 patent) does not convey possession of claims 1-3	48
i. There is no unrestricted disclosure of “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” in the ’559 application	48
ii. Additional broad disclosures in the ’559 application do not convey possession of the subject matter of the Challenged Claims.....	52
iii. Additional narrow disclosures in the ’559 application do not convey possession of	

TABLE OF CONTENTS
(cont'd)

	Page No.
the subject matter of the Challenged Claims.....	54
d. U.S. Application Nos. 15/348,716, 16/151,653, 16/706,323, and 17/152,394 (which are cross- referenced in the '349 patent) do not convey possession of claims 1-3	61
e. The preliminary amendment of the '275 application (which ultimately issued as the '349 patent) adding new claims 35-37 is the only possible support for claims 1-3	62
B. Introduction to Wilson	65
C. Wilson Anticipates Claims 1-3 of the '349 patent.....	66
1. Claim 1 of the '349 patent is anticipated by Wilson	66
a. Preamble of claim 1	67
b. The inclusion of “Compound IB”	68
c. The inclusion of “one or more fillers”	68
d. The inclusion of “one or more disintegrants”	69
e. The inclusion of “one or more glidants”	70
f. The inclusion of “one or more lubricants”	71
g. A “tablet or capsule” pharmaceutical composition.....	72

TABLE OF CONTENTS
(cont'd)

	Page No.
h. A composition “essentially free of process byproducts or contaminants”	72
2. Claim 2 of the ’349 patent is anticipated by Wilson	73
3. Claim 3 of the ’349 patent is anticipated by Wilson	73
a. Preamble of claim 3	75
b. The inclusion of “Compound IB”	75
c. The inclusion of “one or more fillers”	75
d. The inclusion of “one or more disintegrants”	76
e. The inclusion of “one or more glidants”	76
f. The inclusion of “one or more lubricants”	76
g. A “tablet or capsule” pharmaceutical composition.....	76
h. A composition “essentially free of 6,7-dimethoxy-quinoline-4-ol”	77
IX. GROUND 2: THE CHALLENGED CLAIMS WERE OBVIOUS	77
A. Introduction to Brown	78
B. Introduction to Remington in Relation to Obviousness	80
1. Claim 1 would have been obvious	82
a. Preamble of claim 1	82
b. The inclusion of “Compound IB”	83

TABLE OF CONTENTS

(*cont'd*)

	Page No.
c. The inclusion of “one or more fillers”	84
d. The inclusion of “one or more disintegrants”	87
e. The inclusion of “one or more glidants”	89
f. The inclusion of “one or more lubricants”	92
g. A “tablet or capsule” pharmaceutical composition.....	94
h. A composition “essentially free of process byproducts or contaminants”	96
i. A pharmaceutical composition containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol would have been obvious	96
j. There was a motivation to combine Brown and Remington’s disclosures.....	102
2. Claim 2 is obvious over Brown in view of Aulton.....	103
3. Claim 3 obvious over Brown in view of Aulton.....	104
a. Preamble of claim 3	104
b. The inclusion of “Compound IB”	105
c. The inclusion of “one or more fillers”	105
d. The inclusion of “one or more disintegrants”	105
e. The inclusion of “one or more glidants”	105
f. The inclusion of “one or more lubricants”	106

TABLE OF CONTENTS
(*cont'd*)

	Page No.
g. A “tablet or capsule” pharmaceutical composition.....	106
h. A composition “essentially free of 6,7-dimethoxy-quinoline-4-ol”	106
i. Motivation to Combine Brown and Remington	107
X. NO SECONDARY CONSIDERATIONS.....	107
XI. CONCLUSION.....	108

LIST OF DOCUMENTS CITED

Exhibit No.	Description
1001	U.S. Patent 11,298,349 (“the ’349 patent”)
1002	U.S. Patent 9,717,720 (“Wilson”)
1003	WO 2010/083414 (“Brown”)
1004	Remington: The Science and Practice of Pharmacy, 21st Edition (2005) (“Remington”)
1005	CABOMETYX® Product Insert
1006	COMETRIQ® Product Insert
1008	U.S. Patent 7,579,473 (“the ’473 patent”)
1009	Mark Gibson, “Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form,” Informa Healthcare USA, Inc. (2009) (“Gibson”)
1010	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 168 (D.Del.) (Exelixis’ Proposed Findings of Fact On Infringement of U.S. Patent No. 11,298,349)
1013	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 176 (D.Del.) (Exelixis’ Answering Proposed Findings of Fact On the Validity of the Asserted Patents)
1014	Prosecution History excerpt for U.S. Application Serial No. 17/170,275
1015	U.S. Provisional Application Serial No. 61/441,520 (“the ’520 provisional”)
1016	U.S. Provisional Application Serial No. 61/441,527 (“the ’527 provisional”)
1017	Prosecution History excerpt for U.S. Application Serial No. 13/984,559 (“the ’559 application”)

Exhibit No.	Description
1018	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 175 (D.Del.) (Exelixis' Responsive Post-Trial Brief)
1019	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 163 (D.Del.) (Trial Volume III)
1020	Prosecution History excerpt for U.S. Application Serial No. 15/348,716 ("the '716 application")
1021	Prosecution History excerpt for U.S. Application Serial No. 16/151,653 ("the '653 application")
1022	Prosecution History excerpt for U.S. Application Serial No. 16/706,323 ("the '323 application")
1023	Prosecution History excerpt for U.S. Application Serial No. 17/152,394 ("the '394 application")
1025	Rowe et al., "Handbook of Pharmaceutical Excipients," 6 th Ed. (2009)
1026	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 186 (D.Del.)
1034	Aulton's Pharmaceuticals: The Design and Manufacture of Medicines, Chapter 31 ("Dosage Form Design and Manufacture") 3 rd Edition (2007)
1036	Toxicological Review of Quinoline (2001) by the U.S. Environmental Protection Agency
1037	Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (2008)
1038	European Medicines Agency, Guideline on the Limits of Genotoxic Impurities (2006)

1. I, Graham Buckton, Ph.D., have been retained by Windels Marx Lane & Mittendorf, LLP, counsel for Azurity Pharmaceuticals, Inc. (“Azurity”). I understand that Azurity is petitioning for *inter partes* review (“IPR”) of U.S. Patent No. 11,298,349 (“the ’349 patent,” Ex. 1001) and requests that the United States Patent and Trademark Office (“PTO”) cancel claims 1-3 of the ’349 patent as unpatentable. The following discussion and analysis provides my opinions as to why claims 1-3 are anticipated, and would have been obvious to a person of ordinary skill in the art.

I. BACKGROUND AND QUALIFICATIONS¹

2. I am a pharmaceutical consultant and an Emeritus Professor of Pharmaceutics in the UCL School of Pharmacy of the University of London and work as a pharmaceutical consultant. I was employed at the School of Pharmacy of the University of London from 1988 to 2015, initially as Lecturer, then Senior Lecturer, Reader and Professor, during which time I served as the Head of the Department of Pharmaceutics between January 2001 and April 2007. I served as

¹ I have included section headings and sub-headings for the reader’s convenience. Often, information discussed in one section will be of interest to the reader in another section. I have attempted to include cross-citations in such instances to avoid being repetitive. Any omission of a cross-citation is inadvertent.

Chair of the Master of Pharmacy (MPharm) Exam Board between 2002 and 2012, and have been an MPharm (or Bachelors in Pharmacy, BPharm) Examiner at Queens University of Belfast, Cardiff University, University of Nottingham, Kings College, University of Colombo, Sri Lanka, Robert Gordon University and the University of East Anglia.

3. I have a degree in Pharmacy and registered as a pharmacist in 1982 (registration lapsed 2024). I received my Ph.D. in Pharmaceutics from Kings College London in 1985. I received a Doctor of Science degree (DSc) from the University of London in 1997.

4. In 2000 I founded a contract services company called Pharmaterials Ltd. I sold the majority stake to a U.S. company, Pharmaceutics International Inc. (PII), in 2008 and the remaining stake in 2012, at which time I exited. I was Chief Executive Officer from 2000-2012. During my time at the company, Pharmaterials carried out materials characterisation, salt selection, polymorph screening, pre-formulation, formulation development, assay development and clinical trial manufacture. The formulations were primarily for a range of tablet and capsule solid oral dosage forms and inhalation products.

5. I have served on the Committee on Safety of Medicines (CSM), which is the regulatory body in the UK that grants (and revokes) marketing authorisations (the equivalent of the FDA in the US), and I chaired its Chemistry, Pharmacy and

Standards (CPS) sub-committee. As such I have reviewed the regulatory assessments and documents for each new drug product, and at least the first generic product, that sought to become a licensed medicinal product. I retired as a member of CPS of the Commission on Human Medicines (a renamed version of CSM) in September 2022 after over 20 years' service. I have been a member of the British Pharmacopoeia Commission and have been a member of working parties for the European and the United States Pharmacopoeias.

6. My research has focused on investigating the behaviour of pharmaceutical materials, especially interfacial interactions between two or more material surfaces, and their use in processing and drug delivery. Examples of my research include studies of surface interactions, adaptation of physical properties of powders by crystallisation and physical manipulation such as milling. The research was applied to, and involved, the formulation and preparation of drug dosage forms. This included the granulation process, the formulation, manufacture and testing of solid oral dosage forms (tablets and capsules) as well as further processes such as tablet coating. Other formulations included dry powder and metered dose inhalation dosage forms. I have published on my work in this field.

7. My research has been funded by such organisations as the Engineering and Physical Sciences Research Council (EPSRC), Pfizer, AstraZeneca, GSK, and Novartis, as well as other foundations and companies in industry.

8. I served a 10 year term as Editor of the International Journal of Pharmaceutics and have been a member of the editorial boards of a number of journals, including Pharmaceutical Research, the AAPS Journal and AAPS Pharm SciTec.

9. I have authored a book on Interfacial Phenomena in Drug Delivery and Targeting. I have also authored or co-authored over 185 peer-reviewed journal articles, of which numerous articles present original research related to solid dosage forms. In addition, I have authored or co-authored more than 110 abstracts and book reviews. Additionally, I have lectured at over 130 conferences, seminars, and symposia around the world and have served as a testifying expert witness on at least 37 cases.

10. I was course organiser and lectured on the Royal Pharmaceutical Society's Tableting Technology course from 1986 until 2017, during this time I taught the majority of industrial scientists working in the European pharmaceutical industry about tablet formulation, excipients and testing.

11. I have received numerous awards and honours, specifically, the appointment in 2003 as the Science Chairman for the British Pharmaceutical Conference, the first recipient of the Academy of Pharmaceutical Sciences Medal in 2000, the 1998 Stig Sunner Award, the 1998 Foss Near Infrared European Users

Group Award, the 1993 British Pharmaceutical Conference Science Medal, and the 1992 Pfizer Award for “excellence in published research.”

12. A summary of my education, experience, publications, awards and honours, patents, publications, and presentations is provided in my CV, a copy of which is attached as Exhibit A to this Declaration.

13. I am being compensated for my time in connection with this IPR at my standard consulting rate, which is £500 per hour. My compensation is not dependent in any way upon the outcome of this matter.

II. MATERIALS CONSIDERED

14. At the front of this document is a list of materials that I considered and reviewed in connection with providing this declaration.

III. LEGAL STANDARDS

15. I am not a patent attorney nor have I independently researched the law on patentability.

A. Prior Art Date

16. I understand from counsel that the relevant date for determining whether a reference is prior art may not be the actual filing date of a patent application. I also understand from counsel that a patent may be entitled to an earlier effective filing date if the claimed invention was previously described in an earlier

patent application. I further understand from counsel this is sometimes called a “priority” date of the claimed invention.

B. Written Description and Priority

17. I understand from counsel that a claimed invention can only be entitled to an earlier priority date if the invention was sufficiently described in an earlier patent application to which the patent claims priority. I also understand from counsel that this requirement is referred to as the “written description” requirement.

18. I understand from counsel that the PTAB cannot consider invalidity of patent claims based on their written description, but can consider written description in order to decide on priority dates of patent claims. The written description requirement requires that the patent application clearly allows persons of ordinary skill in the art to recognise that the inventor(s) invented what is claimed. I also understand from counsel that the key to meeting the written description requirement is an evaluation of the patent application itself. I understand from counsel that demonstration of invention of the claimed subject matter using evidence outside of the patent application is insufficient to fulfill the written description requirement. That is, I understand from counsel that the written description requirement is met only if the disclosure of the earlier application itself reasonably conveys to a person skilled in the art that the inventor had invented claimed subject matter as of the earlier filing date. I further understand from counsel that this inquiry is carried out

from the perspective of a skilled artisan at the time of the earlier application. Accordingly, I understand from counsel that the written description requirement focuses on whether the earlier disclosure demonstrates to a skilled artisan that the inventor actually invented the later claimed invention.

19. I understand from counsel that an applicant can meet the written description requirement by providing a representative number of species falling within a genus, or by showing structural features which are common to members of the genus so that one of skill in the art can visualise or recognise the members of the genus.

20. I understand from counsel that an earlier patent application does not need to use the exact words of the later claim to satisfy the written description requirement. I also understand from counsel that a disclosure that makes a later claim obvious, however, is not enough to meet the written description requirement.

C. Anticipation

21. I understand from counsel that the “prior art” includes patents and printed publications that existed before the earliest filing date (the “effective filing date”) of the claim in the patent.

22. I understand from counsel that if each and every limitation or step of a claim is disclosed within the “four corners” of a prior art reference, that claim is said

to be “anticipated” by that single prior art reference and is invalid under 35 U.S.C. § 102 because the claimed invention is not, in fact, new or novel.

23. I also understand from counsel that a prior art reference can disclose a claim feature because the feature is expressly described, or because the feature is inherent in the disclosure. I understand from counsel that something is inherent in a prior art reference if the missing description matter must necessarily be present, and it would be so recognised by a person of ordinary skill in the art. I also understand from counsel that inherency cannot be established by probabilities or possibilities, and that the mere fact that something may result from a given set of circumstances is not sufficient to show inherency.

24. I understand from counsel that a prior art document can disclose a claim feature, and anticipate a claimed invention, if that feature is described in another document that has been incorporated by reference. I also understand from counsel that, to incorporate by reference, the document doing the incorporation (i.e., the host document) must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the incorporated document. I further understand from counsel that, in making the determination of the extent to which material is incorporated into a host document, the standard of a person skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity.

25. I also understand from counsel that it is acceptable to consider evidence other than the information in a particular prior art document to determine if a feature is necessarily present or inherently described by that reference.

D. Obviousness

26. I understand from counsel that 35 U.S.C. § 103 governs the determination of obviousness. I understand from counsel that 35 U.S.C. § 103 states:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

27. I further understand from counsel that the four factors to be considered in an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations including long-felt need, commercial success, and unexpected results.

28. I further understand from counsel that when there is some recognised reason to solve a problem, and there are a finite number of identified, predictable

solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the anticipated success, it is likely the result is a product of ordinary skill and common sense, not innovation.

29. I also understand from counsel that when a patent simply arranges old elements with each element performing the same function it had been known to perform and the combination yields no more than one would expect from such an arrangement, the claim to the combination is obvious.

IV. THE PERSON OF ORDINARY SKILL IN THE ART

30. I understand from counsel that the legal standards of claim construction, written description, priority, and obviousness are analysed from the perspective of a hypothetical person of ordinary skill in the art.

31. I understand from counsel that Exelixis has proposed that a person of ordinary skill in the art (“POSA”) related to the ’349 patent would have had at least a bachelor’s degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with several years of experience working in pharmaceutical development and/or solid-state chemistry and would also have been part of a team which would have included synthetic organic chemists and process chemists, formulation scientists, analytical scientists and clinicians. Ex. 1010 (Exelixis’ Proposed Findings of Fact On Infringement of U.S. Patent No.

11,298,349) ¶11. I take this to mean that the POSA is a member of a team charged with developing a pharmaceutical composition with the goal of developing a formulation suitable for human administration and licensing (otherwise clinicians would not be involved), within the formulator would have several years experience in the relevant subject area and who would draw on the knowledge and experience of the other members of the team to carry out the development tasks. I have been asked to apply this definition. Accordingly, my opinions, as set forth herein, are from the perspective of a POSA, as set forth above.

32. Given my educational and professional background, and my collaborations with other scientists and clinicians in my career, I would meet the definition of a POSA.

33. I understand from counsel that one of the issues in this proceeding is whether the claims of the '349 patent were adequately disclosed in the initial applications. I further understand from counsel that the earliest alleged priority application listed on the '349 patent is dated February 10, 2011. Ex. 1001 ('349 patent) at (60) ("Provisional application No. 61/441,520, filed on Feb. 10, 2011, provisional application No. 61/441,527, filed on Feb. 10, 2011."). I understand from counsel that, as a result, any publications from February 9, 2011 or earlier are available as prior art. Thus, I have carried out my analysis of obviousness from the perspective of a POSA using February 9, 2011 as the relevant time frame.

34. However, as I explain herein, it is my opinion that the claims of the '349 patent are not entitled to a priority date of February 10, 2011. *See* Section VIII.A., below. I understand from counsel that if the Board finds the '349 patent is not entitled to the earlier priority date, it will change the relevant timeframe for the obviousness analysis. However, my opinions on obviousness would not change if the Board assigns a later priority date.

V. CLAIM CONSTRUCTION

35. I understand from counsel that “claim construction” is the interpretation of the meaning of patent claims. I also understand from counsel that, in an IPR, words of a claim are generally given their plain and ordinary meaning, which is the meaning the term or phrase would have to a POSA at the time of the invention. I understand from counsel that both intrinsic and extrinsic evidence can be used to assist in understanding the meaning of a claim. Intrinsic evidence includes the claim language, language in other claims of the patent, the specification, and the prosecution history. I further understand from counsel that, unless required by the claim language or specification, claims should generally not be limited to embodiments in the specification, including preferred embodiments. I also understand from counsel that extrinsic evidence, which consists of all evidence external to the patent and prosecution history including expert and inventor testimony, dictionaries, and technical publications, including those known and

authoritative in a particular technical field, may also be relevant to claim construction. I further understand from counsel that a patent applicant may act as his or her own lexicographer and set forth a special definition of a claim term in the specification.

36. I understand from counsel that the '349 patent includes a definition for the phrase “essentially free of process byproducts or contaminants” that appears in claim 1. Ex. 1001 ('349 patent) at 8:15-20 (“‘Essentially free’ as used in the phrase ‘essentially free of process byproducts or contaminants,’ means that a compound or composition as disclosed here in is admixed with 200 parts per million (ppm) or less of such byproducts or contaminants.”). I have used this definition from the specification in my analysis and applied it when considering claims to pharmaceutical compositions.

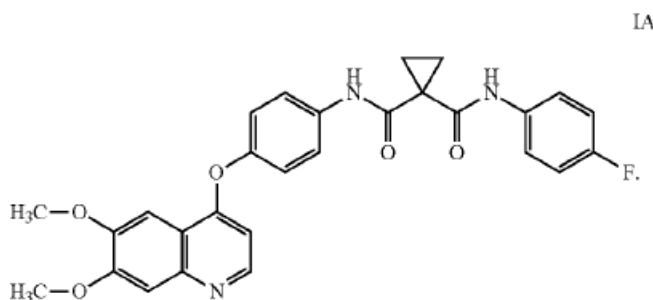
37. I have reviewed the '349 patent and I have been asked by counsel to apply a numerical limit of “200 ppm or less of 6,7-dimethoxy-quinoline-4-ol” to the term “essentially free of 6,7-dimethoxy-quinoline-4-ol” that is recited in claim 3 of the '349 patent. I have done so in my analysis.

38. Unless otherwise indicated, I have utilised the plain and ordinary meaning of all other claim terms in my analysis.

VI. INTRODUCTION TO THE '349 PATENT

39. The '349 patent is entitled “Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds.” Ex. 1001 ('349 patent) at (54).

40. In a section entitled “Background of the Invention,” the '349 patent identifies “compound IA” and provides its structure as set forth below:



Ex. 1001 ('349 patent) at col. 2, line 66 to col. 3, line 13.

41. In this same section, the '349 patent states: “WO2005/030140 describes the synthesis of compound IA (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by reference.” Ex. 1001 ('349 patent) at col. 3, lines 14-19.

42. The '349 patent further indicates that “[a]lthough therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can

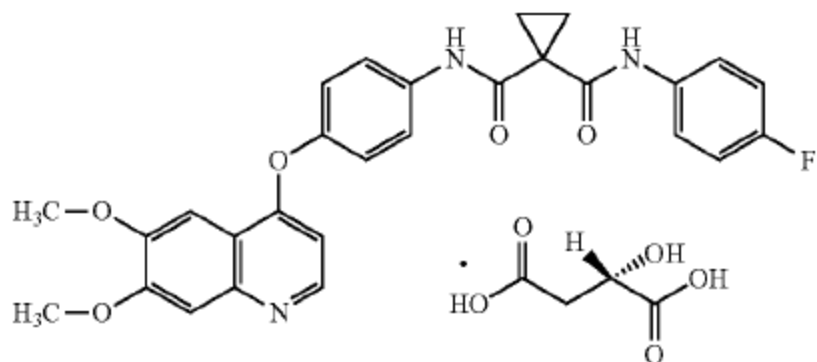
be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug.” Ex. 1001 (’349 patent) at col. 3, lines 20-28.

43. The background section concludes by stating: “there is a need for the discovery of new processes for making quinolines such as compound IA that minimize the formation of undesirable process contaminants or byproducts. There is also a need for new pharmaceutical compositions containing quinolines such as compound IB that are essentially free of process byproducts.” Ex. 1001 (’349 patent) at col. 3, lines 29-34.

44. There are 3 claims in the ’349 patent, and each relates to a “pharmaceutical composition.” Ex. 1001 (’349 patent) at col. 34, lines 5-51. The “Challenged Claims” with respect to invalidity in this matter are Claims 1-3. These claims are recited in full below:

1. A pharmaceutical composition for oral administration comprising Compound IB;

IB

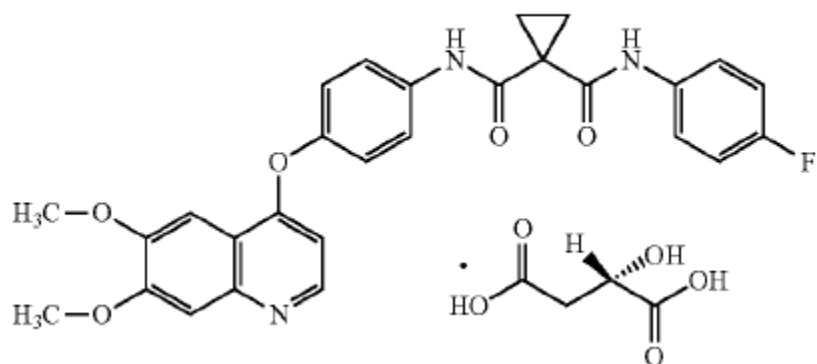


one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

2. The pharmaceutical composition of claim 1, wherein the process byproduct or contaminant is 6,7-dimethoxyquinoline-4-ol in the pharmaceutical composition.

3. A pharmaceutical composition for oral administration comprising Compound IB

IB



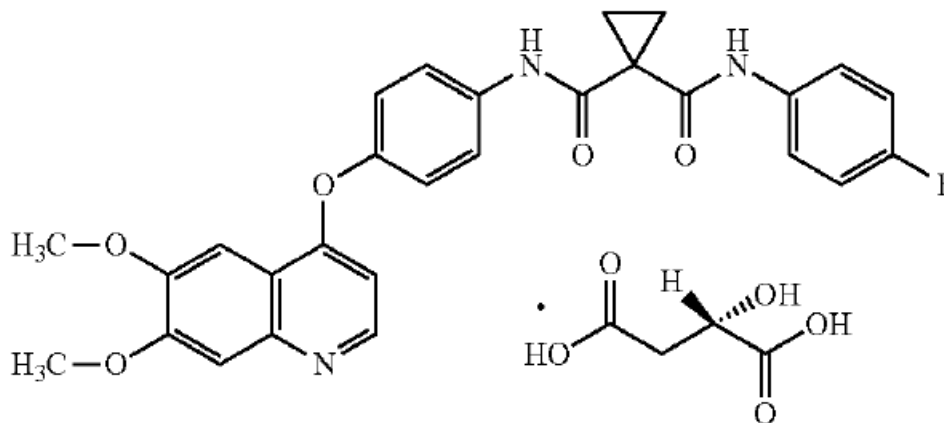
one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition; and wherein the pharmaceutical composition is essentially free of 6,7-dimethoxyquinoline-4-ol.

VII. TECHNICAL BACKGROUND AND STATE OF THE ART

A. Cabozantinib and the (L)-Malate Salt of Cabozantinib

45. Exelixis received FDA approval in 2012 to market tablets (CABOMETYX®) and capsules (COMETRIQ®) containing the (L)-malate salt of cabozantinib for the treatment of certain cancers. Ex. 1005 (Cabometyx® Insert); Ex. 1006 (Cometriq® Insert).

46. The (L)-malate salt of cabozantinib is identified as “Compound IB” in the '349 patent. *See, e.g.*, Ex. 1001 at col. 4, lines 1-14, claims 1 and 3. It has the following structure:



Sometimes I may refer to Compound IB as cabozantinib (L)-malate.

47. On the other hand, cabozantinib is identified as “Compound IA” in the ’349 patent. *See, e.g.*, Ex. 1001 at col. 2, line 66 to col. 3, line 13; *id.* at col. 4, lines 15-27. The primary difference between cabozantinib and cabozantinib (L)-malate is the absence (for cabozantinib) and presence (for cabozantinib (L)-malate) of a salt formed with (L)-malic acid.

48. As it pertains to the ’349 patent and the subject matter therein, cabozantinib was a known compound (i.e., it had been earlier described in the prior art). For example, Exelixis identified cabozantinib in U.S. Patent No. 7,579,473, which is a member of a patent family that dates back to 2003. Ex. 1008 (’473 patent) at (60) (identifying “provisional application No. 60/506,181, filed on Sep. 26, 2003). Cabozantinib’s structure can be found in U.S. Patent No. 7,579,473 at column 199 (entry 12, providing both structure and name, “N-(4-{[6,7-bis(methoxy)quinoline-4-yl]oxy}phenyl)-N’-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide”). As I indicated above, the ’349 patent admitted in the background that cabozantinib (referring to “Compound IA”) was a known compound. Ex. 1001 (’349 patent) at col. 3, lines 14-19.

49. U.S. Patent No. 7,579,473 (Ex. 1008, “the ’473 patent”) identifies Exelixis, Inc. as the assignee. Ex. 1008 (’473 patent) at (73). The ’473 patent indicates that oral administration of its compounds is preferred. Ex. 1008 (’473

patent) at col. 273, lines 20-22 (“One preferably route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.”).

50. The '473 patent further indicates that capsules and tablets are “[s]olid dosage forms for oral administration.” Ex. 1008 ('473 patent) at col. 273, lines 23-24. It further explains:

In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Ex. 1008 ('473 patent) at col. 273, lines 24-44. Thus, the '473 patent identifies materials such as “fillers,” “disintegrating agents,” and “lubricants” as “customary excipients” for inclusion in a solid dosage form. *Id.*

51. Cabozantinib is specifically claimed in the '473 patent as “a pharmaceutically acceptable salt.” Ex. 1008 ('473 patent) at col. 412, lines 34-51 (claim 5). Pharmaceutical compositions and the inclusion of an excipient is also claimed in the '473 patent. *Id.* at col. 412, lines 53-57 (claims 6 and 7). Accordingly, cabozantinib, pharmaceutically acceptable salts of cabozantinib, solid dosage forms, and pharmaceutical tablet/capsule compositions were all disclosed by Exelixis in the '473 patent.

52. As it pertains to the '349 patent and the subject matter therein, cabozantinib (L)-malate (i.e., “Compound IB”) was also a known salt form (i.e., it had been earlier described in the prior art). Exelixis disclosed cabozantinib (L)-malate in International Publication No. WO 2010/083414 (Ex. 1003, “Brown”), which identifies January 16, 2009 in a section entitled “Priority Data.” Ex. 1003 (Brown) at (30). As a representative example of cabozantinib (L)-malate’s disclosure, I have quoted Brown’s Abstract below:

Disclosed are malate salts of *N*-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-

dicarboxamide,² including a (L)-malate salt, a (D)-malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salts [sic] of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Ex. 1003 (Brown) at Abstract. The emphasised name above in bold is the same name used in the '473 patent to identify cabozantinib. Ex. 1008 ('473 patent) at col. 199 (entry 12). I have further emphasised, by underlining, the identification of the (L)-malate salt in Brown's Abstract.

53. Similar to the earlier '473 patent, Brown identifies "Exelixis, Inc." as one of the Applicants. Ex. 1003 (Brown) at (71). Likewise, Brown identifies a "tablet" and a "capsule" for the preparation of pharmaceutical compositions that incorporate cabozantinib (L)-malate. Ex. 1003 (Brown) at [0078]. Brown further explains that such pharmaceutical compositions are to be prepared by "methods

² Unless otherwise indicated, all emphases are added.

know[n] in the pharmaceutical formulation art” as taught, for example, by “Remington’s Pharmaceutical Sciences, 18th Ed.” Ex. 1003 (Brown) at [0082].

54. Brown also contains an explanation of solid dosage forms that is nearly verbatim to that provided in the earlier ’473 patent:

In a solid dosage forms [sic], Compound I is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Ex. 1003 (Brown) at [0082].

55. Cabozantinib (L)-malate is specifically claimed in Brown. Ex. 1003 (Brown) at claim 4. Crystalline forms, such as the N-1 and N-2 form, are also claimed. *Id.* at claims 6-9. Brown further claims pharmaceutical compositions of cabozantinib (L)-malate in combination with a “pharmaceutically acceptable excipient.” *Id.* at claim 11.

56. Accordingly, cabozantinib (L)-malate, crystalline forms N-1 and N-2, and their inclusion in a capsule/tablet pharmaceutical composition along with excipients such as “fillers,” “disintegrating agents,” and “lubricants” were all disclosed in Brown.

B. Pharmaceutical Compositions

57. The development of a pharmaceutical composition requires research to obtain an active pharmaceutical ingredient, an assessment of safety of the ingredients/product, a suitable clinical effect, regulatory consideration and suitable marketing/commercial drive, as well as the design of the dosage form itself (see Ex. 1009 (Gibson) at 2). When designing a pharmaceutical dosage form, it is elementary knowledge that active pharmaceutical ingredients (“APIs”) are rarely administered solely as pure chemical substances. Instead, they are almost always administered to a patient as part of a formulated preparation containing inert material referred to as “excipients.” Ex. 1004 (Remington) at 889, 891.

58. Oral administration is the most frequently used route of administration for pharmaceutical compositions. Ex. 1004 (Remington) at 889; Ex. 1009 (Gibson) at 367; Ex. 1034 (Aulton) at 442. As compared to other routes, the oral route is simpler, more convenient for the patient, and is a safer means of drug administration. Ex. 1009 (Gibson) at 367. Accordingly, tablets and capsules dosage forms have garnered widespread popularity. Ex. 1004 (Remington) at 889.

59. Tablet and capsule dosage forms have been in existence since the 19th century and remain the most frequently used dosage form. Ex. 1034 (Aulton) at 442; Ex. 1009 (Gibson) at 367; Ex. 1004 (Remington) at 889. The oral route is the most common way of administering drugs and tablets are the most common type of solid dosage form in contemporary use. Ex. 1034 (Aulton) at 442. Tablets provide several advantages to the manufacturer and the patient:

- Simplicity and economy of preparation;
- stability;
- convenience in packaging, shipping, and dispensing;
- accuracy of dosage;
- compactness;
- Improved stability;
- portability;

- blandness of taste; and
- ease of administration.

Ex. 1004 (Remington) at 889; Ex. 1034 (Aulton) at 442 (indicating why “[t]ablets are popular for several reasons”).

60. Compressed tablets are prepared by using a tablet press. Ex. 1009 (Gibson) at 385 (section entitled “Tablet Machines”); Ex. 1004 (Remington) at 889-891. “Powder is filled to a specified depth in a die and compressed between two punches. The compression force is ended by removal of the upper punch, and the lower punch then moves upward in the die to eject the tablet.” Ex. 1009 (Gibson) at 385; *see also* Ex. 1004 (Remington) at 890-891. Depending upon the machine, thousands of tablets to more than one million tablets can be prepared per hour. Ex. 1009 (Gibson) at 385.

61. In addition to the drug/API, tablets include additional substances that are referred to as “excipients.” Ex. 1004 (Remington) at 891. Various compendia exist that attempt to compile useful information regarding substances that have been utilised as an excipient. One such compendium is the “Handbook of Pharmaceutical Excipients.” Editions of this compendium are updated periodically, with the 6th edition having been published in 2009. The 6th edition contains information on 340 individual excipients. Ex. 1025 (Handbook) at x (Preface).

62. Moreover, although I have described excipients as being “inert,” that simply means that they have no independent pharmacological action, and should not be taken to mean that they do not have a potential to alter the therapeutic efficacy of the drug substance in the tablet.

63. Excipients are selected based on the properties of the drug substance in order to develop a suitable formulation. The properties of the drug substance are determined in “preformulation” studies, which evaluate factors such as stability (of the active in different states and between individual excipients and the active ingredient), solubility, which can relate to bioavailability, and other physico-chemical properties which will inform formulation decisions. “Preformulation data from solubility, stressed stability, excipient compatibility, and other preformulation studies may influence the selection of the formulation dosage form and excipients.” Ex. 1009 (Gibson) at 174.

64. Certain categories or classes of excipients are typically included in tablet dosage forms. Ex. 1004 (Remington) at 891. These categories include “diluent,” “binders,” “glidants,” “lubricants,” “disintegrants,” “surfactants,” and “colors.” *Id.*; Ex. 1009 (Gibson) at 399 (“The drug substance, probably a filler, a disintegrant, and a lubricant will be common to most formulations, while glidants, colorants, and wetting agents may also be included.”), 420 (“As with tablets, most capsules will contain a combination of ingredients including some or all of the

following: the active drug substance, filler(s), disintegrant, binder, glidant, and lubricant.”). The Challenged Claims all explicitly require the inclusion of four of these excipient categories. These categories are discussed in further detail below.

1. Fillers

65. In the formulation arts, the terms “filler” and “diluent” are synonymous. Ex. 1034 (Aulton) at 449 (referring to the category of “Filler (or diluent)”); Ex. 1025 (Handbook) at 867 (“Fillers *see* Diluents (tablet/capsule)”). These names are functionally descriptive, for example a filler/diluent is a category of excipient that is added to a formulation “to increase the bulk to make the tablet a practical size for compression.” Ex. 1004 (Remington) at 891; Ex. 1009 (Gibson) at 390 (“[F]or low-dose drugs, it will be necessary for the tablet to be bulked out with an inactive material termed a diluent. High-dose formulations may also use a diluent to overcome compaction problems experienced with an active substance.”); Ex. 1034 (Aulton) at 449.

66. Many excipients are categorised as a filler/diluent. One need only consult a compendium such as the “Handbook of Pharmaceutical Excipients” to realise many options that are available. Ex. 1025 (Handbook) at 864 (Index) (listing approximately 45 excipients under the category “Diluents” for a “tablet/capsule”).

67. Gibson provides a table that lists commonly utilised fillers/diluents in tablet compositions:

Table 8 Common Tablet Diluents

Diluent	Pharmacopoeia	Comments
Lactose	USP, Ph Eur, JP	Available as anhydrous and monohydrate. Anhydrous material used for direct compression due to superior compressibility.
Microcrystalline cellulose	USP, Ph Eur, JP	Originally a direct compression excipient, now often included in granulations due to its excellent compressibility.
Dextrose, glucose Sucrose	USP, Ph Eur, JP USP, Ph Eur, JP	Direct compression diluent, often used in chewable tablets. Was widely used as a sweetener/filler in effervescent tablets and chewable tablets. Less popular nowadays due to cariogenicity.
Starch and derivatives	USP, Ph Eur, JP	Versatile material can be used as diluent binder and disintegrant.
Calcium carbonate	USP, Ph Eur, JP	Brittle material
Dicalcium phosphate	USP, Ph Eur, JP	Excellent flow properties. Brittle material.
Magnesium carbonate	USP, Ph Eur, JP	Direct compression diluent.

Ex. 1009 (Gibson) at 391.

68. Microcrystalline cellulose is a very popular choice of filler. Ex. 1004 (Remington) at 891 (“Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas. However, its presence in 5–15% concentrations in wet granulations has been shown to be beneficial....”). Gibson echoes Remington’s sentiments by referring to microcrystalline cellulose as “[o]riginally a direct compression excipient, now often included in granulations due to its excellent compressibility.” Ex. 1009 (Gibson) at 391 (Table 8), 401 (Table 12) (identifying microcrystalline cellulose as “[p]robably the most widely used direct compression excipients” with “[e]xcellent compactibility” and “high-dilution capacity”).

2. Disintegrants

69. Disintegrants are a category of excipient that are “added to a tablet to facilitate its breakup or disintegration after administration.” Ex. 1004 (Remington) at 893; Ex. 1009 (Gibson) at 397 (“To maximize the dissolution rate of a drug substance from a tablet, it is necessary to overcome the cohesive strength produced by the compression process and break the tablet into the primary particles as rapidly as possible This is achieved by adding disintegrants, which will induce this process.”). As Gibson explains, “once an immediate-release tablet is taken by the patient, it is important that it breaks up rapidly to ensure quick dissolution of the active ingredients.” Ex. 1009 (Gibson) at 397.

70. Many excipients are categorised as a disintegrant. Once again, one need only consultant compendia such as the “Handbook of Pharmaceutical Excipients” to realise that many options are available. Ex. 1025 (Handbook) at 865 (Index) (listing 22 excipients under the category “Disintegrants” for a “tablet/capsule”).

71. Gibson provides a table that lists commonly utilised disintegrants in tablet compositions:

Table 11 Commonly Used Disintegrants

Disintegrant	Normal usage concentration (%)	Comments
Starch	5–10	Probably work by wicking; swelling is minimal at body temperature.
Microcrystalline cellulose		Strong wicking action. Loses disintegrant action when highly compressed.
Insoluble ion exchange resins		Strong wicking tendencies with some swelling action.
Sodium starch glycolate	2–8	Free-flowing powder that swells rapidly on contact with water.
Croscarmellose sodium	1–5	Swells on contact with water.
Gums—agar, guar, xanthan	<5	Swell on contact with water; form viscous gels that can retard dissolution, thus limiting concentration that can be used.
Alginic acid, sodium alginate	4–6	Swell like the gums but form less viscous gels.
Crospovidone	1–5	High wicking activity.

Ex. 1009 (Gibson) at 398.

72. Certain disintegrants, known as “super disintegrants,” have gained in popularity. Ex. 1004 (Remington) at 893. For example, Gibson indicates that “super disintegrants” such as “croscarmellose sodium, sodium starch glycolate, and crospovidone” have largely superseded the first disintegrants used in tablet manufacture. Ex. 1009 (Gibson) at 397-398. Such disintegrants “display excellent disintegration activity at low concentrations and possess better compression properties than starches.” *Id.*

3. Glidants

73. “Glidants” are a category of excipient that are included in a tablet dosage form to facilitate the transfer of the particulate formulation into the tablet die for compression. Ex. 1004 (Remington) at 893 (“A glidant is a substance that

improves the flow characteristics of a powder mixture.”); Ex. 1009 (Gibson) at 388 (“The formulation should have sufficient flowability to ensure that the appropriate quantity of powder flows into the dies of the tablet machine on a consistent basis.”), 389 (“The flow properties of a powder can be enhanced by the inclusion of a glidant.”). Inadequate flow can cause manufacturing difficulties. It can also result in non-uniform tablet production if uneven amounts of particulates flow into the tablet die.

74. One need only consultant compendia such as the “Handbook of Pharmaceutical Excipients” to realise that several options of excipients which function as glidants are available. Ex. 1025 (Handbook) at 868 (Index) (listing 9 excipients under the category “Glidants”).

75. Gibson provides a table that lists commonly utilised glidants in tablet compositions:

Table 7 Commonly Used Glidants

Glidant	Typical percentage
Talc	1–5
Fumed silicon dioxide	0.1–0.5
Aerosil	–
Cab-O-Sil	–
Syloid	–
Starch	1–10
Calcium silicate	0.5–2.0
Magnesium carbonate (heavy)	1–3
Magnesium oxide (heavy)	1–3
Magnesium lauryl sulfate	0.2–2.0
Sodium lauryl sulfate	0.2–2.0

Ex. 1009 (Gibson) at 389.

76. Colloidal silicon dioxide, which is sometimes referred to as fumed silicon dioxide, colloidal silica, or fumed silica, is the most commonly used glidant. Ex. 1004 (Remington) at 893; Ex. 1034 (Aulton) at 452. Gibson also indicates that “[t]he *fumed silicon dioxides* are perhaps the most effective glidants.” Ex. 1009 (Gibson) at 390.

4. Lubricants

77. “Lubricants,” more correctly ‘die wall lubricants’ to differentiate from other functions such as antiadherents and glidants, are a category of excipient that are included in a tablet dosage form³ to facilitate removal of the formed tablet from the die of the tablet machine. Ex. 1009 (Gibson) at 391-392 (explaining the role of “die-wall lubricant excipients, which reduce the friction between the tablet surface and the die wall during and after compaction to enable easy ejection of the tablet”).

³ Lubricants, and the other classes of excipients that I discuss here, are also included in capsule dosage forms. See Ex. 1009 (Gibson) at 420 (“As with tablets, most capsules will contain a combination of ingredients including some or all of the following: the active drug substance, filler(s), disintegrant, binder, glidant and lubricant.”).

78. One need only consultant compendia such as the “Handbook of Pharmaceutical Excipients” to realise that several options of excipients which function as die-wall lubricants are available. Ex. 1025 (Handbook) at 873 (Index) (listing 22 excipients under the category “Lubricants” for a “tablet/capsule”).

79. Gibson provides a table that lists commonly utilised lubricants in tablet compositions:

Table 9 Lubricants and Their Usage

Lubricant	Level required (%)	Comments
Boundary lubricants		
Magnesium stearate	0.2–2.0	Hydrophobic, variable properties between suppliers.
Calcium stearate	0.5–4.0	Hydrophobic.
Sodium stearyl fumarate	0.5–2.0	Less hydrophobic than metallic stearates, partially soluble.
Polyethylene glycol 4000 and 6000	2–10	Soluble, poorer lubricant activity than fatty acid ester salts.
Sodium lauryl sulfate	1–3	Soluble, also acts as wetting agent.
Magnesium lauryl sulfate	1–3	Acts as wetting agent.
Sodium benzoate	2–5	Soluble.
Fluid lubricants		
Light mineral oil	1–3	Hydrophobic, can be applied to either formulation or tooling.
Hydrogenated vegetable oils	1–5	Hydrophobic, used at higher concentrations as controlled-release agents.
Stearic acid	0.25–2	Hydrophobic.
Glyceryl behenate	0.5 –4.0	Hydrophobic also used as controlled-release agent.

Ex. 1009 (Gibson) at 392.

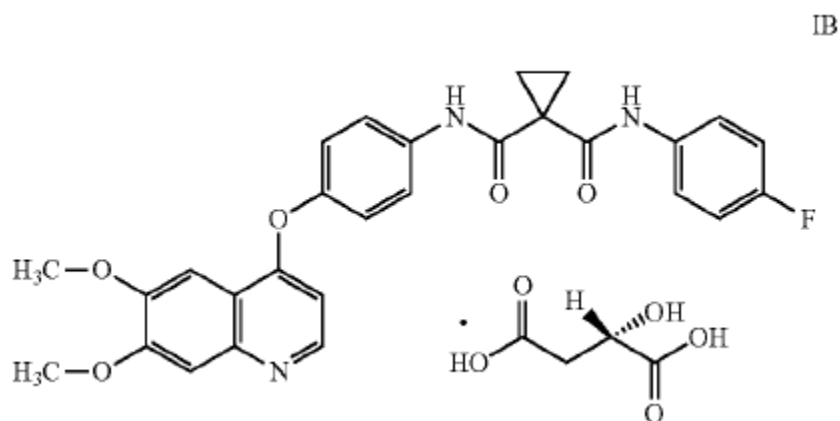
80. Similarly, Remington indicates that “[c]ommonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, hydrogenated vegetable oils, and polyethylene glycol (PEG).” Ex. 1004 (Remington) at 892.

VIII. GROUND 1: ANTICIPATION OF CLAIMS 1-3 BY WILSON

A. The Challenged Claims Are Not Entitled to an Earlier Priority Date

81. The '349 patent has claims relating to a pharmaceutical composition, broad categories of excipients and a purity/stability limitation, *see* for example claim 1:

1. A pharmaceutical composition for oral administration comprising Compound IB;



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

In the section below, I have considered whether claims 1-3 are entitled to an earlier priority date, by considering whether the priority documents contain a written description that would support the scope of these claims. This analysis also

determines whether or not earlier documents should be considered as prior art to the '349 patent.

82. The '349 patent cites to Wilson (Ex. 1002) in the section titled "Related U.S. Application Data." Ex. 1001 ('349 patent) at (60) (citing application No. 13/984,559, filed as application No. PCT/US2012/024591 on Feb. 10, 2012, now Pat. No. 9,717,720). Accordingly, I understand from counsel that if the Challenged Claims are able to claim priority through earlier filed applications back to Wilson, or an even earlier application, then Wilson will not be prior art to the Challenged Claims and will not anticipate as explained above. However, it is my opinion that claims 1-3 are only entitled to priority as of February 8, 2021, which is the filing date of the application that issued as '349 patent, and are not entitled to a priority date of February 10, 2011.

83. I have reviewed the prosecution history of U.S. Application No. 17/170,275 ("the '275 application"; Ex. 1014), which issued as the '349 patent, to understand if the Examiner addressed this issue of the Challenged Claims' entitlement to an earlier effective filing date. I noticed that on February 8, 2021, the '275 application was filed with 34 claims. None of the original 34 claims recited each of the limitations of claims 1-3 that issued in the '349 patent. Ex. 1014 ('275 application) at 47-55 (Claims 1-34 identified with the heading WO 2012/109510). However, that same day, Exelixis submitted a document entitled "Preliminary

Amendment Under 37 C.F.R. § 1.115.” Ex. 1014 (’275 application) at 57. This document contained a section entitled “Amendments to the Claims” and indicated that claims 1-34 were “Cancelled” and claims 35-37 were “New.” Ex. 1014 (’275 application) at 58. Contained within this Amendment was a statement that: “The new claims are supported by the specification and claims as originally filed and do not introduce new matter.” Ex. 1014 (’275 application) at 60. For the reasons set forth below, I disagree with this statement regarding support for the new claims in the earlier-filed applications.

84. I understand from counsel that claims 35-37 were the ones examined by the Patent Office in an Office Action dated March 31, 2021. Ex. 1014 (’275 application) at 72-78. While I am not a patent attorney, I have reviewed the section entitled “Detailed Action.” Ex. 1014 (’275 application) at 74-78. I do not see any citations or analysis by the Examiner concerning support for claims 35-37 in the earlier-filed specification or original claims as alleged by Exelixis in its preliminary amendment. Nor do I see any argument by the Examiner explaining how claims 35-37 are entitled to the benefit of an earlier effective filing date.

85. I have also reviewed the claim amendments that Exelixis made in a document dated June 30, 2021. Ex. 1014 (’275 application) at 79-90. Claims 35, 38, and 39, as amended appear to be substantively identical to the claims that issued in the ’349 patent. I note that in a section entitled “Remarks,” Exelixis stated:

“Currently amended claim 35 is supported by the specification and claims as originally filed and does not introduce new matter.” Ex. 1014 (’275 application) at 82. However, I do not see any citations or analysis that would support this assertion. I also note that with respect to claims 38 and 39, Exelixis stated: “The new claims are supported by the specification as originally filed and do not present new matter.” Ex. 1014 (’275 application) at 82. Again, I do not see any citations or analysis that would support this assertion.

86. I understand from counsel that claims 35, 38, and 39 were the ones examined by the Patent Office in an Office Action dated July 20, 2021. Ex. 1014 (’275 application) at 91-99. While I am not a patent attorney, I have reviewed the section entitled “Detailed Action.” Ex. 1014 (’275 application) at 93-99. Once again, I do not see any citations or analysis by the Examiner concerning support for claims 35, 38, and 39 in the specification or original claims as filed as alleged by Exelixis when it amended the claims. Nor do I see any argument by the Examiner explaining how claims 35, 38, and 39 are entitled to the benefit of an earlier effective filing date.

1. Exelixis’s prior statements regarding the claimed subject matter

87. I have reviewed several documents that set forth statements by Exelixis or an expert on Exelixis’s behalf regarding the pharmaceutical arts and the subject matter of claims 1-3 of the ’349 patent. *See, e.g.*, Ex. 1010 (Exelixis’ Proposed

Findings of Fact On Infringement of U.S. Patent No. 11,298,349); Ex. 1013 (Exelixis' Answering Proposed Findings of Fact On the Validity of the Asserted Patents); Ex. 1018 (Exelixis' Responsive Post-Trial Brief); Ex. 1019 (Trial Volume III). Numerous statements by Exelixis and its experts that characterise the pharmaceutical arts in an unpredictable light can be found, *inter alia*, at the following citations:

- Ex. 1019 at 712:19-713:2 (Exelixis expert answering “No, because as we’ve seen, the process of blending with excipients and making it into the drug product can result in increase in the 1-1⁴ impurity. Thus, it’s possible to start with an API that’s essentially free, but end up with a drug product that’s not essentially free due to the additional formation of the 1-1”).
- Ex. 1019 at 729:12-17 (Exelixis expert stating: “Well, first of all, the formulation of any drug product requires you to understand the dosage form, the dose, and the physicochemical properties of the API. So, before you know how you're -- how you're going to formulate

⁴ Short hand used in court to describe the specific impurity (i.e., 6,7-dimethoxy-quinoline-4-ol) that is claimed in the '349 patent.

something, you have to do all that work. And then you can decide what classes of excipients you're going to employ.”);

- Ex. 1019 at 730:16-20 (Exelixis expert stating: “Well, it turns out that cabozantinib (L)-malate could decompose to the 1-1 impurity when exposed to moisture, heat, and in the presence of certain excipients. In addition, it was poorly flowing. The API was poorly flowing.”)
- Ex. 1019 at 730:21-731:1 (Exelixis expert testifying that the chemical stability and flowability of cabozantinib (L)-malate were not known in the prior art)
- Ex. 1019 at 733:9-14 (Exelixis expert stating: “each formulation is a unique – unique development project”)
- Ex. 1019 at 734: 5-13 (Exelixis expert stating: “each formulation of a new API is a unique problem. And you might run into problems with flow or chemical stability or the ability to make a tablet that is -- doesn't break into pieces or is -- has appropriate hardness, has the right dissolution properties. So, in fact, in my own experience, you go through lots and lots of iterations of excipients and blends and tablet press pressures and various other things to make a safe and effective and reliable formulation.”)

- Ex. 1019 at 739:3-740:5 (Exelixis expert indicating that to formulate cabozantinib (L)-malate into a drug product that was ‘essentially free’ of the claimed impurity one “would have to know about [the API’s] chemical stability . . . you would also have to know the list of physicochemical properties I mentioned before, including the excipient compatibility studies” and admitting that none of these properties were known in the prior art)
- Ex. 1018 at 55 (Exelixis arguing: “[A]chieving API with the claimed purity does not mean that any resulting formulation would have necessarily had the same purity.”);
- Ex. 1013 at ¶68 (Exelixis arguing: “Achieving API essentially free of the [6,7-dimethoxy-quinoline-4-ol] impurity does not necessitate that a formulation of that API would be similarly pure.”);
- Ex. 1019 at 712:15-713:14 (Exelixis expert indicating, *inter alia*, that “We first saw the excipient compatibility studies which showed that the 1-1 could -- would increase in contact with a number of different excipients. Secondly, we see the Exelixis studies that showed that the 1-1 impurity would increase when exposed to temperature, heat -- heat,

moisture, and potentially physical force, which are used in manufacturing of tablets and capsules);

- Ex. 1019 at 733:21-734:3 (Exelixis expert arguing: “The correct selection and balance of excipient materials for each active ingredient or ingredient combination in a tablet formulation to achieve the desired response (i.e. production of a safe, effective, and highly reliable product) is not in practice a simple goal to achieve.”);
- Ex. 1019 at 773:5-24 (Exelixis’s expert admitting that “[o]ther than disclosing a synthetic process that makes an API [having an] exceptionally low [level of the impurity], [the ’349 patent] doesn’t then have an additional – anything additional that would control for [6,7-dimethoxy-quinoline-4-ol]”)

88. I have compiled these statements to make an observation regarding what Exelixis has expressed as unpredictability in the art of formulation as well as to identify information that Exelixis has argued was necessary to successfully formulate cabozantinib (L)-malate (e.g., chemical stability, flowability, excipient compatibility studies, impact of processing such as compaction force). Such statements and arguments are relevant, although not dispositive, to my review of the priority applications and whether they would convey to a POSA the possession of the later-claimed subject matter. For example, it is either the situation that Exelixis

is correct about the unpredictable nature of each formulation that is attempted, and if so, there is no written description support for claims 1-3 of the '349 patent given their breadth and the unpredictability of formulation. Or Exelixis is incorrect, in which case the claims of the '349 patent are obvious over the prior art (*see* Section IX, below).

89. As I captured in my citations above, Exelixis's experts were forceful in arguing that critical information (e.g., chemical stability, flowability, excipient compatibility studies, impact of processing such as compaction force) was not known in the prior art. It is clear from my review of the priority documents that this information is not present. For example, the priority documents do not say anything about cabozantinib (L)-malate's flowability. The priority documents do not describe any excipient compatibility study with cabozantinib (L)-malate, rather the only information in certain documents that touches upon stability is presented for two very specific capsule formulations (*see, e.g.*, Ex. 1001 ('349 Patent) at cols 31-34), which I discuss below. The two formulations are very similar:

TABLE 3

Ingredient	mg/unit dose
Compound IB (10% drug load as Compound IA)	25
Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

TABLE 4

Ingredient	mg/unit dose
Compound IB (50% drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

90. The tested formulations contain (in different amounts) microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica and stearic acid (Table 3) and silicified microcrystalline cellulose (which is co-processed microcrystalline cellulose and fumed silica), *see* Ex. 1025 (Handbook) at 139, croscarmellose sodium, sodium starch glycolate, fumed silica and stearic acid (Table

4).⁵ The priority documents do not contain a study of cabozantinib (L)-malate's chemical stability that would aid a POSA in manufacturing any dosage form beyond the two, highly similar capsule formulations set forth in Tables 3 and 4, which themselves show that very minor changes in formulation have substantial changes in stability (*see* summary here in footnote 5, and the actual data at '349 patent at columns 31-33, Tables 7A and 8A, showing that Table 3 capsules degrade at a faster rate than Table 4 capsules under the same conditions, despite being capsules prepared in the same way and being composed of the same chemicals as added excipients). The priority documents provide no information on tablets and associated compression processes despite the opinion by Exelixis that physical force (e.g., compression when forming a tablet) is potentially important for stability⁶. In

⁵ For example, the stability data for the two very similar formulations show different stability, e.g. 3 months at 40° C/75% RH yields 22-24 ppm, and 6 months yields 40-43 ppm for Table 3 capsules, whereas for Table 4 capsules 3 months at 40° C/75% RH yields up to 10-12 ppm and 6 months yields 11-17 ppm. *See* Ex. 1001 ('349 Patent) at cols 31-33 (Tables 7A and 8A).

⁶ One obvious way in which compaction can result in changes in degradation rate is that the drug and excipients are in extreme close contact in a compacted tablet and

sum, the information that Exelixis and its experts has indicated as being necessary to prepare additional dosage forms of cabozantinib (L)-malate is simply not present in the priority documents.⁷ Consequently, the priority documents provide no teaching of how to make the formulations encompassed by the broad claims of the '349 patent, which Exelixis' experts state would be required. I discuss this in detail below.

2. The '349 patent's "priority" applications do not convey possession of claims 1-3

a. U.S. Provisional Application No. 61/441,520 (which is cross-referenced in the '349 patent) does not convey possession of claims 1-3

91. I have reviewed U.S. Provisional Application No. 61/441,520 ("the '520 provisional;" Ex. 1015). This application "relates to methods of preparing compounds useful for modulating kinase enzymatic activity." Ex. 1015 ('520 provisional) at [0001]. There are no pharmaceutical compositions or even excipients

will therefore have a greater interface for reaction, and hence faster degradation than would be seen in a loose packed powder with less contact between materials.

⁷ Although my observations provided in Paragraphs 89-90 pertain to the documents cited in the '349 patent's priority claim, it is equally true that the information is missing from the '349 patent as well.

that are mentioned in the application. I do not see any mention of “process byproducts or contaminants” or even the identification of “6,7-dimethoxy-quinoline-4-ol” as being a process byproduct or contaminant with respect to a pharmaceutical composition.

92. Accordingly, the ’520 provisional would not convey to a POSA that the inventors were in possession of the subject matter of claims 1-3.

b. U.S. Provisional Application No. 61/441,527 (which is cross-referenced in the ’349 patent) does not convey possession of claims 1-3

93. I have reviewed U.S. Provisional Application No. 61/441,527 (“the ’527 provisional;” Ex. 1016). This application relates to “[p]harmaceutical compositions and unit dosage forms.” Ex. 1016 (’527 provisional) at Abstract.

94. Although “6,7-dimethoxy-quinoline-4-ol” is referred to in the ’527 provisional, it specifically relates to impurity levels of the active substance that is used to make a formulation, and indeed the claims also are limited to the impurity level of the active “Compound 1”, not that of the composition. (e.g. claim 3: “The pharmaceutical composition of claims 1 or 2m [sic], wherein Compound 1 is admixed with 100 ppm or less of 6,7-dimethoxy-quinolone-4-ol.”).

95. I do not see any discussion of “process byproducts or contaminants” in a pharmaceutical composition as required by the ’349 claims. The ’527 provisional also does not discuss the excipient categories of fillers, disintegrants, glidants, or

lubricants and does not use the phrase “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” as recited in claims 1 and 3 of the ’349 patent. Accordingly, the ’527 provisional would not convey to a POSA that the inventors were in possession of these limitations as recited in claims 1-3.

96. In fact, there is only one reference to an “excipient” in the ’527 provisional:

Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are disclosed in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. ***The amount of carriers and excipients used in a composition can be varied according to the amount of active ingredient used (that is, Compound I).***

Ex. 1016 (’527 provisional) at [0018]. But this reference to the use of an excipient is in relation to “Compound I”, not “Compound IB” as recited in the Challenged Claims. Accordingly, this reference would not convey to a POSA the possession of a composition that included “Compound IB” with any excipient.

97. Moreover, the reference to “excipient,” “carriers,” or the citation to Remington’s for “various carriers” that may be disclosed therein in [0018] is not an instruction or disclosure for a POSA to select and include each of the categories of

“one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” that the Challenged Claims require. Nor is it clear from the ’527 provisional whether “carriers” are co-extensive, broader, or narrower than “excipients” due to separate listing of “carriers and excipients” in paragraph [0018].

98. Lastly, to the extent a POSA would rely on paragraph [0018] to attempt to stitch together the excipient categories recited in the Challenged Claims, nothing at all is disclosed about the purity that might result from the use of any excipient, carrier, or combination thereof to manufacture any dosage form under any conditions.

99. Accordingly, the ’527 provisional would not convey to a POSA that the inventors were in possession of the subject matter of claims 1-3.

c. U.S. Application No. 13/984,559 (which is cross-referenced in the ’349 patent) does not convey possession of claims 1-3

100. I have reviewed U.S. Application No. 13/984,559 (“the ’559 application;” Ex. 1017). The ’559 application does not contain a description that would convey to a POSA that the inventors possessed the subject matter of claims 1-3. The ’559 application subsequently issues as Wilson (Ex. 1002), which I discuss below in relation to my anticipation analysis.

i. There is no unrestricted disclosure of “one or more fillers; one or more disintegrants; one or more

glidants; and one or more lubricants” in the ’559 application

101. Unlike the earlier provisional applications, the ’559 application contains two recitations of the ’349 patent’s claim limitations “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants.” Ex. 1017 (’559 application) at [00104]-[00109] and [00127]-[00132]. However, it is clear from the description of the embodiments that recite this phrase that it was not the inventors’ intention that this phrase be unrestricted in regard to the excipients that must be present.

102. As an example, I have quoted the full description of the first embodiment of the ’559 application that utilises the categorical excipient limitations below:

[00104] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; *one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants.*

[00105] *In this embodiment, the filler comprises microcrystalline cellulose.*

[00106] *In this embodiment, the disintegrant comprises croscarmellose sodium.*

[00107] *In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.*

[00108] *In this embodiment, the glidant comprises fumed silica.*

[00109] *In this embodiment, the lubricant comprises stearic acid.*

Ex. 1017 ('559 application) at [00104]-[00109]. It is self-evident from the description of this “embodiment” that specific excipients are present “in this embodiment” as stated. For example, microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid must be present according to the inventors’ description. These paragraphs would not convey to a POSA that the inventors possessed an embodiment of a pharmaceutical composition that would allow for the use of any filler, any disintegrant, any glidant, and any lubricant. That would expressly contradict the description in paragraphs [00105]-[00109] for “this embodiment.” Moreover, this description says nothing about the amount of “process byproducts or contaminants”, including 6,7-dimethoxyquinoline-4-ol, that may be present in a pharmaceutical composition.

103. The only other recitation of the categorical excipient limitations does not fare any better in conveying possession of the subject matter of the Challenged Claims. I have quoted the full description of this second instance in the '559 application below

[00104] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; *one or more fillers; one or more disintegrants; one or more glidants; and*

one or more lubricants admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

[00105] *In this embodiment, the filler comprises microcrystalline cellulose.*

[00106] *In this embodiment, the disintegrant comprises croscarmellose sodium.*

[00107] *In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.*

[00108] *In this embodiment, the glidant comprises fumed silica.*

[00109] *In this embodiment, the lubricant comprises stearic acid.*

Ex. 1017 ('559 application) at [00127]-[00132]. It is again self-evident from the description of this “embodiment” that specific excipients must be present “in this embodiment” as stated. In fact, they are the exact same excipients that were recited when the same categorical excipient language was first used in the '559 application. As it concerns the categorical excipient limitations of the Challenged Claims, this description would not convey possession of any subject matter that is unrestricted as to the identity of the excipients that must be present in a pharmaceutical composition for the reasons I previously provided.

104. Therefore, these two embodiments of the '559 application would not convey to a POSA that the inventors were in possession of the subject matter of claims 1-3.

ii. **Additional broad disclosures in the '559 application do not convey possession of the subject matter of the Challenged Claims**

105. I have considered the remainder of the description in the '559 application to determine whether it would convey possession of a pharmaceutical composition that includes “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” in an unrestricted manner in a tablet/capsule having less than 200 ppm of “process byproducts or contaminants” (claim 1) or less than 200 ppm of “6,7-dimethoxy-quinoline-4-ol” (claims 2 and 3). It does not do so.

106. The '559 application contains a section entitled “Pharmaceutical Compositions” in which it introduces the concept with the following broad statement:

[0096] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound I, IA, or IB. Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein and are described in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J.C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of

carriers and excipients used in a composition can be varied proportionally according to the amount of active ingredient used (that is, Compound I, IA or IB).

Ex. 1017 ('559 application) at [0096]. This paragraph is nearly verbatim to a paragraph from the '527 provisional that I addressed above regarding “carriers” and “excipients.” For the same reasons, such broad references to excipients and carriers, while coupled with citations to books on formulations which contain general information on excipients therein, does not convey possession to a POSA of the selection of each of the individual categories of filler, disintegrant, glidant, and lubricant as recited in the '349 patent's claims. Moreover, it does not address the resulting purity of any composition that one might prepare from the selection of any excipient or combination thereof embedded within such a paragraph.

107. From my review, I have also identified other paragraphs in the '559 application that broadly refer to the inclusion of a “pharmaceutically acceptable carrier.” *See, e.g.*, Ex. 1017 ('559 application) at [0027], [00119]. For the same reasons as I have provided above, such broad terminology would not convey possession to a POSA of the subject matter of the Challenged Claims.

iii. **Additional narrow disclosures in the '559 application do not convey possession of the subject matter of the Challenged Claims**

108. I have also considered whether the disclosure of embodiments in the '559 application that are narrower than the subject matter of the Challenged Claims would convey possession of such to a POSA. Again, I conclude it would not do so.

109. The only evidence in the '559 application for the purity of any pharmaceutical composition is provided in Tables 7A, 7B, 8A, and 8B. These data correspond to the two capsule formulations provided in Tables 3 and 4. Ex. 1017 ('559 application) at [00161]-[00163]. There are no additional data in the '559 application concerning any other dosage form from which a POSA could reasonably evaluate possession of compositions that exhibit the claimed purity requirement.⁸

⁸ For example, I note that in Paragraphs [0025]-[0026] of the '559 application, two capsule formulations are provided in Tables 5 and 6. However, these tables recite the same excipients as provided in Table 3 (i.e., microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid). The only apparent difference is in the amount of each excipient. There is no evidence of purity reported for these capsules. Additionally, I note that Paragraphs [0020], [0021], and [0022] of the '559 application report the composition of three tablet

Indeed, despite the Challenged Claims expressly encompassing tablet compositions, there are no data in the '559 application providing the purity of any tablet composition.

110. The contents of the capsule compositions of Tables 3 and 4 are provided below:

formulations. However, Paragraphs [0020] and [0021] report the inclusion of “Compound I” rather than “Compound IB.” Moreover, none of these tablet compositions have any associated measurement of purity reported in the '559 application. Accordingly, these dosage forms do not provide any additional information from which a POSA could reasonably evaluate possession of compositions that exhibit the claimed purity requirement.

Table 3

Ingredient	mg/unit dose
Compound IB (10 % drug load as Compound IA)	25
Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

Table 4

Ingredient	mg/unit dose
Compound IB (50 % drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

Ex. 1017 ('559 application) at [00161]. As it pertains to the identity of the excipients included in these two capsule compositions, they are in all respects the same. *See* also Paragraph 89-90, above. Both include stearic acid, fumed silica, sodium starch glycolate, and croscarmellose sodium. The only difference in identity of excipients between the two is the inclusion of microcrystalline cellulose (Table 3) and silicified microcrystalline cellulose (Table 4), however, this is no difference in identity at all. Silicified microcrystalline cellulose is a co-processed mixture of microcrystalline cellulose and fumed silica. Ex. 1025 (Handbook) at 139. Thus, both of these excipients are present in the capsule of Table 3. As discussed above (see Paragraphs

89-90) the actual data ('349 patent at columns 31-33, Tables 7A and 8A) show that Table 3 capsules degrade at a faster rate than Table 4 capsules under the same conditions, despite being capsules prepared in the same way and being composed of the same chemicals as added excipients. A POSA would understand that the differences in stability seen for these two very similar capsules would be expected to be amplified to a great extent for certain different formulations. The very limited examples are not representative of the full scope of any filler, disintegrant, glidant, lubricant combination in any pharmaceutical composition for oral administration.

111. Even if a POSA could extrapolate information regarding the results for purity for these two capsules to any other dosage form, which Exelixis and its prior experts have argued against (*see* Section VIII.A.1, above), the inclusion of identical excipients in each of these capsule compositions would not allow a POSA to make a prediction regarding whether different excipients might be utilised in any capsule or tablet dosage form to obtain a composition that would have the requisite purity of the Challenged Claims. The two examples, being essentially identical excipients in capsules, for which stability data are presented are not representative of the range of formulations (for tablets and capsules with many possible excipients of different chemical types), which fall into the remit of the claims of the '349 patent. (see a more detailed explanation above at Paragraph 89).

112. Take the claimed category of “one or more fillers,” for example. If one looks up “filler” in the index of the Handbook, it directs the reader to the category or “Diluents (tablet/capsule).” Ex. 1025 (Handbook) at 867. Under this heading for “Diluents (tablet/capsule),” one will see ionic compounds listed (e.g., ammonium alginate and calcium lactate, calcium sulfate), different sugars (e.g., confectioner’s sugar, dextrose, lactose, fructose, mannitol and sorbitol), organic acids (e.g., fumaric acid), organic esters (e.g., glyceryl palmitostearate), modified celluloses (e.g. ethylcellulose), and polymeric carboxylates (e.g., polymethacrylates). Ex. 1025 (Handbook) at 864. There are many obvious differences between the materials. Each would be expected to behave differently in a given formulation. Microcrystalline cellulose and (the chemically identical microcrystalline cellulose in) silicified microcrystalline cellulose are only two examples (in this context essentially just a single example) of (a) known filler(s) amongst the many other known, very different alternatives (see para 129 for further explanation). A POSA would not consider microcrystalline cellulose or silicified microcrystalline cellulose to be representative of the remaining species of known fillers. Likewise, microcrystalline cellulose and silicified microcrystalline cellulose do not have structural features that would allow a POSA to visualise other types of “fillers.” There is simply too much diversity within the group and there is no information

provided in the '349 patent to navigate between selections. *See* Section VIII.A.1, above (collecting Exelixis and its Expert's prior admissions).

113. The same exercise that I have provided above for “filler” applies to each of the remaining categories of excipients. If one looks up “Disintegrants (tablet/capsule)” in the index of the Handbook, one will see organic acids (e.g., alginic acid), ionic compounds (e.g., calcium alginate and docusate sodium), amino acids (e.g., glycine), starches, celluloses, and different modified celluloses. Ex. 1025 (Handbook) at 864. There are obvious differences between the materials. Each would be expected to behave differently in a given formulation. Croscarmellose sodium and sodium starch glycolate are both super disintegrants and they are not representative of such a category or even the broader category of “disintegrants” as claimed. Likewise, Croscarmellose sodium and sodium starch glycolate do not have structural features that would allow a POSA to visualise other types of “disintegrants.” There is simply too much diversity within the group and there is no information provided in the '349 patent to navigate between selections. *See* Section VIII.A.1, above (collecting Exelixis and its Expert's prior admissions).

114. Again, the same exercise applies to the claimed category of “one or more glidants.” The Handbook identifies ionic compounds (e.g., calcium phosphate and magnesium oxide), silicates, an organic polymer (cellulose), and a mineral (talc). Ex. 1025 (Handbook) at 868. There are obvious differences between the

materials. Each would be expected to behave differently in a given formulation. Fumed silica is not representative of the category of “glidant” as claimed. Likewise, fumed silica does not have structural features that would allow a POSA to visualise other types of “glidants.” There is simply too much diversity within the group and there is no information provided in the ’349 patent to navigate between selections. *See* Section VIII.A.1, above (collecting Exelixis and its Expert’s prior admissions).

115. Finally, for the claimed category of “one or more lubricants,” the same issue exists. The Handbook identifies acids (e.g., palmitic, myristic, stearic), salt species (e.g., calcium stearate and magnesium stearate), esters, oils, polymers, and a mineral (talc). Ex. 1025 (Handbook) at 873. There are obvious differences between the materials. Each would be expected to behave differently in a given formulation. Stearic acid is not representative of the category of “lubricant” as claimed. Likewise, stearic acid does not have structural features that would allow a POSA to visualise other types of “lubricants.” There is simply too much diversity within the group and there is no information provided in the ’349 patent to navigate between selections. *See* Section VIII.A.1, above (collecting Exelixis and its Expert’s prior admissions).

116. Accordingly, the disclosure of information on the disparate purity for two capsule compositions that contain essentially identical excipient types (and only different amounts) is remarkably narrow when considering the breadth of the Challenged Claims. Such data would not convey possession to a POSA of any non-

capsule composition or even a capsule composition containing different excipients in view of the purity requirement recited in the Challenged Claims. Indeed, as I previously explained, even such similar capsules afforded very different results when evaluated for their content of 6,7-dimethoxy-quinoline-4-ol.

d. U.S. Application Nos. 15/348,716, 16/151,653, 16/706,323, and 17/152,394 (which are cross-referenced in the '349 patent) do not convey possession of claims 1-3

117. I understand that the '349 patent also claims the benefit of priority through each of U.S. Application Nos. 15/348,716 ("the '716 application," Ex. 1020), 16/151,653 ("the '653 application," Ex. 1021), 16/706,323 ("the '323 application," Ex. 1022), and 17/152,394 ("the '394 application," Ex. 1023). Ex. 1001 ('349 patent) at (60). Aside from their having an updated priority claim, the descriptions in each of these applications appear identical. I have also checked to see whether these applications were filed with a preliminary amendment that could have introduced a new description. However, no claim amendments were filed with these applications.

118. Accordingly, none of the '716 application (Ex. 1020), the '653 application (Ex. 1021), the '323 application (Ex. 1022), and the '394 application (Ex. 1023) added any description that would convey to a POSA that the inventors were in possession of the broad subject matter of the Challenged Claims.

- e. **The preliminary amendment of the '275 application (which ultimately issued as the '349 patent) adding new claims 35-37 is the only possible support for claims 1-3**

119. As I previously indicated, when the '275 application was filed, Exelixis submitted claim amendments that cancelled claims 1-34 and added new claims 35-37. Each of the “pharmaceutical composition” claims that were cancelled recited specific excipients that were present in very specific amounts (to two decimal places of mg (i.e. control to tens of nanograms level)). Ex. 1014 ('275 application) at 52-55 (claims 21-34). One example of such specificity is captured in cancelled claim 26, which is reproduced below:

26. A pharmaceutical composition according to Table 5.

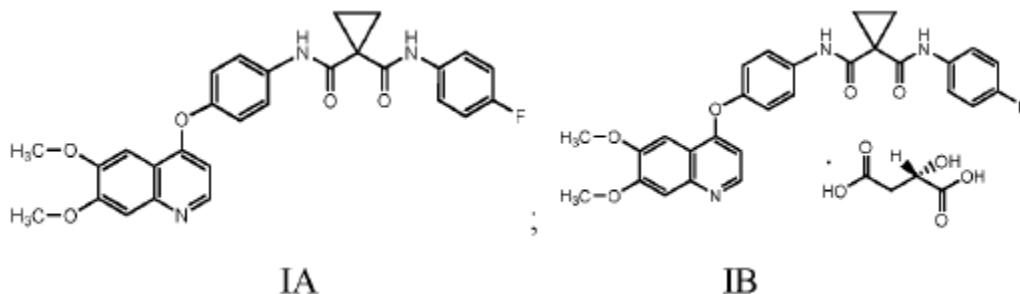
Table 5

	mg/unit dose
Ingredient	50mg
Compound IB (10 % drug load as Compound IA)	63.35
Microcrystalline Cellulose	95.39
Croscarmellose sodium	9.05
Sodium starch glycolate	9.05
Fumed Silica	0.54
Stearic acid	3.62
Total Fill Weight	181.00

Ex. 1014 at 54. This claim is specific in both excipient identification and amount per unit dose.

120. In contrast to the cancelled claims, new claims 35-37 are recited in full below:

35. (New) A pharmaceutical composition comprising Compound IA or IB;



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

36. (New) The pharmaceutical composition according to claim 35, wherein the pharmaceutical composition comprises Compound IA.

37. (New) The pharmaceutical composition according to claim 35, wherein the pharmaceutical composition comprises Compound IB.

Ex. 1014 ('275 application) at 58. Unlike their predecessors, these new claims (and indeed, what later issued as claims 1-3) are far broader as they identify no specific excipients or amounts.

121. New claim 35 is the first instance in any of the applications or their prosecution histories in which the phrase “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” is used in an unrestricted manner that did not require or identify any specific example of excipient

be present. If one uses the numbers of potential fillers, disintegrants, glidants, and lubricants that I have previously indicated are listed in the Handbook of Pharmaceutical Excipients (Ex. 1025), the permutations of possibilities are extremely large, and this expands as different amounts of excipients are used. It expands even more when tablets as well as capsule formulations are considered, as well as different production methods. As such, new claim 35 is broader than any of the earlier disclosures that I have addressed above.

122. Accordingly, new claim 35 is the first instance in which there was any attempt to convey possession of such claim breadth.⁹ There is no written description support in any of the prior applications for these new broad claims, as such, the

⁹ I understand from counsel that the U.S. Patent Office is allowed to evaluate a claim's compliance with the written description requirement in the context of a priority claim, rather than as a reason for invalidity per se. Consequently, I do not take any position here as to whether the Challenged Claims should be deemed invalid for lack of written description, but I reserve my right to do so in the appropriate forum. Instead, I understand from counsel that it is sufficient for the purposes of this declaration to establish that the Challenged Claims are not entitled to a priority date any earlier than February 8, 2021 because the earlier filed applications do not provide written description support for claims 1-3.

Challenged Claims cannot be entitled to an effective filing date earlier than February 8, 2021 i.e. the date of filing the '275 application with the inclusion of new claim 35. On this basis, Wilson (Ex. 1002) (discussed above as the '559 application) should be considered as prior art to the '349 patent.

B. Introduction to Wilson

123. Wilson issued on August 1, 2017 as U.S. Patent No. 9,717,720. Wilson was filed as U.S. Application No. 13/984,559 on February 10, 2012. Ex. 1002 (Wilson) at (10), (21)-(22). As I previously mentioned, the '349 patent cites to Wilson in the section titled "Related U.S. Application Data." Ex. 1001 ('349 patent) at (60) (citing "application No. 13/984,559, filed as application No. PCT/US2012/024591 on Feb. 10, 2012, now Pat. No. 9,717,720"). However, I explained in Section VIII.A, above, why the Challenged Claims are not entitled to claim priority back to any earlier application, including the one that issued as Wilson, and therefore why Wilson should be considered as prior art for the '349 patent. The points I make below regarding anticipation are made on the understanding that Wilson is prior art.

124. Wilson contains a nearly identical disclosure as the '349 patent, with what appear to be a few changes that relate to the section in each entitled "Cross-Reference to Related Applications." *Compare* Ex. 1002 (Wilson) at col. 1, lines 9-13 *with* Ex. 1001 ('349 patent) at col. 1, lines 9-23. Such changes are unrelated to,

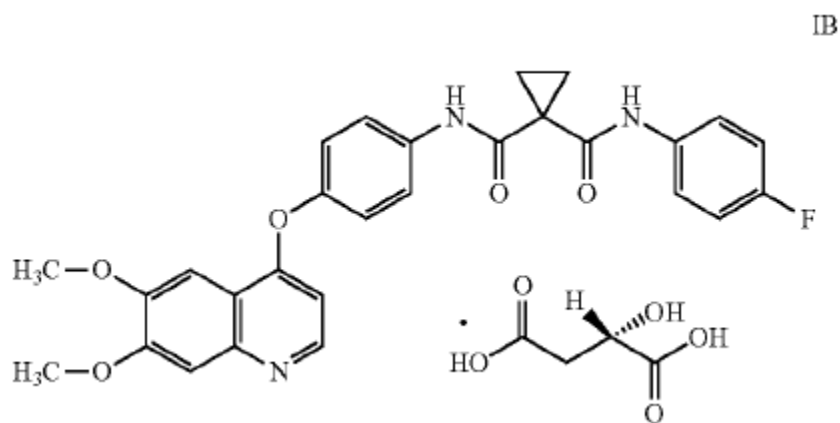
for example, the type of capsule composition described in Table 3 of the section entitled “Examples” that I rely on for my opinions regarding anticipation. *Compare* Ex. 1002 (Wilson) at col. 32, lines 24-40 *with* Ex. 1001 (’349 patent) at col. 30, line 65 to col. 31, line 10.

C. Wilson Anticipates Claims 1-3 of the ’349 patent

1. Claim 1 of the ’349 patent is anticipated by Wilson

125. This section demonstrates that Wilson discloses a pharmaceutical capsule composition that possesses all the limitations recited in claim 1 of the ’349 patent. Claim 1 of the ’349 patent is recited in full below:

1. A pharmaceutical composition for oral administration comprising Compound IB;



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

Ex. 1001 ('349 patent) at col. 34, lines 5-26.

a. Preamble of claim 1

126. The preamble of claim 1 recites: “A pharmaceutical composition for oral administration.” Ex. 1001 ('349 patent) at col. 34, lines 5-6.

127. The title of Wilson is “Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds.” Wilson refers to a “pharmaceutical composition for oral administration.” Ex. 1002 (Wilson) at col. 5, lines 36-38 (“In another aspect, the disclosure provides pharmaceutical compositions containing the compound of formula I, compound IA, or compound IB *for oral administration*”). Wilson contains an example of a “pharmaceutical capsule composition[.]” Ex. 1002 (Wilson) at col. 32, lines 24-40 (inclusive of Table 3).

128. Capsules are a type of solid dosage form that are used for oral administration. See Ex. 1004 (Aulton) at 4-5 (“The most popular *oral dosage forms* are tablets, *capsules*, suspensions, solutions and emulsions. . . . Capsules are solid dosage forms . . . enclosed in a hard or soft shell composed of gelatin. . . . The gelatin shell readily ruptures and dissolves following *oral administration*. . . .”); *see also* Section VII.B, above.

129. Accordingly, Wilson discloses an example of “[a] pharmaceutical composition for oral administration.”

b. The inclusion of “Compound IB”

130. Claim 1 requires the inclusion of “Compound IB” and also provides its structure. Ex. 1001 (’349 patent) at col. 34, lines 7-20.

131. Wilson indicates that “Compound IB” was incorporated in the pharmaceutical capsule composition recited in Table 3. Ex. 1002 (Wilson) at col. 32, lines 24-40. Although Table 3 does not provide the structure for “Compound IB,” Wilson does identify “Compound IB” by structure in other places. Ex. 1002 (Wilson) at col. 4, lines 1-20; *id.* at col. 4, lines 45-65; *id.* at col. 18, lines 5-20. The structure for compound IB provided in Wilson is the same as the structure of Compound IB recited in claim 1.

132. Accordingly, Wilson discloses including “Compound IB” in a pharmaceutical capsule composition.

c. The inclusion of “one or more fillers”

133. Claim 1 requires the inclusion of “one or more fillers.” Wilson indicates that “Microcrystalline Cellulose” was incorporated in the pharmaceutical capsule composition recited in Table 3. Ex. 1002 (Wilson) at col. 32, lines 24-40.

134. Table 3 in Wilson does not indicate that microcrystalline cellulose is a filler. However, another name for “filler” is “diluent” (*see* Ex. 1034 (Aulton) at 449) and the prior art taught that microcrystalline cellulose was one example of a diluent. Ex. 1004 (Remington) at 891 (discussing microcrystalline cellulose under the

heading “Diluents”); Ex. 1025 (Handbook) at 129 (referring to microcrystalline cellulose as a “tablet and capsule diluent” under the heading “Functional Category”); Ex. 1034 (Aulton) at 450 (“Apart from sugars, perhaps the most widely used fillers are powdered cellulose of different types The most common type of cellulose powder used in tablet formulation is microcrystalline cellulose.”); *see also* Section VII.B.1, above.

135. Accordingly, Wilson discloses including “one or more fillers” in a pharmaceutical capsule composition.

d. The inclusion of “one or more disintegrants”

136. Claim 1 requires the inclusion of “one or more disintegrants.” Wilson indicates that “Croscarmellose sodium” and “Sodium starch glycolate” were incorporated in the pharmaceutical capsule composition recited in Table 3. Ex. 1002 (Wilson) at col. 32, lines 24-40.

137. Table 3 in Wilson does not indicate that croscarmellose sodium and sodium starch glycolate are disintegrants. However, the prior art taught that each of these compounds are an example of a disintegrant. Ex. 1004 (Remington) at 893 (identifying croscarmellose and sodium starch glycolate as “super disintegrants”); Ex. 1009 (Gibson) at 398 (Table 11) (identifying sodium starch glycolate and croscarmellose sodium as “Commonly Used Disintegrants”); *see also* Section VII.B.2, above.

138. Accordingly, Wilson discloses including “one or more disintegrants” in a pharmaceutical capsule composition.

e. The inclusion of “one or more glidants”

139. Claim 1 requires the inclusion of “one or more glidants.” Wilson indicates that “Fumed silica” was incorporated in the pharmaceutical capsule composition recited in Table 3. Ex. 1002 (Wilson) at col. 32, lines 24-40.

140. Table 3 in Wilson does not indicate that fumed silica is a glidant. However, the prior art taught that fumed silica was one example of a glidant. Ex. 1025 (Handbook) at 185 (identifying “fumed silica” and “fumed silicon dioxide” as synonyms of “colloidal silicon dioxide” and listing “glidant” under the heading “Functional Category”); Ex. 1004 (Remington) at 893 (“Colloidal silicon dioxide Cab-o-sil (Cabot) is the most commonly used glidant. . . .”); Ex. 1009 (Gibson) at 389-390 (identifying “Fumed silicon dioxide” as a glidant); Ex. 1034 (Aulton) at 452 (“Today, the most commonly used glidant is probably colloidal silica. . . .”); *see also* Section VII.B.3, above.

141. Accordingly, Wilson discloses including “one or more glidants” in a pharmaceutical capsule composition.

f. **The inclusion of “one or more lubricants”**

142. Claim 1 requires the inclusion of “one or more lubricants.” Wilson indicates that “Stearic acid” was incorporated in the pharmaceutical capsule composition recited in Table 3. Ex. 1002 (Wilson) at col. 32, lines 24-40.

143. Table 3 in Wilson does not indicate that stearic acid is a lubricant. However, the prior art taught that stearic acid was one example of a lubricant. Ex. 1025 (Handbook) at 697 (identifying stearic acid as a “tablet and capsule lubricant” under the heading of “Functional Category”); Ex. 1004 (Remington) at 892 (“Commonly used ***lubricants*** include talc, magnesium stearate, calcium stearate, ***stearic acid***, glyceryl behenate, hydrogenated vegetable oils, and polyethylene glycol (PEG).”) ¹⁰; Ex. 1009 (Gibson) at 392 (Table 9) (identifying “Stearic Acid” under the sub-heading “Fluid lubricants”); Ex. 1034 (Aulton) at 453 (“The most effective of the boundary lubricants are stearic acid or stearic acid salts, primarily magnesium stearate.”); *see also* Section VII.B.4, above.

144. Accordingly, Wilson discloses including “one or more lubricants” in a pharmaceutical capsule composition.

¹⁰ Unless otherwise indicated, all bold emphases are added.

g. A “tablet or capsule” pharmaceutical composition

145. Claim 1 also recites: “wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition.” Table 3 of Wilson is an example of a “pharmaceutical *capsule* composition.” Ex. 1002 (Wilson) at col. 32, lines 24-40. Accordingly, Wilson discloses “a tablet or capsule pharmaceutical composition.”

h. A composition “essentially free of process byproducts or contaminants”

146. Claim 1 of the '349 patent further recites: “wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.” Accordingly, claim 1 requires the pharmaceutical composition to exhibit a particular property. As indicated in Section V, above, “essentially free of process byproducts or contaminants” was defined in the specification as “200 parts per million (ppm) or less of such byproducts or contaminants.” Wilson identifies “6,7-dimethoxy-quinoline-4-ol” as a type of contaminant or process byproduct. Ex. 1002 (Wilson) at col. 21, line 63 to col. 22, line 14 (stating, *inter alia*, that “[m]inimizing the concentration of contaminants or byproducts such as 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions destined for human administration is desirable”).

147. Wilson tested the capsule composition reported in Table 3 for the initial presence and subsequent formation of 6,7-dimethoxy-quinoline-4-ol and provided the results in Tables 7A-7B. Ex. 1002 (Wilson) at col. 32, line 24 to col. 33, line 40.

The results reported in Tables 7A and 7B for the capsule composition of Table 3 suggest that the result of the testing was less than 200 ppm of 6,7-dimethoxyquinoline-4-ol present in the capsule initially and over a 9 month time period. Wilson also characterises these results as indicating “that formation of 6,7-dimethoxyquinoline-4-ol was minimized to 50 ppm or less over time in the capsule formulations.” Ex. 1002 (Wilson) at col. 34, lines 62-65.

148. Accordingly, Wilson discloses an example of a pharmaceutical capsule composition that is “essentially free of process byproducts or contaminants.”

2. Claim 2 of the '349 patent is anticipated by Wilson

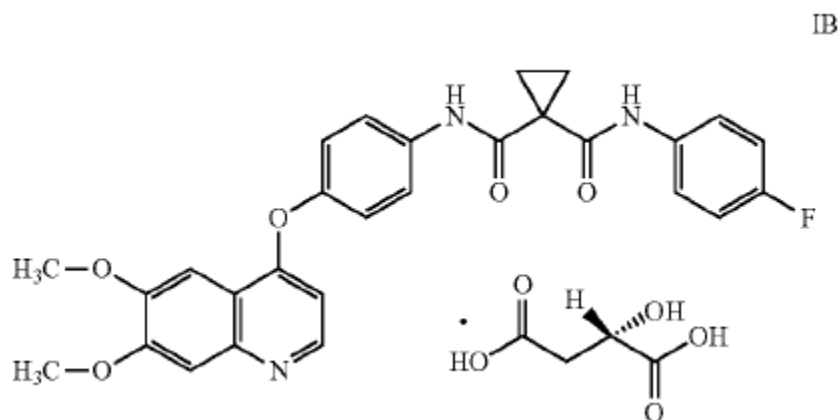
149. Claim 2 recites: “The pharmaceutical composition of claim 1, wherein the process byproduct or contaminant is 6,7-dimethoxyquinoline-4-ol in the pharmaceutical composition.” Ex. 1001 ('349 patent) at col. 34, lines 27-29.

150. I explained in Section VIII.C.1, above, how the disclosure of Wilson anticipates claim 1. I also explained in Section VIII.C.1.h, above, that the pharmaceutical capsule composition reported in Table 3 of Wilson contained 200 ppm or less of 6,7-dimethoxyquinoline-4-ol. Accordingly, for the reasons discussed above with respect to claim 1, Wilson also anticipates claim 2.

3. Claim 3 of the '349 patent is anticipated by Wilson

151. Claim 3 is recited in full below:

3. A pharmaceutical composition for oral administration comprising Compound IB;



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and wherein the pharmaceutical composition is essentially free of 6,7-dimethoxyquinoline-4-ol.

Ex. 1001 ('349 patent) at col. 34, lines 30-51.

152. The only difference between claims 1 and 3 is that claim 1 broadly requires that the pharmaceutical composition be “essentially free of process byproducts or contaminants” while claim 3 specifies that the pharmaceutical composition is “essentially free of 6,7-dimethoxy-quinoline-4-ol.” Ex. 1001 ('349 patent) at col. 34, lines 5-51.

153. In the context of claim 1, I previously explained how Wilson anticipates a pharmaceutical composition containing 200 ppm or less of 6,7-

dimethoxyquinoline-4-ol. *See* Section VIII.C.1, above. For those same reasons, Wilson anticipates claim 3.

154. However, in the interest of being thorough, I have set forth an analysis of claim 3 below explaining how Wilson anticipates claim 3.

a. Preamble of claim 3

155. The preamble of claim 3 recites: “A pharmaceutical composition for oral administration.” Ex. 1001 (’349 patent) at col. 34, lines 30-31. I explained in Section VIII.C.1.a, above, how Wilson discloses an example of “[a] pharmaceutical composition for oral administration.” My analysis applies equally to claim 3.

b. The inclusion of “Compound IB”

156. Claim 3 requires the inclusion of “Compound IB” and also provides its structure. Ex. 1001 (’349 patent) at col. 34, lines 31-45. I explained in Section VIII.C.1.b, above, how Wilson discloses including “Compound IB” in a pharmaceutical capsule composition. My analysis applies equally to claim 3.

c. The inclusion of “one or more fillers”

157. Claim 3 requires the inclusion of “one or more fillers.” Ex. 1001 (’349 patent) at col. 34, lines 46-47. I explained in Section VIII.C.1.c, above, how Wilson discloses including “one or more fillers” in a pharmaceutical capsule composition. My analysis applies equally to claim 3.

d. The inclusion of “one or more disintegrants”

158. Claim 3 requires the inclusion of “one or more disintegrants.” Ex. 1001 (’349 patent) at col. 34, lines 46-47. I explained in Section VIII.C.1.d, above, how Wilson discloses including “one or more disintegrants” in a pharmaceutical capsule composition. My analysis applies equally to claim 3.

e. The inclusion of “one or more glidants”

159. Claim 3 requires the inclusion of “one or more glidants.” Ex. 1001 (’349 patent) at col. 34, lines 46-47. I explained in Section VIII.C.1.e, above, how Wilson discloses including “one or more glidants” in a pharmaceutical capsule composition. My analysis applies equally to claim 3.

f. The inclusion of “one or more lubricants”

160. Claim 3 requires the inclusion of “one or more lubricants.” Ex. 1001 (’349 patent) at col. 34, lines 46-47. I explained in Section VIII.C.1.f, above, how Wilson discloses including “one or more lubricants” in a pharmaceutical capsule composition. My analysis applies equally to claim 3.

g. A “tablet or capsule” pharmaceutical composition

161. Claim 3 also recites: “wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition.” Ex. 1001 (’349 patent) at col. 34, lines 48-49. I explained in Section VIII.C.1.g, above, how Wilson discloses “a tablet or capsule pharmaceutical composition.” My analysis applies equally to claim 3.

h. A composition “essentially free of 6,7-dimethoxy-quinoline-4-ol”

162. Claim 3 further recites “wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.” Ex. 1001 (’349 patent) at col. 34, lines 50-51. I have been asked to apply a numerical limit of “200 ppm or less of 6,7-dimethoxy-quinoline-4-ol” with respect to this claim limitation. *See* Section V, above. Accordingly, if the pharmaceutical capsule composition of Wilson contains less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol, then it would meet this limitation. I explained in Section VIII.C.1.h, above, how Wilson discloses an example of a pharmaceutical capsule composition that contained less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol. My analysis applies equally to claim 3.

IX. GROUND 2: THE CHALLENGED CLAIMS WERE OBVIOUS

163. In this section, I explain why claims 1-3 would have been obvious to a POSA. As I explained above, in my opinion it is either the situation that Exelixis is correct about the unpredictable nature of each formulation that is attempted, and if so, there is no written description support for claims 1-3 of the ’349 patent given their breadth and the unpredictability of formulation, and the ’349 is therefore not entitled to an earlier priority date and invalid for anticipation, or Exelixis is incorrect, in which case the claims of the ’349 patent are obvious over the prior art. In setting forth my obviousness opinions, I have been asked to assume that it would have been

obvious to prepare cabozantinib (L)-malate having less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol. I understand from counsel that another expert for Petitioner will explain why that is obvious. Accordingly, my opinions are limited to the obviousness of formulating such material to arrive at the limitations of the Challenged Claims.

A. Introduction to Brown

164. Brown is titled “Malate Salt of [Cabozantinib], and Crystalline Forms Thereof for the Treatment of Cancer.” Brown relates to the (L)-, (D)-, and (DL)-malate salts of cabozantinib (referred to as “N-(4-{[6,7-bis(methoxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide”) and pharmaceutical compositions of this material. Ex. 1003 (Brown) at Abstract, [0002]-[0003], [0013]-[0014].

165. Brown describes the preparation of pharmaceutical tablet compositions. Ex. 1003 (Brown) at [0066], [0078]. Regarding the preparation of such dosage forms, Brown explains:

The pharmaceutical compositions of this disclosure may be prepared by methods know[n] in the pharmaceutical formulation art, for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). In a solid dosage forms Compound (I) is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) *fillers* or

extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) ***disintegrating agents***, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) ***lubricants***, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Id. at [0082]. For the readers convenience, I have emphasised the identification of the excipient classes recited in the Challenged Claims as they appear in Brown. Brown singles out the (L)-malate salt (which it refers to as “Compound I”) as being preferred for pharmaceutical development. *Id.* at [0051]-[0052]. Brown also teaches a preference for “solid dosage forms” and identifies capsules and tablets for oral administration as being particularly preferred. *Id.* at [0087].

166. In comparing the description of pharmaceutical compositions in both Brown and the ’349 patent, I note that Brown contains a much fuller description of those compositions and the excipients in them than that provided by the ’349 patent.

Compare Ex. 1003 (Brown) at [0082] *with* Ex. 1001 ('349 patent) at col. 20, lines 38-52. For example, Brown identifies classes of excipients such as “filler,” “disintegrating agent,” and “lubricants” while also providing specific examples of such materials. No such corresponding description is present in the comparable portion of the '349 patent.

167. Moreover, I note that both Brown and the '349 patent cite to an edition of Remington as supplying “known techniques” of preparing pharmaceutical compositions. *Compare* Ex. 1003 (Brown) at [0082] *with* Ex. 1001 ('349 patent) at col. 20, lines 38-52. I confirm that at the time of the supposed priority date of the '349 patent, which I am accepting only for purposes of this obviousness position, these basic techniques of preparing formulations were known.

B. Introduction to Remington in Relation to Obviousness

168. Remington is a treatise entitled “Remington: The Science and Practice of Pharmacy.” Remington is self-described as “[a] treatise on the theory and practice of the pharmaceutical sciences A textbook and reference work for pharmacists, physicians, and other practitioners of the pharmaceutical and medical sciences.” Ex. 1004 (Remington) at 5. Thus, a POSA would consult Remington for its description of known methods concerning the practice of pharmaceutical sciences (e.g., preparing a pharmaceutical composition). Indeed, when discussing pharmaceutical compositions, both Brown and the '349 patent cite

to Remington. Ex. 1003 (Brown) at [0082] (citing the 18th Edition of Remington); Ex. 1001 ('349 patent) at 20:38-52 (citing the 21st Edition of Remington).

169. The 45th Chapter of Remington is devoted to a discussion of “Oral Solid Dosage Forms.” Tablets and capsules receive the bulk of attention in Remington, because “[d]rug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules.” Ex. 1004 (Remington) at 889. “Tablets have been in widespread use since the latter part of the 19th century, and their popularity continues.” *Id.* They remain popular “because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste, and ease of administration).” Compressed tablets (i.e., tablets formed by compression) represent the majority of tablets in commercial use today. *Id.*

170. Remington’s explains that “[i]n addition to the active or therapeutic ingredient, tablets contain a number of inert materials” that are known as additives or excipients. Ex. 1004 (Remington) at 891. Excipients such as “diluent, binders, glidants, and lubricants” are added to a tablet formulation because such materials “help to impart satisfactory processing and compression characteristics to the formulation.” *Id.* A second group of excipients, which includes materials such as “disintegrants, surfactants, [and] colors” for non-chewable tablets are included

because they “help[] to give additional desirable physical characteristics to the finished tablet.” *Id.* Thus, it is not at all surprising that claims 1-3 of the ’349 patent require each of a filler, disintegrant, glidant, and lubricant because Remington explains that such classes of excipient are normally incorporated into tablet formulations. Indeed filler, disintegrant and lubricant can be regarded as ubiquitous in tablet formulation, and glidant addition is very common.

1. Claim 1 would have been obvious

171. This section explains why it would have been obvious to a POSA to formulate cabozantinib (L)-malate (i.e., “Compound IB”) to arrive at the pharmaceutical composition of claim 1.

a. Preamble of claim 1

172. The preamble of claim 1 recites: “A pharmaceutical composition for oral administration.” Ex. 1001 (’349 patent) at col. 34, lines 5-6. Brown refers repeatedly to pharmaceutical composition. Ex. 1003 (Brown) at Abstract (“Also disclosed are pharmaceutical compositions...”), [0002]-[0003], [0013]-[0014], [0066], [0078], and [0082]. Brown further teaches that “[s]olid dosage forms for oral administration” are preferred. *Id.* at [0087]. This is not surprising because it was common knowledge in the art that orally administered pharmaceutical compositions were preferred. *See* Section VII.B, above.

173. Accordingly, it would have been obvious to a POSA to prepare “[a] pharmaceutical composition for oral administration” in view of Brown.

b. The inclusion of “Compound IB”

174. Claim 1 requires the inclusion of “Compound IB.” Ex. 1001 (’349 patent) at col. 34, lines 7-20. Brown teaches the formulation of cabozantinib (L)-malate (i.e., “Compound IB” or the (L)-malate salt of “N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N’-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide”) as a pharmaceutical composition. Ex. 1003 (Brown) at Abstract, [0002], [0051]-[0052], [0054], [0066]. [0077]-[0078], and claim 11.

175. Brown would have motivated a POSA to include Compound IB in a tablet formulation because Brown teaches that cabozantinib (L)-malate has preferable properties for development. Ex. 1003 (Brown) at [0051] (indicating that each of the (L)-malate salt, (D)-malate salt, and (DL)-malate salt “has improved properties over N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N’-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide and its other salts”), [0054]. In particular, Brown singles out the (L)-malate salt of cabozantinib (which is referred to as “Compound I” in Brown) as having a “preferred combination of pharmaceutical properties for development” and proceeds to identify stability at 25°C/60% relative humidity (RH) and 40 °C/60%RH along with “[s]uitable solubility, and chemical/physical stability” as examples of these properties. *Id.* at [0052], [0054].

176. A POSA would have also had a reasonable expectation of success in formulating Compound IB as a pharmaceutical tablet composition. I note that both Brown and the '349 patent explicitly state that known techniques are to be used to prepare compositions. Ex. 1003 (Brown) at [0082]; Ex. 1001 ('349 patent) at col. 20, lines 38-52. I have not used hindsight in my obviousness analysis, but subsequent to the analysis I note that, in the '349 patent there are no working examples of any composition other than a capsule that was “prepared by mixing the ingredients according to processes known in the art.” *Id.* at col. 30, lines 65-67. This further supports my obviousness view that a POSA must have had a reasonable expectation of preparing a tablet composition that included Compound IB and met the recited purity limitation, if that were not the case then the '349 patent would have needed to explain to a POSA how to prepare such a composition that would do so.

177. Accordingly, it would have been obvious to a POSA to incorporate “Compound IB” into a pharmaceutical composition such as a tablet in view of Brown.

c. The inclusion of “one or more fillers”

178. Claim 1 requires the inclusion of “one or more fillers.” Brown teaches the inclusion of “fillers” in the pharmaceutical compositions of Compound IB. Ex. 1003 (Brown) at [0082] (“In a solid dosage form, Compound I [i.e., cabozantinib

(L)-malate] is admixed with at least one pharmaceutically acceptable excipient such as . . . (a) fillers or extenders . . .”).

179. It was also common to include a filler in a tablet formulation. *See* Section VII.B.1, above. A diluent is another name for “filler.” Ex. 1025 (Handbook) at 867 (“Fillers *see* Diluents (tablet/capsule)”). Remington explains that fillers/diluents are added to tablet formulations in order to provide enough bulk so that a reasonably sized tablet can be prepared. Ex. 1004 (Remington) at 891 (“Frequently, the single dose of the active ingredient is small, and an inert substance is added to increase the bulk to make the tablet a practical size for compression.”). Gibson (Ex. 1009 (Gibson) at 390) supports this as a representation of the knowledge of the POSA “for low-dose drugs, it will be necessary for the tablet to be bulked out with an inactive material termed a diluent. High-dose formulations may also use a diluent to overcome compaction problems experienced with an active substance.” Because Brown teaches that pharmaceutical compositions of cabozantinib (L)-malate may include as little as 1% of the drug, a POSA would have recognised that it would be necessary to include a filler in such low dosage tablets. Ex. 1003 (Brown) at [0078] (“The pharmaceutical compositions generally contain about 1 % to about 99% by weight of the active compound(s), or a crystalline form of the active compound(s), and 99% to 1 % by weight of a suitable pharmaceutical excipient.”). A filler is also used to improve the compressibility of the formulation, even for

higher dose drugs. Ex. 1009 (Gibson) at 390. Thus, a POSA would have been motivated to include a filler.

180. Microcrystalline cellulose is a popular example of a filler that a POSA would be likely to select for preparation of a tablet. It is “widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.” Ex. 1025 (Handbook) at 130 (internal citations omitted). Microcrystalline cellulose also exhibits “some lubricant and disintegrant properties that make it useful in tableting.” *Id.* (internal citations omitted). Remington indicates that microcrystalline cellulose “usually is used as an excipient in direct-compression formulas.” Ex. 1004 (Remington) at 891. It was also known to have “excellent compressibility.” Ex. 1009 (Gibson) at 391 (Table 8 – Common Tablet Diluents) (“Originally a direct compression excipient, now often included in granulations due to its excellent compressibility.”). Accordingly, a POSA would have been motivated to include microcrystalline cellulose as the “filler” in the tablet composition with Compound IB.

181. A POSA would have also had a reasonable expectation of success in formulating Compound IB as a pharmaceutical tablet composition in which it would have been obvious to use a filler such as microcrystalline cellulose. I note that both Brown and the '349 patent explicitly state that known techniques are to be used to

prepare compositions. Ex. 1003 (Brown) at [0082]; Ex. 1001 ('349 patent) at col. 20, lines 38-52. I have not used hindsight in my obviousness analysis, but subsequent to the analysis I note that, in the '349 patent there are no working examples of any composition other than a capsule that was “prepared by mixing the ingredients according to processes known in the art.” *Id.* at col. 30, lines 65-67. This further supports my obviousness view that a POSA must have had a reasonable expectation of preparing a tablet composition that included a filler such as microcrystalline cellulose and met the recited purity limitation. If that were not the case then the '349 patent would have needed to explain to a POSA how to prepare such a composition that would do so.

182. Accordingly, a POSA would have found it obvious to include “one or more fillers” in a pharmaceutical composition such as a tablet in view of Brown alone. A POSA would have further found it obvious to specifically include microcrystalline cellulose in further view of Remington.

d. The inclusion of “one or more disintegrants”

183. Claim 1 requires the inclusion of “one or more disintegrants.” Brown teaches the inclusion of disintegrants (i.e., “disintegrating agents”) in the pharmaceutical compositions of Compound IB. Ex. 1003 (Brown) at [0082] (“In a solid dosage form, Compound I [i.e., cabozantinib (L)-malate] is admixed with at

least one pharmaceutically acceptable excipient such as . . . (d) disintegrating agents, as for example . . . croscarmellose sodium . . .”).

184. It was also common to include a disintegrant in a tablet formulation. *See* Section VII.B.2, above. “A disintegrant is a substance or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration.” Ex. 1004 (Remington) at 893. A disintegrant facilitates the release of the drug from the tablet, which is intended to occur “as efficiently as possible to allow rapid dissolution” of the drug. *Id.* Thus, a POSA would have been motivated to include a disintegrant in the tablet composition with Compound IB.

185. Brown identified “croscarmellose sodium” as an example of a disintegrant to include in its pharmaceutical compositions with Compound IB. Ex. 1003 (Brown) at [0082]. Croscarmellose sodium is a “super disintegrant,” which is a type of disintegrant that has gained in popularity for its efficient disintegration properties. Ex. 1004 (Remington) at 893 (identifying croscarmellose, crospovidone, and sodium starch glycolate as super disintegrants). Thus, popularity aside, a POSA would have been motivated to select croscarmellose sodium for inclusion as a disintegrant in view of Brown and Remington’s.

186. A POSA would have also had a reasonable expectation of success in formulating Compound IB as a pharmaceutical tablet composition, in with it would have been obvious to use a disintegrant such as croscarmellose sodium. I note that

both Brown and the '349 patent explicitly state that known techniques are to be used to prepare compositions. Ex. 1003 (Brown) at [0082]; Ex. 1001 ('349 patent) at col. 20, lines 38-52. I have not used hindsight in my obviousness analysis, but subsequent to the analysis I note that, in the '349 patent there are no working examples of any composition other than a capsule that was “prepared by mixing the ingredients according to processes known in the art.” *Id.* at col. 30, lines 65-67. This further supports my obviousness view that a POSA must have had a reasonable expectation of preparing a tablet composition that included a disintegrant, including croscarmellose sodium, and met the recited purity limitation. If that were not the case then the '349 patent would have needed to explain to a POSA how to prepare such a composition that would do so.

187. Accordingly, a POSA would have found it obvious to include “one or more disintegrants” in a pharmaceutical composition such as a tablet in view of Brown alone. A POSA would have further found it obvious to specifically include croscarmellose sodium in view of either Brown or Remington.

e. The inclusion of “one or more glidants”

188. Claim 1 requires the inclusion of “one or more glidants.” It was common knowledge to include a glidant in a tablet formulation. *See* Section VII.B.3, above. Glidants were a recognised manufacturing aid known to improve the flow of the particulate tablet formulation into the tablet die for compression. *Id.* Ex. 1004

(Remington) at 893. Glidants accomplish this “by interposing between particles to reduce surface rugosity, thus preventing interlocking of particles and lowering the interparticulate friction.” Ex. 1009 (Gibson) at 389. Remington identifies “[c]olloidal silicon dioxide” as “the most commonly used glidant.” Synonyms of “colloidal silicon dioxide” include the term “fumed silica.” Ex. 1025 (Handbook) at 185. The ’349 patent uses the “fumed silica” nomenclature rather than the term “colloidal silicon dioxide.” Ex. 1001 (’349 patent) at Table 3.

189. A POSA would have been motivated to include a glidant in a tablet formulation to capitalise on the improvement in resulting flow properties to aid manufacturing as explained above. It was known that a formulation with good flow would be less likely to have unacceptable variations in tablet weight which can result from non-uniform transfer of the formulation to the tablet die. Furthermore, a POSA would have been motivated to select fumed silica as the glidant for inclusion in a tablet formulation because, popularity and normal use aside, “[t]he fumed silicon dioxides are perhaps the most effective glidants.” Ex. 1009 (Gibson) at 390; Ex. 1025 (Handbook) at 186 (“Colloidal silicon dioxide is widely used in pharmaceuticals....”). “Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.” Ex. 1025

(Handbook) at 186. Accordingly, a POSA would have been motivated to select fumed silica as the glidant.

190. A POSA would have also had a reasonable expectation of success in formulating Compound IB as a pharmaceutical tablet composition with a glidant such as fumed silica. I note that both Brown and the '349 patent explicitly state that known techniques are to be used to prepare compositions. Ex. 1003 (Brown) at [0082]; Ex. 1001 ('349 patent) at col. 20, lines 38-52. I have not used hindsight in my obviousness analysis, but subsequent to the analysis I note that, in the '349 patent there are no working examples of any composition other than a capsule that was “prepared by mixing the ingredients according to processes known in the art.” *Id.* at col. 30, lines 65-67. This further supports my obviousness view that a POSA must have had a reasonable expectation of preparing a tablet composition that included a glidant, including fumed silica, and met the recited purity limitation. If that were not the case then the '349 patent would have needed to explain to a POSA how to prepare such a composition that would do so.

191. Accordingly, a POSA would have found it obvious to include “one or more glidants” in a pharmaceutical composition such as a tablet in view of Brown and Remington. A POSA would have further found it obvious to specifically include fumed silica as the glidant in view of Brown and Remington.

f. The inclusion of “one or more lubricants”

192. Claim 1 requires the inclusion of “one or more lubricants.” Brown teaches the inclusion of lubricants in its pharmaceutical compositions. Ex. 1003 (Brown) at [0082] (“In a solid dosage form, Compound I [i.e., cabozantinib (L)-malate] is admixed with at least one pharmaceutically acceptable excipient such as . . . (i) lubricants, as for example . . . magnesium stearate . . .”).

193. It was common knowledge to include a lubricant in a tablet formulation. *See* Section VII.B.4, above. Lubricants, or more correctly “die wall lubricants,” facilitate removal of the tablet from the die of the tablet machine after compaction. *See, e.g.*, Ex. 1004 (Remington) at 892 (“facilitate ejection of the tablets from the die cavity”); Ex. 1009 (Gibson) at 391-392 (explaining the role of “die-wall lubricants excipients, which reduce the friction between the tablet surface and the die wall during and after compaction to enable easy ejection of the tablet”). Thus, a POSA would have been motivated to include “one or more lubricants” in the tablet composition to facilitate manufacturing of the tablet.

194. It is not surprising that Brown identified “magnesium stearate and the like” as an example of a lubricant for use in its compositions with cabozantinib (L)-malate. Ex. 1003 (Brown) at [0082]. “Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, hydrogenated vegetable oils, and polyethylene glycol (PEG).” Ex. 1004 (Remington) at 892.

However, there are reasons why a POSA may prefer to use one lubricant over another common lubricant. For example, compatibility of the lubricant with the active ingredient may be of concern. *Id.* at 892 (“In selecting a lubricant, proper attention must be given to its compatibility with the drug agent.”).

195. Remington’s provides 18 examples of tablet formulations. Ex. 1004 (Remington) at 912-914. Six of these examples used stearic acid as the lubricant. *Id.* Five of these examples used magnesium stearate as the lubricant. *Id.* Four of these examples used calcium stearate as the lubricant. *Id.* See also Ex. 1025 (Handbook) at 697 (“Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant.”) Thus, a POSA would have been motivated to select a commonly used lubricant such as magnesium stearate or stearic acid for inclusion in a tablet composition.

196. A POSA would have also had a reasonable expectation of success in formulating Compound IB as a pharmaceutical tablet composition with a lubricant such as magnesium stearate or stearic acid. I note that both Brown and the ’349 patent explicitly state that known techniques are to be used to prepare compositions. Ex. 1003 (Brown) at [0082]; Ex. 1001 (’349 patent) at col. 20, lines 38-52. I have not used hindsight in my obviousness analysis, but subsequent to the analysis I note that, in the ’349 patent there are no working examples of any composition other than

a capsule that was “prepared by mixing the ingredients according to processes known in the art.” *Id.* at col. 30, lines 65-67. This further supports my obviousness view that a POSA must have had a reasonable expectation of preparing a tablet composition that included a lubricant, such as magnesium stearate or stearic acid, and met the recited purity limitation. If that were not the case then the ’349 patent would have needed to explain to a POSA how to prepare such a composition that would do so.

197. Accordingly, a POSA would have found it obvious to include “one or more lubricants” in a pharmaceutical composition such as a tablet in view of Brown and Remington. A POSA would have further found it obvious to include a lubricant such as magnesium stearate or stearic acid in view of Brown and Remington.

g. A “tablet or capsule” pharmaceutical composition

198. Claim 1 also recites: “wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition.” I previously explained that tablets and capsules are the two most common solid oral dosage forms. *See* Section VII.B, above; Ex. 1004 at 889 (“Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules.”).

199. However, tablets are the most popular dosage forms. Ex. 1009 (Gibson) at 188. I previously listed nine advantages of tablets that were straight from Remington’s discussion of why tablets are such a popular dosage form. Ex.

1004 (Remington) at 889. A POSA would have been motivated to prepare a pharmaceutical tablet composition of Compound IB in view of these advantages. Indeed, tablets were a “particularly preferred” version of solid dosage forms identified in Brown. Ex. 1003 (Brown) at [0087] (“Because the active compound(s), or a crystalline form of the active compound(s), is maintained during their preparation, solid dosage forms are preferred for the pharmaceutical composition of this disclosure. Solid dosage forms for oral administration, which includes capsules, *tablets*, pills, powders, and granules, are particularly preferred.”).

200. A POSA would have also had a reasonable expectation of success in formulating Compound IB as a pharmaceutical tablet composition. I note that both Brown and the '349 patent explicitly state that known techniques are to be used to prepare compositions. Ex. 1003 (Brown) at [0082]; Ex. 1001 ('349 patent) at col. 20, lines 38-52. I have not used hindsight in my obviousness analysis, but subsequent to the analysis I note that, in the '349 patent there are no working examples of any composition other than a capsule that was “prepared by mixing the ingredients according to processes known in the art.” *Id.* at col. 30, lines 65-67. This further supports my obviousness view that a POSA must have had a reasonable expectation of preparing a tablet composition that met the recited purity limitation. If that were not the case then the '349 patent would have needed to explain to a POSA how to prepare such a composition that would do so.

201. Accordingly, a POSA would have found it obvious to prepare “a tablet or capsule pharmaceutical composition” in view of Brown alone or in view of both Brown and Remington.

h. A composition “essentially free of process byproducts or contaminants”

202. Claim 1 further recites: “wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.” Accordingly, claim 1 requires the pharmaceutical composition to exhibit a particular result. As indicated in Section V, above, “essentially free of process byproducts or contaminants” was defined in the specification as “200 parts per million (ppm) or less of such byproducts or contaminants.” I have applied this impurity limit in my obviousness analysis below.

i. A pharmaceutical composition containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol would have been obvious

203. I have been asked by counsel to assume for purposes of my opinions expressed herein that it would have been obvious to obtain “Compound IB” containing 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol. I understand from counsel that someone else will address whether it would have been obvious to obtain such material. Accordingly, my opinions expressed herein relate to whether a POSA would have found it obvious to formulate such material to obtain a pharmaceutical

composition that still contained 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol. My conclusion is that it would have been obvious.

204. As a general matter, a POSA would have been motivated to prepare a pharmaceutical composition that limited impurities, to the extent possible and certainly to within acceptable limits. Additionally, a POSA would have known that quinoline was genotoxic¹¹. Ex. 1036 (EPA) at 11-13 which would provide motivation to investigate and consider a limit for 6,7-dimethoxy-quinoline-4-ol present in both the API to be formulated or in the formulation itself. Exelixis's expert also admitted that a quinoline-containing compound such as 6,7-dimethoxy-quinoline-4-ol was potentially genotoxic. *Id.*; Ex. 1019 (Trial Volume III) at 769:5-770:4 (Exelixis expert stating: "it's a structure that has to be furtherly -- further evaluated. Because, of course, as we know, there are lots of quinolines that are actually drugs. And there are quinolines that are -- that are genotoxic. So you have to -- you have to say -- you have to study each particular quinoline to determine whether it's useful, not harmful or harmful."). Accordingly, a POSA would have

¹¹ I use the definition of POSA as proposed by Exelixis (see Paragraph 31), where the POSA is part of a team of scientists of different skill sets that are developing a composition ("...a team which would have included synthetic organic chemists and process chemists, formulation scientists, analytical scientists and clinicians").

been motivated to consider regulatory guidance regarding the identification and treatment of known or suspected genotoxic impurities.

205. Regulatory guidance on “Genotoxic and Carcinogenic Impurities in Drug Substances and Products” requires identifying and evaluating starting materials, anticipated reaction products, and/or impurities with known or suspected genotoxic or carcinogenic potential. Ex. 1037 (FDA Guidance) at 1 (“This guidance provides specific recommendations regarding the safety qualification of impurities with known or suspected genotoxic or carcinogenic potential. . . . This guidance addresses synthetic impurities and degradants in drug substances, but does not otherwise address the genotoxicity or carcinogenicity of actual drug substances or intended drug product ingredients. This guidance also applies to known starting materials or anticipated reaction products.”). I understand from counsel that another expert for Azurity has identified 6,7-dimethoxy-quinoline-4-ol is a starting material, degradant, and potential impurity in cabozantinib (L)-malate. *See also* Ex. 1019 (Trial Volume III) at 759:8-12 (Exelixis expert confirming that “1-1” [i.e., 6,7-dimethoxy-quinoline-4-ol] could form as a degradation product when cabozantinib (L)-malate was exposed to heat and water). Accordingly, pursuant to regulatory guidance, a POSA would have been motivated to assess the genotoxicity, and then as appropriate to test for its presence as a synthetic impurity and degradant in the cabozantinib (L)-malate drug substance and drug product and institute any necessary

limits on 6,7-dimethoxy-quinoline-4-ol to comply with the guidance. *See, e.g.*, Ex. 1037 (FDA Guidance) at 6 (“However, in cases where the presence of an impurity with genotoxic or carcinogenic potential is identified or where such an impurity may be expected based on the synthetic pathway, steps should be taken during the clinical development stage to address safety concerns associated with these impurities.”); *id.* at 11 (“In cases where attempts to prevent the formation of an impurity of concern and/or to reduce the impurity to an acceptable level, as per Table 1 are not possible, further characterization of the genotoxic and carcinogenic potential should be conducted”). This indicates that the first approach is to modify the substance/composition in order to eliminate the impurity of potential concern, and if that is not possible to test it for its risk and set appropriate limits for it. *See id.* at 12 (Table 2) “[i]f [an] impurity with genotoxic and carcinogenic potential is identified” then options are to “Modify synthetic pathway to eliminate the impurity, if possible” or “Conduct genotoxicity assays to characterize the genotoxic potential if not already known” and/or “Set specification to that associated with a potential daily impurity exposure supported by compound-specific risk assessment or relevant qualification threshold (see Table 1)”.

206. Both the FDA and the EMEA limit the amount of a genotoxic impurity (in the “Table 1” that is mentioned in the sections that I cite to the paragraph above) to be between less than 120 µg/day to less than 1.5 µg/day depending upon the

duration of treatment. Ex. 1037 (FDA Guidance) at 7, 11 (Table 1); Ex. 1038 (EMA Guidance) at 6-7. A POSA would have known from the initial disclosure of cabozantinib in U.S. 7,579,473 that the amount of the compound stated to be administered to a patient was “about 0.1 to about 1,000 mg per day.” Ex. 1008 (’473 patent) at 274:52-57. Thus, a POSA could use the guidance documents to determine the suggested limit of a potentially genotoxic impurity such as 6,7-dimethoxy-quinoline-4-ol. For the range of 0.1 mg to 1000 mg per day, the limit for such a genotoxic impurities would have been < 120 ppm to as low as < 1.5 ppm depending upon treatment duration. *See* Ex. 1038 (EMA Guidance) at 7 (Eq. 1) (substituting 1000 mg or 1 g as the dose and either 120 µg/day or 1.5 µg/day as the Threshold of Toxicological Concern). Accordingly, a POSA would have been motivated to attempt to prevent the formation of, or if not possible then to test and/or set a specification to limit the amount of, a potentially genotoxic impurity, such as 6,7-dimethoxy-quinoline-4-ol, to be at least as low as permitted by the guidance. *See, e.g.,* Ex. 1037 (FDA Guidance) at 12 (Table 2) (identifying these options for both an IND and a marketing application). Reducing the amount of impurity would have been a team effort between chemists preparing the API and the formulators preparing the finished dosage form.

207. With respect to the formulation of cabozantinib (L)-malate, and as I have previously explained, a tablet dosage form would contain excipients in addition

to cabozantinib (L)-malate. I understand that Exelixis and experts on its behalf have previously argued that simply having cabozantinib (L)-malate with 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol is not necessarily sufficient to formulate it and retain such purity. *See* Section VIII.A.1, above (identifying these statements). As I previously indicated, if these experts are correct in their arguments regarding unpredictability, then claims 1-3 of the '349 patent are at a minimum not entitled to their priority date.

208. Despite these statements, in Sections IX.B.1.c-f, above, I explained why the classes of excipients, and indeed the individual excipients chosen by Exelixis for use in the composition reported in Table 3 (i.e., microcrystalline cellulose, croscarmellose sodium, fumed silica, and stearic acid) would have been obvious excipient selections for the preparation of a tablet composition. Moreover, the '349 patent later confirmed that a capsule composition could be prepared using the obvious excipients that I have identified, and such a composition contained 200 ppm or less of 6,7-dimethoxy-quinoline-4-ol (although, as I previously indicated, the different amounts of excipients had a substantial effect on the measured amount of this impurity). Ex. 1001 ('349 patent) at Table 7A-7B.

209. Once again, I note that both Brown and the '349 patent explicitly state that known techniques are to be used to prepare compositions. Ex. 1003 (Brown) at [0082]; Ex. 1001 ('349 patent) at col. 20, lines 38-52. Moreover, in the '349 patent

that the capsule composition was “prepared by mixing the ingredients according to processes known in the art.” *Id.* at col. 30, lines 65-67. The only instruction as to preparing a tablet is: “Tablet formulations are prepared by combining, blending, and compacting the components of the tablet compositions.” Ex. 1001 (’349 patent) at col. 21, lines 41-43. Thus, a POSA must have had a reasonable expectation of preparing tablet and capsule compositions that exhibited the requisite purity from obvious components or else the ’349 patent would have needed to provide a more detailed explanation of the materials and methods that were necessary to do so.

210. Accordingly, a POSA would have had a reasonable expectation of obtaining a tablet of Compound IB containing “one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants” that contained less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol.

j. **There was a motivation to combine Brown and Remington’s disclosures**

211. As I have explained above, Brown alone discloses nearly all the limitations of claim 1 (i.e., pharmaceutical composition for oral administration, Compound IB, fillers such as microcrystalline cellulose, disintegrants such as croscarmellose sodium, lubricants such as magnesium stearate and the like, and tablets). To the extent that any remaining limitation of the formulation, or the particular choice of species to include in the formulation, was not provided by Brown

and common knowledge in the formulation arts, then it would have been obvious for a POSA to turn to Remington, which is cited in Brown, or any standard text on pharmaceutical formulation (such as those which I refer to in this declaration) to supply any additional knowledge.

212. First, Brown itself directs a reader to consider known references, including the 18th Edition of Remington, for preparing pharmaceutical compositions. Ex. 1003 (Brown) at [0082] (“The pharmaceutical compositions of this disclosure may be prepared by methods know[n] in the pharmaceutical formulation art, for example, see Remington’s Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990).”). Brown further invites the reader to explore formulation references by referring to certain excipients “and the like.” *Id.* By calling the reader’s attention to explore “like” excipients without their identification, there is an implication in Brown that a reader should consult other references. Accordingly, a POSA would have been motivated to consider the Remington treatise.

2. Claim 2 is obvious over Brown in view of Aulton

213. Claim 2 recites: “The pharmaceutical composition of claim 1, wherein the process byproduct or contaminant is 6,7-dimethoxyquinoline-4-ol in the pharmaceutical composition.” Ex. 1001 (’349 patent) at col. 34, lines 27-29.

214. I explained in Section IX.B.1, above, why the pharmaceutical composition of claim 1 would have been obvious. I also explained in Sections IX.B.1.h-i, above, why a pharmaceutical tablet composition containing 200 ppm or less of 6,7-dimethoxyquinoline-4-ol would have been obvious. Accordingly, for the reasons discussed above with respect to claim 1, claim 2 would have been obvious.

3. Claim 3 obvious over Brown in view of Aulton

215. The only difference between claims 1 and 3 is that claim 1 broadly requires that the pharmaceutical composition is “essentially free of process byproducts or contaminants” while claim 3 specifies that the pharmaceutical composition is “essentially free of 6,7-dimethoxy-quinoline-4-ol.” Ex. 1001 (’349 patent) at col. 34, lines 5-51.

216. I previously explained, in the context of claim 1, why a pharmaceutical composition containing 200 ppm or less of 6,7-dimethoxyquinoline-4-ol would have been obvious. *See* Section IX.B.1, above. Accordingly, for the reasons discussed above with respect to claim 1, claim 3 would have been obvious.

217. However, in the interest of being thorough, I have set forth an analysis of claim 3 below explaining how Wilson anticipates claim 3.

a. Preamble of claim 3

218. The preamble of claim 3 recites: “A pharmaceutical composition for oral administration.” Ex. 1001 (’349 patent) at col. 34, lines 30-31. I explained in

Section IX.B.1.a, above, why such a preamble would have been obvious. My analysis applies equally to claim 3.

b. The inclusion of “Compound IB”

219. Claim 3 requires the inclusion of “Compound IB” and also provides its structure. Ex. 1001 (’349 patent) at col. 34, lines 31-45. I explained in Section IX.B.1.b, above, why including “Compound IB” in a pharmaceutical tablet composition would have been obvious. My analysis applies equally to claim 3.

c. The inclusion of “one or more fillers”

220. Claim 3 requires the inclusion of “one or more fillers.” Ex. 1001 (’349 patent) at col. 34, lines 46-47. I explained in Section IX.B.1.c, above, why including “one or more fillers” in a pharmaceutical tablet composition would have been obvious. My analysis applies equally to claim 3.

d. The inclusion of “one or more disintegrants”

221. Claim 3 requires the inclusion of “one or more disintegrants.” Ex. 1001 (’349 patent) at col. 34, lines 46-47. I explained in Section IX.B.1.d, above, why including “one or more disintegrants” in a pharmaceutical tablet composition would have been obvious. My analysis applies equally to claim 3.

e. The inclusion of “one or more glidants”

222. Claim 3 requires the inclusion of “one or more glidants.” Ex. 1001 (’349 patent) at col. 34, lines 46-47. I explained in Section IX.B.1.e, above, why

including “one or more glidants” in a pharmaceutical tablet composition would have been obvious. My analysis applies equally to claim 3.

f. The inclusion of “one or more lubricants”

223. Claim 3 requires the inclusion of “one or more lubricants.” Ex. 1001 (’349 patent) at col. 34, lines 46-47. I explained in Section IX.B.1.f, above, why including “one or more lubricants” in a pharmaceutical tablet composition would have been obvious. My analysis applies equally to claim 3.

g. A “tablet or capsule” pharmaceutical composition

224. Claim 3 also recites: “wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition.” Ex. 1001 (’349 patent) at col. 34, lines 48-49. I explained in Section IX.B.1.g, above, why prepared a pharmaceutical tablet composition would have been obvious. My analysis applies equally to claim 3.

h. A composition “essentially free of 6,7-dimethoxy-quinoline-4-ol”

225. Claim 3 further recites “wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.” Ex. 1001 (’349 patent) at col. 34, lines 50-51. I have been asked to apply a numerical limit of “200 ppm or less of 6,7-dimethoxy-quinoline-4-ol” with respect to this claim limitation. I explained in Section IX.B.1.h-i, above, why a pharmaceutical tablet composition that contained

less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol would have been obvious. My analysis applies equally to claim 3.

i. Motivation to Combine Brown and Remington

226. I explained in Section IX.B.1.j, above, why a POSA would have been motivated to combine the disclosures of Brown and Remington. My analysis applies equally to claim 3.

X. NO SECONDARY CONSIDERATIONS

227. I understand that in the district court litigation between MSN and Exelixis, that Exelixis asserted three secondary considerations, long-felt but unmet need, unexpected results, and commercial success. Ex. 1026 (Trial Opinion) at 57. However, the district court stated: “Exelixis has not proven by a preponderance of the evidence that Cabometyx met a long-felt but unmet need, or that there were unexpected results.” *Id.* Although the district court did state that “Exelixis has proven by preponderance of the evidence that Cabometyx was a commercial success and that there is a nexus between Claim 3 of the ’349 patent and the secondary considerations,” the court further noted that “the commercial success of Cabometyx is not a strong indicator of non-obviousness.” *Id.*

228. I also understand from counsel that the law recognises that a claim that is clearly obvious is not saved by secondary considerations, particularly weak ones.

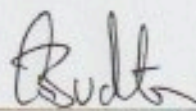
229. Accordingly, I am not aware of any secondary considerations of non-obviousness that affect my opinions disclosed herein. Should Exelixis provide any in response, I reserve my right to address them.

XI. CONCLUSION

230. For the reasons described above, claims 1-3 of the '349 patent are anticipated by Wilson and a POSA would have found it obvious over Brown in view of Remington to formulate cabozantinib (L)-malate having less than 200 ppm of 6,7-dimethoxy-quinoline-4-ol to arrive at claims 1-3.

231. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further 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: 18 November 2024

By: 

Graham Buckton, Ph.D.

Exhibit A

Graham Buckton

BPharm, AKC, C.Dir, PhD, DSc, CChem, FRSC, FAPS, FAAPS, FRPharmS

1) Personal Details

Name: Graham Buckton **Date of Birth:** 30.4.60 **Status:** Married, 2 children

Nationality: British **Born:** Brighton, Sussex.

2) Fellowship/Membership of Professional Bodies/Associations:

The Royal Pharmaceutical Society of Great Britain **made a Fellow in April 1997;**

The Royal Society of Chemistry **made a Fellow in 1997;**

American Association of Pharmaceutical Scientists **made a Fellow in 1997;**

Academy of Pharmaceutical Sciences **made a Fellow in 2009.**

Member of MENSA. (lapsed)

Associations/Clubs – The Athenaeum. The Worshipful Society of Apothecaries. MCC. North Hants Golf Club. Leander Club.

3) Awards/Honours

2012 Freedom of the City of London.

2003 Science Chairman for the British Pharmaceutical Conference.

2000 First recipient of the Academy of Pharmaceutical Sciences Medal, for services to UK Pharmaceutical Sciences (relating to the establishment of the APS by negotiating a merger between the previously competing activities of "UKAPS" and the "Pharmaceutical Sciences Group").

1998 Stig Sunner Award, presented by the USA Calorimetry Conference "in recognition of research and contributions to thermodynamics and thermochemistry" to a scientist under the age of 40.

1998 Foss Near Infra red European Users Group award for best new work in near-IR spectroscopy

1993 British Pharmaceutical Conference Science Medal

1992 Pfizer Award for "excellence in published research", granted for "imaginative use of thermodynamic principles in the understanding and design of drug delivery systems". The Pfizer Awards are not open to application, and are given on the basis of review of published literature by senior Pfizer scientists, and senior academic advisers

4) Education

Institute of Directors 2012 Diploma in Company Direction

Institute of Directors 2012 Certificate in Company Direction.

University of London 1997 Doctor of Science for research work in pharmaceutical materials science.

King's College (KQC), University of London, Manresa Road.

September 1982 - August 1985 **Ph.D.** Title: Assessment of the wettability of powders
1985-1987 **Associate of King's College** (AKC) Examined course in Philosophy (part time)

Chelsea College, University of London, Manresa Road.

September 1978 - June 1981. **B.Pharm.** (Hons.)

Varndean Sixth Form College, Brighton, Sussex.

September 1976 - July 1978; AO level - Human Biology; 3 A levels - Mathematics, Chemistry and Physics.

Brighton Secondary Technical School.

September 1971 - July 1976, June 1975 3 O levels; June 1976 8 O levels

5) Present Employment

Managing Director of Buckton Consulting

Emeritus Professor of Pharmaceutics, UCL School of Pharmacy, University of London and

5.1) Buckton Consulting (a part of Brighton City Property Ltd)

Consultancy service covering:

- 1) pharmaceutical physical form, formulation development, GMP manufacturing and regulatory considerations.
- 2) Expert witness

I have acted as a consultant to industrial companies in UK, mainland Europe, middle east and USA. This is a diverse role involving advice on materials science, formulation (inhalation and oral products), regulatory, and as an expert witness in patent litigation.

6) Previous employment

Pharmaterials Ltd

I founded Pharmaterials Ltd in 2000 to transfer advanced materials characterisation techniques into a commercial contract service. I developed the company to cover preformulation, especially salt and polymorph selection, formulation development (oral and inhalation) and GMP clinical trial manufacture in a large purpose built facility in Reading UK. The % of my time linked to this activity expanded (to 70%) to keep pace with the needs of the success of a growing enterprise.

Pharmaterials operates on a fee for service basis and has grown through profits on income.

Pharmaterials won the Queen's Award for Enterprise in 2008 for international trade.

At the time of my departure 36 staff were employed.

In keeping with the success of the business, the majority stake in Pharmaterials was sold to PII in January 2008. The remaining stake was sold in September 2012 at which stage I exited from my role as Chief Executive of the company, where I acted to directly oversee the strategic and business planning, financial management, business development, staffing and resource provision.

School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX 1988 - 2015

January 2001 – April 2007 Head of Department of Pharmaceutics.

Management and Leadership

Of the School

As Head of Department much of my time was spent discussing the management of the School, including preparations for previous and future research assessment exercise, teaching quality audit, day-to-day management and strategic directions.

Internal committees:

Member of School Council. Member of the following committees of Council: Finance, Nominations, Governance, Fellowship and Honorary Degrees, Audit Committee.

Other School Committee work: Academic Board, Policy and Resources Executive, Policy and Resources, Research Strategy Task Force, Academic Standards, Undergraduate Studies Management Group, Pharmacy Advisory, Library and Information Services, Joint Committee of Academic Board and Students, Higher Degrees, Taught Postgraduate Studies.

Of the Department of Pharmaceutics

Pharmaceutics had 13 fte academic staff, and some 70 research staff/PhDs, also 5 technicians, and support services (workshop and wash-up). In my time as Head all bar 1 member of academic staff was either appointed or promoted.

I managed the staff development and infrastructure for the departmental activities, to maximise the productivity, whilst working within strict financial limits.

I appointed senior industrialists to positions of visiting professor to develop strategy for direction and funding.

Teaching:

Instigator of MSc in Drug Delivery (developed concept and course, then transferred to staff to manage)

Provide direction for all teaching in Pharmaceutics through regular reviews with staff, informed by staff views and course review reports. Allocate staff to lead the Pharmaceutics teaching in each semester, manage projects and dissertations, and the examination processes.

I was part of the small design team that initiated the review of the BPharm, to produce a matrix management teaching structure (of course coordinators and heads of departments) to allow better subject integration. I was part of the group that assigned subjects to semesters and planned the curriculum, I was one of the first course coordinators. This structure was expanded to form the basis of the existing MPharm.

Examining:

Chair of the MPharm exam board (2002- 2012)

Past-chair of the exam boards for MSc subjects.

Numerous PhD degrees (in recent years venues include: LSOP, Kings College London, Imperial College, Nottingham, Cardiff, Bradford, Brighton, Portsmouth, Manchester, Aston, Greenwich, Canterbury, Uppsala (Sweden), Copenhagen, Oslo).

I have been / am MPharm examiner at Queens University of Belfast, Cardiff, Nottingham, Kings College, University of Colombo, Sri Lanka, and Robert Gordon University

Previously MSc examiner Kings College London and MSc Industrial Pharmacy, University of Brighton.

Previous positions at the School of Pharmacy, University of London

July 1998 Professor of Pharmaceutics;

May 1995 Reader in Pharmaceutics;

February 1991 Senior Lecturer in Pharmaceutics;

September 1988 Lecturer in Pharmaceutics;

Lecturer in Pharmacy (Pharmaceutics)

Chelsea Department of Pharmacy, King's College (KQC), University of London, Manresa Road, London, SW3 6LX.

October 1984 - September 1988

Advanced Drug Delivery Research unit, Ciba-Geigy Pharmaceuticals, Horsham.

July to December 1987 (Secondment)

Charing Cross Hospital, Fulham Palace Road, London.

August 1981 - July 1982. Pre-registration pharmacist

Community Pharmacy Locum work (1982-1988)

7) External activities

Currently

Member of the Chemistry, Pharmacy and Standards Subcommittee of CHM (2000-)

Previously:

Steering Committee of The Handbook of Pharmaceutical Excipients (retired 2021)

British Pharmacopoeia Commissioner (2004-2010)

Member of the BP committee on pharmacy (2005-2012)

Member of a European Pharmacopoeia Working Party (2008-2010)

Member of Committee on Safety of Medicines until it was disbanded in 2005.

Chairman of Chemistry, Pharmacy and Standards sub-committee of CSM and member of this committee previously.

Editor of International Journal of Pharmaceutics (1999-2009)

Editorial board member of: Pharmaceutical Research, The AAPS Journal, AAPS PharmSci Tech

Member of the United States Pharmacopoeia Expert Group on Physical Methods (2010-2016)

Course organiser for RPSGB residential meeting on "Tabletting Technology" (Every year 1989 - 2004)

Member of the Committee of the Pharmaceutical Sciences Group of the Royal Pharmaceutical Society, now the Academy of Pharmaceutical Sciences (1994 - 2001)

Chairman of the RPSGB Pharmaceutical Sciences Group (1995-7).

Member of the RPSGB Science Committee and also British Pharmaceutical Conference Committee (during period 1995-2003)

Chairman for 1997 AAPS/RPSGB Arden House Conference (Europe). Faculty member for Arden House USA.

Member of IUPAC Commission on Thermodynamics task group – Calibration of calorimeters.

The first Chairman of the Academy of Pharmaceutical Sciences of Great Britain (1999-2000).

Chairman for the 2005 AAPS/APS/RPSGB Arden House Conference (Europe), Planning committee Arden House USA. (First person to have chaired this prestigious meeting twice).

Course organizer / Planning Committee member for numerous international conferences across Europe

Editorial Board of Recent Patents on Drug Delivery and Formulation. Advances in Pharmaceutics.

8) Research

The central theme of my research was to investigate the behaviour of materials of pharmaceutical importance in terms of their molecular and interfacial properties and to relate such behaviour to processing and drug delivery.

This work was diverse in application, ranging from fundamental studies on surfaces, through the adaptation of physical properties of powders by crystallisation and physical manipulation (e.g. milling), to the preparation and characterisation of dosage forms (solid oral / inhalation). A major part of my work centered on investigations of powder / water interactions. The implications of powder / water interactions are manifold, influencing many aspects, including product (solid and liquid dosage forms) preparation, usage (e.g. drug release), and stability (microbiological, chemical and physical).

8.1) Grants obtained

- 1987 Glaxo Group Research fully funded PhD student (Effect of processing and chemical structure on surface energetics) ca £25,000.
- 1987 Ciba-Geigy Advanced Drug Delivery Research fully funded PhD student (Binding of opsonising proteins to drug conjugates) ca£23,000.
- 1987 Glaxo Group Research £2,500 to purchase equipment.
- 1987 Lilly Research Ltd. Gift of computing equipment (value £6,000).
- 1988 Wellcome Foundation Ltd. £10,000 for equipment.
- 1988 Wellcome Foundation Ltd. £1,000 for work on surface energetics of polymorphs.
- 1988 Wellcome Foundation Ltd. Fully funded PhD student (Crystal engineering and surface energetics) ca£23,000.
- 1988 SERC CASE - Lilly Research Centre Ltd. PhD student, The stability of inhalation aerosols, plus ongoing gifts of equipment ca £28,000.
- 1988 Upjohn Ltd. Summer studentship £1000.
- 1988 Wellcome Foundation Ltd. Summer studentship £1000.
- 1988 Lilly Research Centre Ltd. Two summer studentships £2000.
- 1988 Wellcome Foundation Ltd., Fully funded PhD student £25,000
- 1988 SERC/ CASE award with Beecham Pharmaceuticals, £25,000
- 1989 Wellcome Foundation Ltd. £1,876 towards equipment.
- 1989 Wellcome Trust Summer Studentship £622
- 1989 Lilly Research Summer Project (£750)
- 1990 British Council Travel Award to visit University of Athens (£2800).

1990 SERC/CASE award with MSD, Computer modelling as a means of predicting powder properties. £30,000

1991 The Wellcome Trust, £29,639 to purchase a microcalorimeter.

1992 The Wellcome Foundation £33,000 for PhD studentship

1992 Thermometric Ltd. - £12,000 of calorimetric equipment.

1993 The Wellcome Foundation Ltd. - £15,000 for employment of a research Technician.

1993 School of Pharmacy studentship for PhD studies, with collaborative funding obtained from MSD (£30,000).

1993 SERC/CASE award with MSD (£30,000).

1993 The Wellcome Trust, Characterisation of powder surface properties, with application to inhaled drug delivery, £100,515

1994 Roche Products Ltd., Surface properties of powders in relation to tableting. ca £40,000 over 3 years.

1994 EPSRC ROPA award (the first of such awards to be made), £47,940 for the purchase of a microcalorimeter.

1994 The Wellcome Foundation, £750 towards maintenance of the microcalorimeter.

1994 Pharmacia Farmitalia, £4,000 towards the cost of a project on bioadhesion.

1994 SERC/CASE award, SB Pharmaceuticals - molecular structure, crystal packing and physico-chemical properties of drugs. (£40,000)

1994 Wellcome Foundation, gift of equipment and software for instrumentation of a tableting machine ca £10,000.

1995 Merck, West Point, USA, £43,000 over 3 years to study drug-surfactant interactions.

1995 Pfizer Central Research, £43,000 over 3 years to study powder mixing.

1995 SB Pharmaceuticals, industrial CASE allocation, to study spray granulation.

1996 Glaxo-Wellcome, £43,500 over 3 years to study microfluidisation technologies.

1996 Mendell ca £21,000 for studies on microcrystalline cellulose.

1997 Astra Charnwood £45,000 over 3 years to study surfactant systems

1997 SB/Roche/Pfizer £190,000 over 3 years to develop inverse phase gas chromatography

1997 EPSCR/MSD Case project ca £45,000 over 3 years to study drying processes.

1997 Mendell £25,000 for further studies on microcrystalline cellulose.

1997 Mendell £7,500 for calorimetry accessories.

1998 ICI, application of isothermal microcalorimetry £60,000

1998 Core Technologies, post-doctoral worker on hydrogel technology, ca £65,000

1998 Elan Pharmaceuticals, post-doctoral worker on surfactant systems, ca £65,000

1998 Pfizer Central Research, PhD on powder mixing, £50,000

1998 Industrial BBSRC/CASE award from SB pharmaceuticals, £50,000

1998 RPSGB Award to Sarah Hogan for PhD studentship, ca £45,000

1999 Novartis studies of dry powder inhaler formulation design £69,000

1999 EPSRC CASE with SB Pharmaceuticals- powder surface characterisation £48,000

2000 BBSRC committee student to study stabilisation of solid state macromolecules £60,000.

2001 EPSRC/GSK - £20,550 to fund study of Dynamic vapour sorption technique

2001 AstraZeneca - £50,000 to fund study on Modification of surfaces of microparticles for inhalation

2001 GSK - £20,550 to fund investigations into predicting physical stability of amorphous compounds

2001 EPSRC - £192,271 to fund study of preparation and characterisation of amorphous pharmaceutical blends from libraries of polymers

2001 Schering Plough - £50,000 The effect of milling process on crystalline materials.

2002 Pfizer Central Research £150,000 to fund Centre for Paediatric Pharmacy (with Ian Wong)

2003 AstraZeneca – 45,000 First studentship rolling scheme.
 2002 £4000 bench fee for visiting scientist (Dr Ohta from Japan)
 2003 Meiji Seika Daisha Ltd – £7,000 Bench fee for visiting Scientist
 2004 Pfizer Central Research £60,000 for PhD student on inhalation formulation.
 2005 EPSRC Academic Fellowship Scheme, £125,000 for Solid state DNA vaccine particles for inhaled drug delivery. (5 year fellowship jointly funded by School), with Prof Alpar.
 2005 BBSRC £50,000 for establishment of distance learning MSc in Drug Delivery.
 2005 Astra Zeneca ca £60,000 for PhD student on the stability of pressurized metered dose inhalers
 2006 Pfizer Central Research ca £80,000 for PhD student on Process Analytical Technology
 2006 Maplethorpe post doctoral grant – surface energy determination using AFM and IGC c £80,000.
 2012 EPSRC DTC with Uni of Nottingham, Pfizer, AZ, GSK and other £1,950,000.
 2014 EPSRC DTC with Nottingham £11,800,000

8.2) Publications

8.2.1) Single authored book

Interfacial phenomena in drug delivery and targeting.

G.Buckton, Harwood Academic Press, Amsterdam, (1995). Part of the series in Targeting and Drug Delivery

8.2.2) Book

Pharmaceutical Thermal Analysis (2nd Edition)
 J Ford, P.Timmins and G.Buckton. (2001) Taylor and Francis.

8.2.3) Full Papers

1) Assessment of the wettability and surface-energy of a pharmaceutical powder by liquid penetration.

G.Buckton and J.M.Newton, (1985), J. Pharm. Pharmacol., 37, (9): 605-609.

2) The significance of contact angles measured on surfaces that have undergone plastic deformation.

G.Buckton and J.M.Newton, (1986), in Gorrod,J.W., Gibson,G.G., and Mitchard,M., (Eds.), Development of Drugs and Modern Medicine, Ellis Horwood, Southampton, pp421-424.

3) Assessment of the wettability of powders by use of compressed powder discs.

G.Buckton and J.M.Newton, (1986), Powder Technol., 46, (2-3): 201-208.

4) Liquid penetration as a method of assessing the wettability and surface energy of pharmaceutical powders.

G.Buckton and J.M.Newton, (1986), J. Pharm. Pharmacol., 38, (5): 329-334

5) A vacuum microbalance technique for studies on the wettability of powders.

G.Buckton, A.E.Beezer and J.M.Newton, (1986), J. Pharm. Pharmacol., 38, (10): 713-720.

6) The potential value of dielectric response measurements in the assessment of the wettability of powders.

G.Buckton, L.A.Dissado, R.M.Hill and J.M.Newton, (1987), Int. J. Pharm., 38, (1-3): 1-7.

- 7) A microcalorimetric study of powder surface energetics.
G.Buckton and A.E.Beezer, (1988), Int. J. Pharm., 41, (1-2): 139-145.

- 8) In vitro dissolution of some commercially available sustained release theophylline preparations.
G.Buckton, D.Ganderton and R.Shah, (1988), Int. J. Pharm., 42, (1-3): 35-39.

- 9) Preservation of oral solid dosage forms.
T.C.Blair, G.Buckton and S.F.Bloomfield, (1988), in Bloomfield, S.F., Leech,R., Baird,R. and Leak,R., (Eds.), Microbial Quality Assurance of Pharmaceuticals, Cosmetics and Toiletries, Ellis Horwood, Southampton, pp104-118.

- 10) Effect of comminution technique on the surface energy of a powder.
G.Buckton, A.Choularton, A.E.Beezer and S.M.Chatham, (1988), Int. J. Pharm. 47, (1-3): 121-128.

- 11) The assessment, and pharmaceutical importance, of the solid / liquid and the solid / vapour interface: a review with respect to powders. Invited review.
G. Buckton, (1988) Int. J. Pharm., 44, (1-3): 1-8.

- 12) Structure-activity relationships for solubility and wettability of a number of substituted barbituric acids.
G.Buckton and A.E.Beezer (1989) Thermochemica Acta., 138, (2): 319-326

- 13) In vitro dissolution testing of oral controlled release preparations in the presence of artificial foodstuffs. I) Exploration of alternative methodology: microcalorimetry.
L.J.Ashby, A.E.Beezer and G.Buckton, (1989), Int. J. Pharm., 51, (3): 245-251.

- 14) In vitro dissolution testing of oral controlled release preparations in the presence of artificial foodstuffs. II) Probing drug / food interactions using microcalorimetry.
G.Buckton, A.E.Beezer, S.M.Chatham and K.K.Patel, (1989), Int J Pharm., 56, (2): 151-157.

- 15) The use of surface-energy values to predict optimum binder selection for granulations.
L.Zajic and G.Buckton, (1990), Int. J. Pharm., 59, (2): 155-164.

- 16) Contact-angle, adsorption and wettability - a review with respect to powders. Invited review.
G.Buckton, (1990), Powder Technol., 61, (3): 237-249.

- 17) Modelling drug release from hydrophobic matrices by use of thermodynamic activation parameters.
M.Efentakis and G.Buckton,(1990), Int. J. Pharm., 60, (3): 229-234.

- 18) Particle growth in aqueous suspension: the influence of surface-energy and polarity.
S.A.Young and G.Buckton, (1990), Int. J. Pharm., 60, (3): 235-241.

- 19) Polyoxyethylene - polyoxypropylene block copolymers: a novel phase transition in aqueous solution of Pluronic F87.
N.Mitchard, A.E.Beezer, N.Rees, J.Mitchell, S.Leharne, B.Chowdhry and G.Buckton, (1990), J.Chem. Soc., Chem. Commun. (13): 900-901.

- 20) The use of thermodynamic activation parameters and compensation analysis to model drug release from hydrophobic matrices.
G.Buckton and M.Efentakis, (1990), Int. J. Pharm., 62, (2-3): 157-163.

- 21) The interaction of various types of microcrystalline cellulose and starch with water.
T.C.Blair, G.Buckton, A.E.Beezer and S.F.Bloomfield, (1990), *Int. J. Pharm.*, 63, (3): 251-257.
- 22) The role of compensation analysis in the study of wettability, solubility, disintegration and dissolution.
G.Buckton, (1990), *Int. J. Pharm.*, 66, (1-3): 175-182.
- 23) Problem based learning - a valuable approach to pharmaceutical education.
G.Buckton and I.P.Bates, (1991), *Int. Pharm. J.*, 5: 7-13.
- 24) Modelling drug release from matrix formulations by use of thermodynamic activation parameters and extrathermodynamics.
G.Buckton, M.Efentakis and Z.Hussain, (1991), *Eur. J. Pharm. Biopharm.*, 37, (3):154-158.
- 25) Solution thermodynamics of 4-hydroxybenzoates in water, 95 % ethanol / water, 1-octanol and hexane.
A.E.Beezer, G.Buckton, S.Forster, W-B.Park and G.J.Rimmer, (1991), *Thermochimica Acta*, 178: 59-65.
- 26) Spreading coefficients: the practical application of surface energy and polarity data. Invited review.
G.Buckton, (1991), *Pharmakeftiki*, 3: 145-149.
- 27) The influence of surfactants on drug release from a hydrophobic matrix.
M.Efentakis, H.Al-Hmoud, G.Buckton and Z.Rajan, (1991), *Int. J. Pharm.*, 70, (1-2): 153-158.
- 28) On the mechanism of kill of microbial contaminants during tablet compression.
T.C.Blair, G.Buckton and S.F.Bloomfield, (1991), *Int. J. Pharm.*, 72, (2): 111-115.
- 29) The effect of surface treatment on the values of contact angles measured on a compressed powder surface.
I.O.Odidi, J.M.Newton and G.Buckton, (1991), *Int. J. Pharm.*, 72, (1): 43-49.
- 30) The importance of chain-length on the wettability and solubility of organic homologs.
S.Forster, G. Buckton and A.E.Beezer, (1991), *Int. J. Pharm.*, 72, (1): 29-34.
- 31) Sustained release (SR) theophylline preparations: A review of biopharmaceutical influences on *in vivo* and *in vitro* drug absorption / release data. Invited review.
G. Buckton, (1991), *J. Biopharm. Sci.*, 2 : 81-96.
- 32) Pharmaceutical microcalorimetry: a selective review. Invited review.
G.Buckton, S.Russell and A.E.Beezer, (1991), *Thermochim. Acta*, 193: 195-214
- 33) The applications of microcalorimetry to the field of physical pharmacy.
G.Buckton and A.E.Beezer, (1991), *Int. J. Pharm.*, 72, (3): 181-191 (Invited review).
- 34) Surface analysis of pharmaceutical powders. I) X-ray photoelectron spectroscopy (XPS) related to powder wettability.
G.Buckton, R.Bulpett and N. Verma, (1991), *Int. J. Pharm.*, 72, (2):157-162.
- 35) The influence of surfactants on drug release from acrylic matrices.
G.Buckton, M.Efentakis, H.Al-Hmoud and Z.Rajan, (1991), *Int. J. Pharm.*, 74, (2-3): 169-174.

- 36) Observations on the biopharmaceutical importance of chain-length in pharmaceutically related compounds.
G.Buckton, A.E.Beezer, S.P.Denyer and S.J.Russell, (1991), *Int. J. Pharm.*, 73, (1): 1-7.
- 37) NMR evidence for novel phase transition in aqueous solutions of pluronic-F87 (poloxamer 237).
A.E.Beezer, J.C.Mitchell, N.H.Rees, J.K.Armstrong, B.Z.Chowdhry, S.Leharne and G.Buckton, (1991), *J. Chem. Res.* (9): 254-255.
- 38) Safety aspects of non-ionic surfactant vesicles: A toxicity study related to the physico-chemical characteristics of non-ionic surfactants.
H.E.J.Hofland, J.A.Bouwstra, J.C.Verhoef, G.Buckton, B.Z.Chowdhry, M.Ponec and H.E.Junginger, (1992), *J. Pharm. Pharmacol.*, 44, (4): 287-294.
- 39) The use of high sensitivity differential scanning calorimetry to characterise dilute aqueous dispersions of surfactants.
G.Buckton, B.Z.Chowdhry, J.K.Armstrong, S.A.Leharne, J.A.Bouwstra and H.E.J.Hofland, (1992), *Int. J. Pharm.*, 83, (1-3): 115-121.
- 40) The extent of errors associated with contact angles obtained using liquid penetration results.
G.E.Parsons, G.Buckton and S.M.Chatham, (1992), *Int. J. Pharm.*, 82, (1-2): 45-150.
- 41) The estimation and application of surface energy data for powdered systems.
G.Buckton, (1992), *Drug Dev. Ind. Pharm.*, 18, (11-12): 1149-1167, Invited Review.
- 42) Drug release from gel bases: A case for enthalpy-entropy compensation.
G.Buckton and S.Tamburic, (1992), *J. Cont. Rel.*, 20, (1): 29-36.
- 43) The use of surface energy and polarity determinations to predict the physical stability of non-polar non-aqueous suspensions.
G.E.Parsons, G.Buckton and S.M.Chatham, (1992), *Int. J. Pharm.*, 83, (1-3): 163-170.
- 44) The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronisation.
J.F.Pinto, G.Buckton and J.M.Newton, (1992), *Int. J. Pharm.*, 83, (1-3): 187-196.
- 45) Temperature effects on the dissolution of promethazine hydrochloride from hydroxypropylmethylcellulose matrix tablets: the role of compensation analysis.
G.Buckton, (1992), *Eur. J. Pharm. Biopharm.*, 38, (5): 172-173.
- 46) High sensitivity scanning microcalorimetry study of phase transitions in dilute solutions of polyoxyethylene-polyoxypropylene block copolymers.
A.E.Beezer, N.Mitchard, J.C.Mitchell, J.K.Armstrong, B.Z.Chowdhry, S.A.Leharne and G.Buckton, (1992), *J. Chem. Res.*, (7): 236-238.
- 47) The relationship between particle size and solubility.
G.Buckton and A.E.Beezer, (1992), *Int. J. Pharm.*, 82, (3): R7-10.
- 48) The effect of surfactant charge on drug release from acrylic matrices.
M.Efentakis, G.Buckton and H. Al-Hmoud, (1992), *STP Pharma Sciences*, 4: 332-336.
- 49) Thermodynamic analysis of scanning calorimetric transitions observed for dilute aqueous solutions of ABA block copolymers.

N.Mitchard, A.E.Beezer, J.C.Mitchell, J.K.Armstrong, B.Z.Chowdhry, S.Leharne and G.Buckton, (1992), J. Phys. Chem., 96, (23): 9507-9512.

50) Assessment of the wettability of pharmaceutical powders.

G.Buckton, (1993), J. Adhesion Sci. Technol., 7, (3): 205-219. Invited Review.

51) Factors influencing the mechanism of release from sustained-release matrix pellets, produced by extrusion / spheronisation.

C.Tapia, G.Buckton and J.M.Newton, (1993), Int. J. Pharm., 92, (1-3): 211-218

52) Comparison of measured wetting behaviour of materials with identical surface energies, presented as particles and plates.

G.E.Parsons, G.Buckton and S.M.Chatham, (1993), J. Adhesion Sci. Technol., 7, (2): 95-104.

53) Isothermal stability of dilute aqueous solutions of block copolymers of polyoxyethylene-polyoxypropylene-polyoxyethylene. A microcalorimetric study of pluronic F 87 (poloxamer 237) and pluronic F88 (poloxamer P238).

J.J.Irwin, A.E.Beezer, J.C.Mitchell, G.Buckton, B.Z.Chowdhry, D.Eagland and N.J.Crowther (1993), J. Phys. Chem., 97, (9): 2034-2036.

54) Swelling studies on mixtures of two hydrophilic excipients.

E.Papadimitriou, G.Buckton, M.Efentakis and N.Choulis, (1993), STP Pharma Sciences, 3: 232-236.

55) Probing the mechanisms of swelling of hydroxypropylmethylcellulose matrices.

E.Papadimitriou, G.Buckton and M.Efentakis, (1993), Int. J. Pharm., 98, (1-3): 57-62.

56) Consideration of adhesion to modified container walls, by use of surface energy and polarity data, and Lewis acid - Lewis base interactions.

G.Buckton and B.Chandaria, (1993) Int. J. Pharm., 94, (1-3): 223-229.

57) Assessment of the wettability of pharmaceutical powders.

G.Buckton, (1993), in Mittal,K.L. (Ed.), Contact Angle, Wettability and Adhesion, VSP, Netherlands, pp 437-451.

58) Pharmaceutical preformulation

G.Buckton, (1994), in W.Lund, (Ed.), The Pharmaceutical Codex: Principles and Practice of Pharmaceutics, 12th Edn., The Pharmaceutical Press, London, pp178-197.

59) An investigation into the structure and properties of Carbopol 934 gels using dielectric spectroscopy and oscillatory rheometry.

D.Q.M.Craig, A.Tamburic, G.Buckton and J.M.Newton, (1994), J. Cont. Rel., 30, (3): 213-223.

60) The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders.

L-E. Briggner, G.Buckton, K.Bystrom and P Darcy, (1994), Int. J. Pharm., 105, (2): 125-135.

61) The extent of errors associated with contact angles. II. Factors affecting data obtained using a Wilhelmy plate technique for powders.

P.L.Sheridan, G.Buckton and D.E.Storey, (1994), Int. J. Pharm., 109, (2): 155-171.

62) The interaction of albumin and drugs with 2 hemofiltration membranes.

C.A.Oborne, G.Buckton and N.Barber, (1994), J. Clin. Pharm. Therapeutics., 19, (2): 119-126.

63) The use of high sensitivity differential scanning calorimetry to characterise dilute aqueous dispersions of surfactants. 2. Further studies on polyoxyethylene alkyl ethers.

G.Buckton, J.K.Armstrong, B.Z.Chowdhry, S.Leharne and A.E.Beezer, (1994), Int. J. Pharm., 110, (2): 179-187.

64) The controlled crystallization of a model powder: I) The effects of altering the stirring rate and the supersaturation profile, and the incorporation of a surfactant (Poloxamer 188).

A.J.Mackellar, G.Buckton, J.M.Newton, B.Z.Chowdhry and C.A.Orr., (1994) Int. J. Pharm., 112, (1): 65-78.

65) The controlled crystallisation of a model powder: II) Investigation into the mechanism of action of poloxamers in changing crystal properties.

A.J.Mackellar, G.Buckton, J.M.Newton and C.A.Orr., (1994), Int. J. Pharm., 112, (1): 79-85.

66) Wilhelmy plate contact angle data on powder compacts: Fractal geometry considerations of plate perimeter.

A.Chawla, G.Buckton, K.M.G.Taylor, J.M.Newton and M.C.R.Johnson, (1994), Eur. J. Pharm. Sci., 2, (3): 253-258.

67) Characterisation of powder surfaces: Understanding sources of variability in products.

G.Buckton, (1994), In Karsa,D.R. and Stephenson,R.A., (Eds.), Excipients and Delivery Systems for Pharmaceutical Formulations, Royal Society of Chemistry, pp59-74.

68) Application of isothermal microcalorimetry in the pharmaceutical sciences.

G.Buckton, (1995), (invited review) Thermochimica Acta, 248: 117-129.

69) The influence of a phase transition in poly(oxyethylene) / poly(oxypropylene) / poly(oxyethylene) surfactants on adsorption behaviour from dilute aqueous solution.

D.Carthew, G.Buckton, G.E.Parsons and S.Poole, (1995), Pharm. Sci., 1: 3-5.

70) Preservation of oral solid dosage forms.

T.C.Flatau, S.F.Bloomfield and G.Buckton (1996), in R.M.Baird and S.F.Bloomfield, (Eds.), Microbial Quality Assurance of Pharmaceuticals, Cosmetics and Toiletries, 2nd Edn., Ellis Horwood, Southampton, pp113-132.

71) The extent of errors associated with contact angles. III. The influence of surface roughness effects on angles measured using a Wilhelmy plate technique for powders.

G.Buckton, P.Darcy and D.McCarthy, (1995), Colloids and Surfaces A: Physicochemical and Engineering Aspects, 95, (1): 27-35.

72) The use of isothermal microcalorimetry in the study of changes in crystallinity of spray dried salbutamol sulphate.

G.Buckton, P.Darcy, D.Greenleaf and P.Holbrook., (1995), Int. J. Pharm., 116, (1): 113-118.

73) Surface characterisation: Understanding sources of variability in the production and use of pharmaceuticals (British Pharmaceutical Conference Science Award Medal manuscript).

G.Buckton, (1995) J. Pharm. Pharmacol., 47, (4): 265-275.

74) Modelling mucoadhesion by use of the Lewis acid-Lewis base approach to surface energy determination.

M.Rilosi and G.Buckton, (1995) Int. J. Pharm., 117, (1): 75-84.

- 75) The use of isothermal microcalorimetry in the study of small degrees of amorphous content of powders.
G.Buckton, P.Darcy and A.J.Mackellar, (1995), *Int. J. Pharm.*, 117, (2): 253-256.
- 76) Modelling mucoadhesion by use of the Lewis acid-Lewis base approach to surface energy determination. II.Studies on anionic, cationic and unionisable polymers.
M.Rillosi and G.Buckton, (1995), *Pharm. Res.*, 12, (5): 669-675.
- 77) A relationship between surface free energy and polarity data and some physical properties of spheroids.
J.Pinto, G.Buckton and J.M.Newton, (1995), *Int. J. Pharm.*, 118, (1): 95-101.
- 78) Development of a flow microcalorimetry method for the assessment of the surface properties of powders.
P.L.Sheridan, G.Buckton and D.E.Storey, (1995), *Pharm. Res.*, 12, (7): 1025-1030.
- 79) The influence of additives on the recrystallisation of amorphous spray dried lactose.
G.Buckton and P.Darcy, (1995), *Int. J. Pharm.*, 121, (1): 81-87.
- 80) Investigations of the relationship between surface energy terms and the thermodynamics of transfer of drugs into sodium dodecyl sulphate micelles.
S.Mall, G.Buckton, T.Gregori and D.A.Rawlins, (1995), *J. Phys. Chem.*, 99, (20): 8356-8361.
- 81) The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders.
G.Buckton and P.Darcy, (1995), *Int. J. Pharm.*, 123, (2): 265-271.
- 82) Microcalorimetric investigation of the interaction of a surfactant (oleic acid) onto crystalline and partially crystalline salbutamol sulphate in non-aqueous suspension.
P.M.Blackett and G.Buckton, *J. Mater. Sci. Letters*, (1995), 14, (17): 1182-1184.
- 83) A microcalorimetric study of surfactant aggregation and surfactant-drug interaction in a model inhalation aerosol system.
P.M.Blackett and G.Buckton, (1995), *Int. J. Pharm.*, 125, (1): 33-139.
- 84) The use of molecular orbital indices to predict the surface properties of pharmaceutical powders.
P.L.Sheridan, G.Buckton and D.E.Storey, (1995), *Int. J. Pharm.*, 125, (1): 141-149.
- 85) Non-ionic surfactant vesicles and colloidal targeting delivery systems: The role of surfactant conformation.
G. Buckton, In Karsa,D.R. and Stephenson,R.A., (Ed.) *Chemical Aspects of Drug Delivery Systems*, Royal Society of Chemistry, 1995, pp77-88.
- 86) A microcalorimetric investigation of the interaction of surfactants with crystalline and partially crystalline salbutamol sulphate in a model inhalation aerosol system.
P.M.Blackett and G.Buckton, (1995), *Pharm. Res.*, 12, (11): 1689-1693.
- 87) The use of isothermal microcalorimetry in the study of small degrees of amorphous content of a hydrophobic powder.
H.Ahmed, G.Buckton and D.A.Rawlins, (1996), *Int. J. Pharm.*, 130, (2): 195-201.
- 88) Dissolution behaviour of sulphonamides into sodium dodecyl sulphate micelles: a thermodynamic approach.
S.Mall, G.Buckton and D.A.Rawlins, (1996), *J. Pharm. Sci.*, 85, (1): 75-78.

- 89) Slower dissolution rates of a drug (sulfamerazine) in aqueous sodium dodecyl sulphate solutions than in water.
S.Mall, G.Buckton and D.A.Rawlins, (1996) *Int. J. Pharm.*, 131, (1): 41-46.
- 90) Water mobility in amorphous lactose below and close to the glass transition temperature
G.Buckton and P.Darcy, (1996), *Int. J. Pharm.*, 136, (1-2): 141-146..
- 91) A comparison of two contact angle methods and inverse gas chromatography to assess the surface energies of caffeine and theophylline
J.W.Dove, G.Buckton and C.Doherty, (1996), *Int. J. Pharm.*, 138, (2): 199-206.
- 92) The effect of temperature on the surface nature of an adsorbed layer of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) block copolymers.
D.L.Carthew, G.Buckton, G.E.Parsons and S.Poole, (1996) *Pharm. Res.*, 13, (11): 1730-1733.
- 93) Dynamic surface tension studies of hydroxypropylmethylcellulose film coating solutions.
G.Buckton and E. Ocha Machiste, (1996) *Int. J. Pharm.*, 145, (1-2): 197-202.
- 94) The interaction between hydroxypropylmethylcellulose and sodium dodecyl sulphate
G.Buckton, A.Kee and M. Efentakis, (1996), *Pharm. Sci.*, 2: 561-562.
- 95) Characterisation of small changes in the physical properties of powders of significance for dry powder inhaler formulations.
G.Buckton, (1997) *Adv. Drug Del. Rev.*, 26, (1):17-27.
- 96) The influence of a phase transition in poly(oxyethylene) / poly(oxypropylene) / poly(oxyethylene) block copolymer surfactants on the properties of material adsorbed from dilute aqueous solution.
D.L.Carthew, G.Buckton, G.E.Parsons and S.Poole, (1997), *J. Adhesion*, 63, (1-3): 89-98.
- 97) Differences between dynamic and equilibrium surface tension of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) block copolymer surfactants (Poloxamers P407, P237 and P338) in aqueous solution.
G.Buckton and E. Ocha Machiste, (1997) , *J. Pharm. Sci.*, 86, (2): 163-166.
- 98) The use of thermal techniques to assess the impact of feed concentration on the amorphous content and polymorphic forms present in spray dried lactose.
O.C.Chidavaenzi, G.Buckton, F.Koosha and R.Pathak, (1997) *Int. J. Pharm.*, 159, (1): 67-74.
- 99) Predicting interaction of powders in binary mixes from their surface energy components.
N.M.Ah Fat, G.Buckton, R.Burrows and M.Ticehurst, (1997) *Int. J. Pharm.*, 156, (1): 89-95.
- 100) The influence of heating/drying on the crystallisation of amorphous lactose after structural collapse
P.Darcy and G.Buckton, (1997) *Int. J. Pharm.*, 158, (2): 157-164.
- 101) The formation of an inclusion complex of methocarbamol with hydroxypropyl- β -cyclodextrin: the effect on chemical stability, solubility and dissolution rate.
E.Antoniadou-Vyza, G.Buckton, S.G.Michaleas, Y.L.Loukas and M.Efentakis, (1997) *Int. J. Pharm.*, 158, (2): 233-240.

- 102) Crystallisation of partially amorphous griseofulvin in water vapour: determination of thermodynamic and kinetic parameters using isothermal heat conduction microcalorimetry. H.Ahmed, G.Buckton and D.A.Rawlins, (1998), *Int. J. Pharm.*, 167, (1-2): 139-146.
- 103) Quantitative assessments of powder crystallinity: Estimates of heat and mass transfer to interpret isothermal microcalorimetry data. Patricia Darcy and Graham Buckton,(1998), *Thermochimica Acta*, 316, (1): 29-36
- 104) Modelling mucoadhesion by use of surface energy terms obtained by the Lewis acid-Lewis base approach. III. An interaction between teflon and carbopol. G.Buckton and M.Cappuccinello, (1998) *Pharm. Res.*, 15, (3): 502-503.
- 105) Crystallisation of bulk samples of partially amorphous spray-dried lactose. P.Darcy and G.Buckton (1998), *Pharm. Dev. Technol.*, 3, (4): 503-507.
- 106) Conversions between different amorphous states and crystal polymorphs of significance for inhalation systems. G.Buckton in R.N. Dalby, P.R.Byron and S.J. Farr (Eds.) *Resp. Drug Del. VI* (1998), Interpharm Press, 145-152.
- 107) The use of near infra-red spectroscopy to detect changes in the form of amorphous and crystalline lactose. G.Buckton, E.Yonemochi, J.Hammond and A.Moffat, (1998) *Int. J. Pharm.*, 168, (2): 231-242.
- 108) Assessment of disorder in crystalline powders - a review of analytical techniques and their application. G.Buckton and P.Darcy, (1999) *Int. J. Pharm.*, 179, (2): 141-158.
- 109) Differences in crystallization behaviour between quenched and ground amorphous ursodeoxycholic acid. E. Yonemochi, Y.Inoue, G.Buckton, A.Moffat, T.Oguchi and K.Yamamoto. (1999) *Pharm. Res.*, 16, (6): 835-840.
- 110) Water sorption and near IR spectroscopy to study the difference between microcrystalline cellulose and silicified microcrystalline cellulose, before and after wet granulation. G.Buckton, E.Yonemochi, W.L.Yoon and A.C.Moffat. (1999) *Int. J. Pharm.*, 181, (1): 41-48.
- 111) A high sensitivity differential scanning calorimetry study of the interaction between poloxamers and dimyristoylphosphatidylcholine and dipalmitoylphosphatidylcholine liposomes. J.D.Castile, K.M.G.Taylor and G.Buckton, (1999) *Int. J. Pharm.*, 182, (1): 101-110.
- 112) Isothermal microcalorimetry and inverse phase gas chromatography to study small changes in powder surface properties G.Buckton, J.W. Dove and P.Davis, (1999), *Int. J. Pharm.*, 193, (1): 13-19.
- 113) Isothermal microcalorimetry water sorption experiments: Calibration issues G.Buckton. (2000) *Thermochimica Acta*. 347, (1-2): 63-71,
- 114) An exploration of inter-relationships between contact angle, inverse phase gas chromatography and triboelectric charging data. N.M.Ahfat, G.Buckton, R.Burrows and M.D.Ticehurst. (2000) *European Journal of Pharm. Sci.*, 9, (3): 271-276.

- 115) Near IR spectroscopy to quantify the silica content and difference between silicified microcrystalline cellulose and physical mixtures of microcrystalline cellulose and silica.
G.Buckton and E.Yonemochi. (2000) Eur. J. Pharm. Sci., 10, (1): 77-80.
- 116) The novel combination of dynamic vapour sorption gravimetric analysis and near infrared spectroscopy as a hyphonated technique.
R.A.Lane and G.Buckton, (2000) Int. J. Pharm., 207, (1-2): 49-56.
- 117) The quantification of small degrees of disorder in lactose using solution calorimetry.
S.E.Hogan and G.Buckton, (2000) Int. J. Pharm., 207, (1-2): 57-64
- 118) The application of near infrared spectroscopy and dynamic vapour sorption to quantify low amorphous contents of crystalline lactose. S.E.Hogan and G.Buckton (2001) Pharm Res., 18, (1): 112-116.
- 119) The effect of co-spray drying with polyethylene glycol 4000 on the crystallinity and physical form of lactose
O.C .Chidavaenzi, G. Buckton and F. Koosha , (2001), Int. J. Pharm., 216, (1-2): 43-49.
- 120) Potential Applications of Microcalorimetry for the Study of Physical Processes in Pharmaceuticals
S. Gaisford and G. Buckton (2001) Thermochemica Acta, 380, (2): 185-198.
- 121) The use of inverse phase gas chromatography to measure the surface energy of crystalline, amorphous and recently milled lactose.
H.E. Newell, G. Buckton, D.A. Butler, F. Thielmann and DR Williams, (2001) Pharm Res., 18, (5): 662-666.
- 122) The influence of incubation temperature and surfactant concentration on the interaction between dimyristoylphosphatidylcholine liposomes and poloxamer surfactants.
J.D. Castile, K.M.G. Talor and G. Buckton, (2001) Int, J. Pharm., 221, (1-2): 197-209.
- 123) The use of inverse phase gas chromatography to study the change of surface energy of amorphous lactose as a function of relative humidity and the processes of collapse and crystallisation.
H.E. Newell, G. Buckton, D.A .Butler, F. Thielmann, D.R. Williams, (2001), Int. J. Pharm., 217, (1-2): 45-56.
- 124) Water sorption/desorption-Near IR and calorimetric study of crystalline and amorphous raffinose
S.E. Hogan and G. Buckton, (2001), Int. J. Pharm., 227, (1-2): 57-69.
- 125) Characterizing physical forms of powders: Impact and advances.
G..Buckton (2001), Pharm. Tec. Eur.,13: 44-55.
- 126) The imidazole catalysed hydrolysis of triacetin: an inter- and intra-laboratory development of a test reaction for isothermal heat conduction microcalorimeters used for determination of both thermodynamic and kinetic parameters.
A.E. Beezer, A.K. Hills, M.A.A..O'Neill, A.C. Morris, K.T.E..Kierstan, R.M. Deal, L.J. Waters, J. Hadgraft, J.C. Mitchell, J.A. Connors, J.E. Orchard, R.J .Willson, T.C. Hofelich, J. Beaudin, G. Wolf, F..Baitalow, S. Gaisford, R.A. Lane, G. Buckton, M.A. Phipps, R.A. Winneke, E.A. Schmidtt, L.D. Hansen, D. O'Sullivan, M.K. Parmar, (2001) Thermochemica Acta, 380, (2): 3-17.

- 127) A study of the crystallisation of amorphous salbutamol sulphate using water vapour sorption and near infrared spectroscopy.
A. Columbano, G. Buckton and P. Wikeley (2002) *Int. J. Pharm.*, 237, (1-2): 171-178.
- 128) The effect of erosion and swelling on the dissolution of theophylline from low and high viscosity sodium alginate matrices
M. Efentakis and G. Buckton (2002) *Pharm. Dev. Technol.* 7, (1): 69-77
- 129) The effect of alkylpolyglycoside surfactants on the crystallisation of spray dried salbutamol sulphate: a gravimetric-near infrared spectrometry study
A. Columbano, G. Buckton and P. Wikeley (2002) *AAPS Pharm Sci.* 4, (3): article 16.
- 130) Solid state properties, G.Buckton, in *Pharmaceutics the Science of Dosage Form Design 2nd Edition*, (2002) M.E.Aulton (Ed), Churchill Livingstone, London. p141-151.
- 131) The effect of spray drying feed temperature and subsequent storage conditions on the physical form of lactose.
O. C. Chidavaenzi, G. Buckton and F. Koosha (2002) *AAPS Pharm. Sci. Tech.*, 3 (4): 37.
- 132) Characterisation of surface modified salbutamol sulphate-alkylpolyglycoside microparticles prepared by spray-drying.
A. Columbano, G. Buckton and P. Wikeley (2003) *Int. J. Pharm.*, 253, (1-2): 61-70.
- 133) Inverse gas chromatography: Considerations about appropriate use for amorphous and crystalline powders
O. Planinsek and G. Buckton (2003) *J Pharm Sci*, 92, (6): 1286-1294
- 134) Quantification of amorphous content in mixed systems: amorphous trehalose with lactose
D. Al-Hadithi G. Buckton and S. Brocchini, (2004) *Thermochimica Acta.*, 417, (2): 193-199
- 135) The use of high speed differential scanning calorimetry (Hyper DSCTM) to study the thermal properties of carbamazepine polymorphs.
C. McGregor, M.H. Saunders, G. Buckton and R.D. Saklatvala, (2004) *Thermochimica Acta.*, 417, (2): 231-237
- 136) Determination of the changes in surface energetics of cefditoren pivoxil as a consequence of processing induced disorder and equilibrium to different relative humidities.
M. Ohta and G. Buckton, (2004) *Int. J. Pharm.*, 269, (1): 81-88.
- 137) The use of inverse gas chromatography to assess the acid-base contributions to surface energies of cefditoren pivoxil and methacrylate copolymers and possible links to instability.
M. Ohta and G. Buckton (2004) *Int J Pharm*, 272: 121-128.
- 138) The potential of high speed DSC (Hyper-DSC) for the detection and quantification of small amounts of amorphous content in predominantly crystalline samples.
M.H. Saunders, K. Podlusi, S. Shergill, C. Blatchford, G. Buckton and P. Royall. (2004) *Int J Pharm*, 274, (1-2): 35-40.
- 139) The use of dynamic vapour sorption and near infra-red spectroscopy (DVS-NIR) to study the crystal transitions of theophylline and the report of a new solid-state transition,
K.L. Vora, G. Buckton and D. Clapham (2004), *Eur. J. Pharm. Sci.*, 22, (2-3): 97-105.

- 140) Inverse gas chromatography: Investigating whether the technique preferentially probes high energy sites for mixtures of crystalline and amorphous lactose
H.E. Newell and G. Buckton. (2004) *Pharm. Res.* 21, (8): 1440-1444.
- 141) The use of inverse phase gas chromatography to study the glass transition temperature of a powder surface.
G. Buckton, A. Amberkane and K. Pincott, (2004) *Pharm. Res.*, 21, (9): 1554-1557
- 142) Approaches to determine the enthalpy of crystallisation, and amorphous content, from isothermal microcalorimetry data.
S.E. Dilworth, G. Buckton, S. Gaisford and R. Ramos. (2004) *Int. J. Pharm.*, 284, (1-2): 83-94
- 143) The crystallisation of a model hydrophobic drug (terfenadine) following exposure to humidity and organic vapours.
R.M. Samra and G. Buckton. (2004) *Int. J. Pharm.*, 284, (1-2): 53-60
- 144) Bilayer to micelle transition of DMPC and alcohol ethoxylate surfactants studied by isoperibol calorimetry.
L.Barriocanal, K.M.G. Taylor and G. Buckton (2005) *J Pharm. Sci.* 94 (8): 1747-1755
- 145) A study of the differences between two amorphous spray-dried samples of cefditoren pivoxil which exhibited different physical stabilities
M. Ohta and G. Buckton. (2005) *Int. J. Pharm.*, 289, (1-2): 31-38.
- 146) A study of liposome formation using solution (isoperibol) calorimeter
L. Barriocanal, K.M.G..Taylor and G. Buckton (2004) *Int. J. Pharm.*, 287, (1-2): 113-121.
- 147) Stability assessment of pharmaceuticals by isothermal microcalorimetry: two component systems.
C.V. Skarai, S. Gaisford, M.A.A. O'Neill, G. Buckton and A.E. Beezer (2005) *Int. J. Pharm.*, 292, (1-2): 127-135.
- 148) Calorimetric study of bovine serum albumin dilution and adsorption onto polystyrene particles.
M.J. Pollitt, G. Buckton, S. Brocchini, H.O. Alpar, *Int. J. Pharm.*, (2005) 298 (2): 333-338
- 149) The use of microcalorimetry in stress testing.
G. Buckton and S. Gaisford in S.W. Baertschi (Ed) *Pharmaceutical Stress Testing*, Taylor and Francis, New York, 2005. pp327-354.
- 150) A comparison of high speed differential scanning calorimetry (Hyper-DSC) and modulated differential scanning calorimetry to detect the glass transition of polyvinyl pyrrolidone: the effect of water content and detection sensitivity in powder mixtures (a model formulation)
R.D. Saklatvala, M.H. Saunders, S. Fitzpatrick and G. Buckton (2005) *J Drug Del. Sci Technol.* 15, (4): 257-260
- 151) Formation and characterization of porous indomethacin-PVP coprecipitates prepared using solvent-free supercritical fluid processing.
K. Gong, R. Viboonkiat, J..A. Darr, I.U. Rehman and G. Buckton, (2005) *J. Pharm. Sci.* 94, (12): 2583-2590
- 152) A comparison of chemical reference materials for solution calorimeters

R. Ramos, S. Gaisford, G. Buckton, P.G. Royall, B.T.S. Yff, M.A.A. O'Neill, (2005) *Int. J. Pharm* 299: 1-2) 73-83

153) Calorimetric determination of amorphous content in lactose: a note on the preparation of calibration curves

R. Ramos, S. Gaisford and G. Buckton, (2005) *Int. J. Pharm.* 300 , (1-2): 13-21

154) The hygroscopicity of moisture barrier film coatings

E. Mwesigwa, G. Buckton, A.W. Basit, (2005) *Drug Dev Ind Pharm.* 13 , (10): 959-968

155) The use of precursor polymers to prepare new excipients

J. Fletcher, A. Godwin, E. Pedone, B. Jahangeer, G. Buckton and S. Brocchini (2005) *J. Drug Del. Sci. Tech.* 15 , (4): 295-299

156) Hyper DSC studies of amorphous polyvinylpyrrolidone in a model wet granulation system

G. Buckton, A.A. Adeniyi, M. Saunders and A. Ambarkhane. (2006) *Int. J. Pharm.* 312, (1-2): 61-65

157) Investigation to find a suitable reference material for use as an inverse gas chromatography system suitability test

J. Stapley, G. Buckton and D. Merrifield. (2006) *Int. J. Pharm.* 318, (1-2): 22-27

158) Solution calorimetry to monitor swelling and dissolution of polymers and polymer blends.

S. Conti, S. Gaisford, G. Buckton and U. Conte. (2006) *Thermochimica Acta*, 450, (1-2): 56-60

159) Isothermal methods to investigate the structural relaxation of amorphous materials

R. Ramos, S. Gaisford and G. Buckton. (2006) *J. Pharm. Pharmacol.*, 58, (1): A22-A22

160) Adjusting and understanding the properties and crystallisation behaviour of amorphous trehalose as a function of spray drying feed concentration

A. Moran and G. Buckton. (2007) *Int. J. Pharm.* 343: 12-17

161) The use of isothermal titration calorimetry to assess the solubility enhancement of simvastatin by a range of surfactants

R. Patel, G. Buckton and S. Gaisford. (2007) *Thermochimica Acta*, 456, (2): 106-113

162) The importance of surface energetics of powders for drug delivery and the establishment of inverse gas chromatography. G. Buckton and H. Gill. (2007) *Advanced Drug Delivery Reviews.* 59, (14): 474-1479.

163) The role of solution calorimetry in investigating controlled-release processes from polymeric drug delivery systems.

S. Conti, S. Gaisford, G. Buckton, L. Maggi and U. Conte. (2008) *Eur. J. Pharm. Biopharm.*; 68, (3): 795-801

164) Determination of outer layer and bulk dehydration kinetics of trehalose dihydrate using atomic force microscopy, gravimetric vapour sorption and near infrared spectroscopy.

M.D. Jones, A.E. Beezer and G. Buckton. *J Pharm Sci.* (2008). 97, (10): 4404-4415.

165) Moisture sorption and permeability characteristics of polymer films: Implications for their use as barrier coatings for solid dosage forms containing hydrolyzable drug substances.

E. Mwesigwa, A.W. Basit and G. Buckton. *J Pharm Sci.* (2008), 97 , (10): 4433-4445.

- 166) Determination of the structural relaxation at the surface of amorphous solid dispersion using inverse gas chromatography.
S. Hasegawa, K.E. Peng and G. Buckton. *J Pharm Sci.* (2009). 98 (6): 2133-9
- 167) Studies of the crystallisation of amorphous trehalose using simultaneous gravimetric vapor sorption/near IR (GVS/NIR) and “modulated” GVS/NIR
A. Moran and G. Buckton. *AAPS Pharm. Sci. Tech.* (2009); 10 ,(1): 297-302.
- 168) Characterisation and aerosolisation of mannitol particles produced via confined liquid impinging jet. Tang, H.K. Chan, H. Chiou, K. Ogawa, M.D. Jones, H. Adi, G. Buckton, R.K. Prud’homme, and J.A. Raper. *Int. J. Pharm.* (2009) 367, (1-2): 51-7.
- 169) Anomalous properties of spray dried solid dispersions. H. Al-Obaidi, S. Brocchini and G. Buckton. *J. Pharm. Sci.* (2009). 98 (12): 4724-37.
- 170) Evaluation of griseofulvin binary and ternary solid dispersions with HPMCAS
H. Al-Obaidi and G. Buckton
AAPS PharmSciTech. (2009) 10 (4): 1172-7
- 171) The relationship between drug concentration, mixing time, blending order and ternary dry powder inhalation performance.
M.D. Jones, J.G. Santo, B. Yakub, M. Dennison, H. Master and G. Buckton. *Int. J. Pharm.* (2010). 31;39 (1-2): 137-47.
- 172) Intermolecular bonding forces – where materials and process come together. G. Buckton in *Pharmaceutical Powder Compaction Technology*, M. Celik (Ed), Informa, New York. pp 1-9. (2011) 1-8.
- 173) Characterisation and stability of ternary solid dispersions with PVP and PHPMA. H. Al-Obaidi and G. Buckton (2011) *Int. J. Pharm.*, 419, 20-17.
- 174) A carbamazepine-indomethacin (1:1) cocrystal produced by milling.
M. Majumder, G. Buckton, C. Rawlinson-Malone, A.C. Williams, M.J. Spillman, N. Shankland and K. Shankland. (2011) *Cryst. Eng. Comm.* 13, 6327-6328.
- 175) Investigation of preparation methods on surface/bulk structural relaxation and glass fragility of amorphous solid dispersions P. Ke, H. Al-Obaidi, G. Buckton. (2012). *Int J Pharm*, 422, 170-178..
- 176) Do amorphous troglitazones prepared from two diastereomer-pairs have the same molecular mobility and crystallization rate at the surface? N. Furuyama, S. Hasegawa, S. Yada, T. Hamaura, N. Wakiyama, E. Yonemochi, K. Terada and G. Buckton. (2012) *Chem. Pharm. Bull.* 59, 1452-1457.
- 177) Application of hydrogen-bond propensity calculations to an indomethacin-nicotinamide (1:1) co-crystal.
M. Majumder, G. Buckton, C.F. Rawlinson-Malome, A.C. Williams, M.J. Spillman, E. Pidcock and K. Shankland. (2013) *Cryst Eng Comm*, 15, 4041-4044.
- 178) Theophylline cocrystals prepared by spray drying: physicochemical properties and aerosolization performance. Alhalaweh, A., Kaialy, W., Buckton, G., Gill, H., Nokhodchi, A., Velega, S.P., *AAPS PharmSciTech*, (2013) 14, 265-276.

- 179) Measuring antibody coatings on gold nanoparticles by optical spectroscopy. M Pollitt, S.Brocchini, G Buckton RSC Advances, (2015), 5, 24521-7
- 180) Nanoparticle agglomerates of indomethacin: the role of poloxamers and matrix formers on aerosolisation efficiency. M Malamatar, S. Somavarapu, M Bloxham, G Buckton, Int. J. Pharm. accepted.
- 181) Using DVS-NIR to assess the water sorption behaviour and stability of a griseofulvin/PVP K 30 solid dispersion. Li.W, Buckton, G., Int. J. Pharm, 495 (2015) 999-1004.
- 182) A new era of pulmonary delivery of nano-antimicrobial therapeutics to treat chronic pulmonary infections. Merchant,Z., Buckton,G., Taylor,K.M.G., Stapleton,P., Saleem,I.Y., Zariwala,M.G. and Somavarapu, S. accepted.
- 183) Solidification of nanosuspensions for the production of solid oral dosage forms and inhalable dry powders. M. Malamatar, S. Sompavarapu, K Taylor and G Buckton. Expert Opinion on Drug Delivery. Accepted
- 184) Atypical effects of incorporated surfactants on stability and dissolution properties of amorphous polymeric dispersions. Al-Obaidi, H., Lawrence, M.J. and Buckton,G., J Pharm. Pharmacol. 68 (2016) 1373-1383
- 185) Comparison of the cohesion-adhesion balance approach to colloidal probe atomic force microscopy and the measurement of Hansen partial solubility parameters by inverse gas chromatography for the prediction of dry powder inhaler performance. Jones, MD., and Buckton, G., Int. J. Pharm. 509 (2016) 419-430
- 186) Preparation of respirable nanoparticle agglomerates of the low melting and ductile drug ibuprofen: impact of formulation parameters. M. Malamatar, S. Sompavarapu, K. Kachrimanis, G.Buckton and K. Taylor Powder Technology, 308(2017)123-134.

9) Abstracts and Book Reviews

- 1) Assessment of the wettability of pharmaceutical powders using compressed discs. G.Buckton and J.M.Newton, (1985), J. Pharm.Pharmacol., 37, 27P.
- 2) An alternative approach to the study of the wettability of a pharmaceutical powder.

- G.Buckton, A.E.Beezer and J.M.Newton, (1986), Proc. 4th. Int. Conf. Pharm. Tech., Paris.
- 3) Problems of assessing the effect of a polymer surface coating on the wetting of paracetamol.
T.C.Blair, G.Buckton and S.F.Bloomfield, (1986), J. Pharm. Pharmacol., 38, 98P.
- 4) Water availability of Enterobacter cloacae contaminating tablets stored at high relative humidities.
T.C.Blair, G.Buckton and S.F.Bloomfield, (1987), J. Pharm. Pharmacol., 39, 125P.
- 5) Use of thermodynamic functions to describe the mechanisms of drug release from a sustained release dosage form.
G.Buckton and M.R.Francis, (1987), J. Pharm. Pharmacol., 39, 132P.
- 6) Effect of particle size on the surface energetics of pharmaceutical powders.
G.Buckton and A.E.Beezer, (1987), J. Pharm. Pharmacol., 39, 126P.
- 7) Drug Formulation, I. Racz.
Book review, (1990), Int. Pharm. J., 4, 108.
- 8) Pharmaceutical Thermal Analysis, J.L.Ford and P.Timmins.
Book review, (1990), Pharm. J., 244, 808.
- 9) Use of thermal methods for the characterisation of pharmaceuticals (report).
Pharm. J., 245 (1990) 183-184.
- 10) The effect of long term storage on the bleeding number and microscopical appearance of processed white soft paraffin.
J.H.King, G.Buckton and S.Poole, (1990), J. Pharm. Pharmacol. Suppl. 131P
- 11) Calorimetric studies of polymer solutions: studies of polymer phase transitions and binding to particles.
A.E.Beezer, N.Mitchard, B.Z.Chowdhry, S.Leharne and G.Buckton, (1990), Acta Pharmaceutica Nordica, 2, 295.
- 12) Physiological Pharmaceutics, C.Wilson and N.Washington.
Book review, (1990), Int. J. Pharm.
- 1) Understanding experimental design and interpretation in pharmaceutics,
N.A.Armstrong and K.C.James., Book review, (1991), Int. J. Pharm., 73, 267.
- 14) The use of compensation analysis to study drug release mechanisms.
G. Buckton, M.Efentakis, H. Al-Hmoud, Intern. Symp. Control. Rel. Bioact. Mater., 18 (1991) 652-653.
- 15) QSAR studies of dissolution of barbituric acids
J.C.Dearden, S.J.A.Bradburne and G.Buckton, J. Pharm. Pharmacol., 1991, Suppl. 70P.
- 16) A relationship between surface free energy and polarity data, and some physical properties of spheroids.
J.F.Pinto, G.Buckton and J.M.Newton, Proc. APV Symposium, (1992), Eur. J. Pharm. Biopharm., 38, 21S.
- 17) The assessment of the wettability of pharmaceutical powders

G.Buckton, Invited contribution, American Chem. Soc., Symposium on Contact Angle, Adhesion and Wettability, San Francisco, April, 1992.

18) Analysis of bioadhesive carbopol gels using dielectric spectroscopy and oscillatory rheology

D.Q.M.Craig, S.Tamburic, G.Buckton and J.M.Newton, Proc. Int. Symp. Control. Rel. Bioact. Mater. 1992

19) The application of percolation theory to swelling studies on mixtures of two hydrophilic excipients.

E.Papadimitriou, G.Buckton, M.Efentakis and N.Choulis, 12th Pharmaceutical Technology Conference, Elsinore, Denmark, 1993.

20) Probing the mechanisms of swelling of hydroxypropylmethylcellulose matrices.

E.Papadimitriou, G.Buckton, M.Efentakis and N.Choulis, 12th Pharmaceutical Technology Conference, Elsinore, Denmark, 1993.

21) Diffusion and Relaxation mechanisms for drug release from different hydrophilic formulations.

E.Papadimitriou, M.Efentakis, N.Choulis and G.Buckton, 12th Pharmaceutical Technology Conference, Elsinore, Denmark, 1993.

22) Applications of isothermal microcalorimetry in the field of physical pharmacy.

G.Buckton, European Society of Thermal Analysis, Calorimetry, Thermodynamics and Chemical Reactivity, Symposium on Pharmacy and Thermal Analysis, Freiberg, Germany, March 1993.

23) Calorimetric studies of powder wettability

G.Buckton, European Society of Thermal Analysis, Calorimetry, Thermodynamics and Chemical Reactivity, Symposium on Pharmacy and Thermal Analysis, Freiberg, Germany, March 1993.

24) Comparison of two methods for the assessment of the wettability of pharmaceutical powders.

P.L.Sheridan, G.Buckton and D.E.Storey, (1993), J. Pharm. Pharmacol., 45, 1097.

25) The relationship between wettability and molecular orbital indices.

P.L.Sheridan, G.Buckton and D.E.Storey, (1993), J. Pharm. Pharmacol., 45, 1149.

26) Surface energy determinations of powders for use in dry powder aerosol formulations.

A.Chawla, G.Buckton, K.M.G.Taylor, J.M.Newton and M.C.R.Johnson, British Pharmaceutical Conference, (1993), J. Pharm. Pharmacol., 45, 1148.

27) Investigations of the relationship between surface energy terms and the thermodynamics of transfer into sodium dodecyl sulphate micelles.

G.Buckton, S.Mall, T.Gregori and D.A.Rawlins. (1994) Proceedings of the 13th Pharmaceutical Technology Conference, Strasbourg, France, vol 2, pp289-298.

28) The use of microcalorimetry as a rapid method of assessing bacterial kill by ciprofloxacin.

I.Morrissey and G. Buckton. (1994) Proceedings of the 13th Pharmaceutical Technology Conference, Strasbourg, France, vol 3, pp119-127.

29) The use of high sensitivity differential scanning calorimetry to characterise dilute aqueous dispersions of surfactants: Further studies on polyoxyethylene alkyl ethers.

G.Buckton, J.A.Armstrong, B.Z.Chowdhry, S.Leharne and A.E.Beezer, (1994), Proceedings of the 13th Pharmaceutical Technology Conference, Strasbourg, France, vol 3, pp 125-158.

30) Prediction of the surface properties of pharmaceutical powders from molecular structure. P.L.Sheridan, G.Buckton, D.E.Storey, (1994), Proceedings of the 13th Pharmaceutical Technology Conference, Strasbourg, France, vol 2, pp 299-323.

31) Delivering pharmaceutical care
G.Buckton, Pharm. J., (1994), 252, 662.

32) Temperature dependence on the adsorption of poloxamer F108 to a model hydrophobic drug.
D.Carthew, G.Buckton, G.E.Parsons and S.Poole (1994) J. Pharm. Pharmacol., 46 (Suppl. 2), 1039.

33) Microcalorimetric study of crystallinity of spray dried salbutamol sulphate.
D.Greenleaf, G.Buckton, P.Darcy and P.Holbrook, AAPS Annual meeting, (1994), Pharm. Res., PT6085, S-152.

34) The effect of temperature on the adsorption of poloxamer P388 to the surface of three hydrophobic solids.
D.Carthew, G.Buckton, G.E.Parsons and S.Poole (1995) 14th Pharmaceutical Technology Conference, Barcelona, Vol. 3 pp50-62.

35) The use of isothermal microcalorimetry in studies on the influence of microcrystalline cellulose or magnesium stearate on the recrystallisation of amorphous spray dried lactose.
G.Buckton and P.Darcy (1995) 14th Pharmaceutical Technology Conference, Barcelona, Vol 3, pp63-75.

36) The use of isothermal microcalorimetry for studies of surfactant aggregation and surfactant - drug interaction in a non-polar fluid (a model inhalation aerosol system).
P. Blackett and G.Buckton (1995) 14th Pharmaceutical Technology Conference, Barcelona, Vol 3, pp122-133.

37) The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders.
G. Buckton and P.Darcy. 1st World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Budapest, May 1995, pp203-204.

38) Adsorption behaviour of a surfactant (oleic acid) onto salbutamol base and salbutamol sulphate in non-aqueous suspension.
P.Blackett and G.Buckton. 1st World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Budapest, May 1995 pp 603-604.

39) Dissolution behaviour of sulphonamides into sodium dodecyl sulphate micelles - a thermodynamic approach.
S.Mall, G.Buckton and D.A.Rawlins. 1st World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Budapest, May 1995 pp 32-33.

40) The use of isothermal microcalorimetry in the study of the amorphous content of a hydrophobic powder.
H.Ahmed, G.Buckton and D.A.Rawlins. 1st World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Budapest, May 1995, pp74-75.

- 41) Dissolution behaviour of sulphonamides into sodium dodecyl sulphate solutions
S.Mall, G.Buckton, D.A.Rawlins, British Pharmaceutical Conference, Warwick, (1995), J. Pharm. Pharmacol., 47, 1067.
- 42) The relationship between surface energy and tensile strength
P.L.Sheridan, G.Buckton and D.E.Storey, British Pharmaceutical Conference, Warwick, (1995), J. Pharm. Pharmacol., 47, 1067.
- 43) Dissolution behaviour of sulphonamides into sodium dodecyl sulphate micelles - a thermodynamic approach.
S.Mall, G.Buckton and D.A.Rawlins. Symposium of Surfactants, Micelles and Microemulsions, University of Florida, August 1995.
- 44) Probing small amounts of amorphous content in crystals of a hydrophobic drug.
H.Ahmed, G. Buckton and D.A.Rawlins, AAPS 10th Annual Meeting, Miami Beach, November 1995 (PDD 7009) Pharm. Res., 12, S-195.
- 45) An overview of the uses of high sensitivity differential scanning calorimetry to characterise di-/triblock copolymers and polyoxyethylene alkyl ethers.
S.A.Leharne, B.Chowdhry, G.Buckton, A.E.Beezer and J.C.Mitchell. 2nd Symp. On Pharmacy and Thermal Analysis, University of Geneva, October 1995, A5.
- 46) Dissolution behaviour of sulphonamides into sodium dodecyl sulphate micelles.
S.Mall, G.Buckton and D.A.Rawlins, AAPS 10th Annual Meeting, Miami Beach, November 1995 (PDD 7096). Pharm. Res., 12, S-216.
- 47) Surfactant Adsorption onto amorphous and crystalline salbutamol sulphate in model inhalation aerosols.
P.M.Blackett and G.Buckton. AAPS 10th Annual Meeting, Miami Beach, November 1995 (PDD 7382). Pharm. Res., 12, S-288.
- 48) New insight into the behaviour of materials
G.Buckton, Asia Pharma. Mfrg. Show 1996 (An Express Pharma Pulse Special Edition) p 4.
- 49) The formation of an inclusion complex between methacarbamol and HP-beta-cyclodextrin: Structure determination, molecular modelling, solubility and dissolution rate studies.
E.Antoniadou-Vyza, M.Efentakis, G.Buckton and Y.Loukas. 15th Pharm. Tec. Conf., March 1996, Oxford, Vol 1. 466-475.
- 50) Water mobility in amorphous lactose below and close to the glass transition temperature.
P.Darcy and G.Buckton., 15th Pharm. Tec. Conf. Oxford, March 1996, Vol 3. 128-133.
- 51) Comparison of wetting behaviour of theophylline and caffeine using various contact angle measurement methods and inverse gas chromatography.
J. Dove, G.Buckton and C.Doherty. 15th Pharm. Tec. Conf. Oxford, March 1996. Vol 3, 50-62.
- 52) Characterisation of adsorbed poloxamer surfactants
D.L.Carthew, G.Buckton, G.E.Parsons and S.Poole, Pharm. Res., (1996), 13 (Suppl.), PDD 7100, S-237.
- 53) The dynamic surface tension of HPMC film coating solutions
E.Ocha Machista and G.Buckton, Pharm. Res., (1996), 13 (Suppl.), PDD 7172, S-275.

- 54) Validation of humidity controlled experiments.
J.W.Dove, G.Buckton, J.Booth and C.Doherty. Pharm. Res., (1996), 13, (Suppl) PDD 7481, S-369..
- 55) Calorimetric and gravimetric water sorption profiles of silicified microcrystalline cellulose (SMCC).
G.Buckton, P.Darcy and B.E.Sherwood. Pharm. Res., (1996), 13, (Suppl) PT 6166, S-198.
- 56) Predicting interaction of powders in binary mixes from their surface energy components.
M.Ah Fat, G.Buckton, R.Burrows and M.Ticehurst, Pharm. Res., (1996), 13, (Suppl.), PDD7463, S-348.
- 57) A comparison between inverse gas chromatography and a novel Wilhelmy plate contact angle method in determining the surface properties of powders.
J.W.Dove, G.Buckton and C.Doherty, Pharm. Res., (1996), 13, (Suppl.), PDD 7548, S-353.
- 58) An investigation into the interaction between poloxamers and liposomes.
J.Castille, K.Taylor and G.Buckton. Pharm. Res., (1996), 13, (Suppl.), PT6035, S-165.
- 59) An innovative technique for the measurement of contact angles of alpha-lactose monohydrate.
N.M.W.Ahfat, G.Buckton, R.Burrows, M.Ticehurst. J. Pharm. Pharmacol., (1997), 49 Suppl, 68.
- 60) The effect of relative humidity on milled and spray dried nedocramil sodium.
E.Y.Ampratwum, K.M.G.Taylor, G.Buckton, K.Chippendale and D.Y.T.Wong, J. Pharm. Pharmacol., (1997), 49 (Suppl), 80.
- 61) The influence of heating on water loss (drying) of collapsed amorphous lactose. P.Darcy and G.Buckton, J. Pharm. Pharmacol., (1997), 49 (Suppl.), 70.
- 62) Measurement of alterations in surface energy characteristics due to different drying processes.
J.W.Dove, G.Buckton and C.Doherty, (1997), 49 (Suppl.), 69.
- 63) Investigations into new salt forms of cimetidine. P.Patel, G. Buckton, D. Elder and D. Eggleston. AAPS Boston 1997.
- 64) Surfactant drug interactions. R. Patel, G. Buckton, D.A. Rawlins and D.E. Storey. AAPS, Boston 1997.
- 65) Crystallization of ground and quenched ursodeoxycholic acid. E.Yonemochi, G. Buckton, T.Oguchi and K.Yamamoto. AAPS Boston 1997.
- 66) The effects of surfactant purity on the solubility and dissolution of a water insoluble drug.
R. Patel, G. Buckton, D.A. Rawlins, and D.E. Storey. AAPS Boston, 1997.
- 67) Moisture uptake and recrystallisation studies for bulk samples of partially amorphous lactose. P. Darcy and G.Buckton. AAPS Boston, 1997.
- 68) Crystallisation of amorphous lactose at different temperatures and humidities. P. Darcy and G. Buckton. AAPS Boston 1997.

- 69) Thermodynamic characterisation of water sorption in microcrystalline cellulose and silicified microcrystalline cellulose (SMCC) before and after wet granulation. G.Buckton and P.Darcy, Pharm. Res.,14, S-199, 1997.
- 70) The use of NIR spectroscopy to study the difference between Emcocel and Prosolv SMCC before and after wet granulation. 17th Pharm. Tech. Conf. , Dublin, March 1998, Vol. 3, pp17-27.
- 71) Performance of moisture barrier film coatings.
M.Whiteman, M.P.Jordan and G.Buckton. APGI/APV 2nd Wld. Meet. Pharm. Biopharm. Pharm.Tec., Paris, 25-28May 1998, 367-8
- 72) Near IR detection of change in form of amorphous and crystalline lactose.
E.Yonemochi, G.Buckton, J.Hammond and A.Moffat. APGI/APV 2nd Wld. Meet. Pharm. Biopharm. Pharm.Tec., Paris, 25-28May 1998, 13-14.
- 73) Physical characterisation of drugs and excipients.
G.Buckton. J. Pharm. Pharmacol., 50 (Suppl.), 60
- 74) The influence of poloxamer surfactants on the thermal pre-transition of DMPC and DPPC liposomes.
J.D.Castile, K.M.G.Taylor and G.Buckton. J. Pharm. Pharmacol., 50 (Suppl.), 147.
- 75) The impact of feed temperature on the polymorphic content of spray dried lactose.
O.C.Chidavaenzi, G.Buckton and F.Koosha. J. Pharm. Pharmacol., 50 (Suppl.), 184.
- 76) The physicochemical basis for enhanced drug absorption: calorimetric studies of drug-surfactant interactions.
R.Patel, G.Buckton, D.A.Rawlins and D.E.Storey. J. Pharm. Pharmacol., 50 (Suppl.), 189.
- 77) Characterisation of microcrystalline cellulose and silicified microcrystalline cellulose.
G.Buckton, E. Yonemochi, W.Yoon and A. Moffat, Pharm. Sci., Suppl. 1998, 1 S-30.
- 78) Electrostatic charging of microcrystalline cellulose and silicified microcrystalline cellulose.
G.Buckton, A.Ghelani and R.Lane, Pharm. Sci., Suppl. 1998, 1 S-311.
- 79) Hygroscopicity of moisture barrier film coatings.
G.Buckton, P.Darcy and M.Whiteman. Pharm. Sci. Suppl., 1998, 1 S-445.
- 80) NIR spectroscopy of microcrystalline cellulose and colloidal silica as physical mixtures and as PROSOLV SMCC.
G.Buckton and E.Yonemochi. Pharm. Sci. Suppl., 1998, 1 S-311.
- 81) Physicochemical characterisation of spray dried lactose prepared at different feed temperatures.
O.Chidavaenzi, G.Buckton and F.Koosha. Pharm. Sci. Suppl., 1998, 1 S-314
- 82) The impact of spray drying lactose in the presence of PEG 4000.
O.Chidavaenzi, G.Buckton and F.Koosha. Pharm. Sci. Suppl., 1998, 1 S-314
- 83) Interaction of poloxamer surfactants with hydrophobic surfaces.
S.Ali, G.Buckton and S.Mills. Pharm. Sci. Suppl., 1998, 1 S-169.
- 84) Characterising amorphous and crystalline trehalose and raffinose: Near IR Studies.

- E.Yonemochi, G.Buckton and A.Moffat., Pharm. Sci. Suppl., 1998, 1 S-404.
- 85) Physicochemical characterisation of Passcal formulations and excipients, Malcolmson, R.H., Buckton, G., Darcy, P., Cox, R.L., Renwick, C.E., and Embleton, J.K. Proc. Rep Drug Del, VI, 1998. p365-367
- 86) Adsorption of alkylpolyglycoside surfactants onto beclomethasone dipropionate. A.Columbano, G.Buckton, M.Grosvenor and P.Wikeley, (1999) J. Pharm. Pharmacol., 51, 62
- 87) Modification of microparticle surfaces by use of alkylpolyglycoside surfactants. A.Columbano, G.Buckton, M.Grosvenor and P.Wikeley (1999) J. Pharm. Pharmacol., 51, 1999, 337
- 88) Inverse gas chromatography on microparticles after adsorption of alkylpolyglycoside surfactants. A.Columbano, G.Buckton and P.Wikeley, (1999) PharmSci Suppl., 1, 502 (abstract 3510)
- 89) Modification of the surface energy of spray dried salbutamol sulphate in the presence of alkylpolyglycoside surfactants. A.Columbano, G.Buckton and P.Wikeley, (1999) PharmSci Suppl., 1, 503 (abstract 3511)
- 90) The novel combination of near infrared and dynamic vapour sorption gravimetric analysis to detect crystallisation in amorphous lactose. R.A. Lane and G. Buckton, (1999) J.Pharm. Pharmacol., 51, 46.
- 91) The development of isothermal titration microcalorimetry to probe interactions in a complex surfactant/polymer system. G.Buckton. Proc. 54th Annual Calorimetry Conference, Tallahassee, Florida, August 1999.
- 92) Surface Properties of α -lactose monohydrate under Humidified Conditions. H.E Newell, G. Buckton, D.A Butler and D.R. Williams (1999) American Association of Pharmaceutical Scientists Annual Meeting, New Orleans. Abstract 2348
- 93) The application of dynamic vapour sorption and near-infrared spectroscopy in combination to quantify small amounts of amorphous lactose S. E. Hogan and G. Buckton, J. Pharm. Pharmacol. 2000, 52 (Supplement): 163.
- 94) Characterisation of maltodextrins using isothermal microcalorimetry A. Shah, G. Buckton and S. Booth, J. Pharm. Pharmacol. 2000, 52 (Supplement)183
- 95) Characterisation of maltodextrins using isothermal microcalorimetry A. Shah, G. Buckton and S. Booth AAPS PharmSci Supplement, 2, 2000,ISSN 1522-0893
- 96) A comparison of Dynamic Vapour Sorption/Near Infrared Spectroscopy and Solution Calorimetry to quantify low amorphous lactose contents S.Hogan and G. Buckton www.aapspharmaceutica.com/scientificjournals/pharmsci/am_abstracts/2000/1982.html
- 97) The use of Solution Calorimetry in assessing partially amorphous dry powder inhalation carriers, D. Al-hadithi, G. Buckton and S. Brocchini. (Oral Presentation), 6th International Conference on Pharmacy and Applied Physical Chemistry (PhandTA 6), Ascona, Switzerland, 2002.

- 98) Partially amorphous carriers in dry powder inhalation, D. Al-hadithi, G. Buckton, S. Brocchini, N. Lowther and D. Singh. *Respiratory Drug Delivery VIII*, Tuscon, Arizona, 2002.
- 99) The *in vitro* evaluation of modified lactose as a novel dry powder inhalation carrier, D. Al-hadithi, G. Buckton, S. Brocchini, N. Lowther and D. Singh. *Abstracts from Drug Delivery to the Lungs XI. Journal of Aerosol Medicine*, 14 (1) 128, 2001.
- 100) Measurement of molecular mobility of molecules in amorphous state using enthalpy relaxation data measured by StepScan DSC, A.V. Ambarkhane, B. Stockton and G Buckton. BPC, Harrogate 2003.
- 101) Estimation of critical relative pressure of water (%cRH) for amorphous indomethacin using Isothermal microcalorimetry. A.V. Ambarkhane, B. Stockton and G. Buckton. BPC, Harrogate 2003.
- 102) The use of inverse phase gas chromatography to study the glass transition temperature of a powder surface. A.V. Ambarkhane, K. Pincott and G. Buckton. BPC, Manchester 2004.
- 103) Calorimetric study of protein adsorption onto polystyrene latex
M.J. Pollitt, G. Buckton, H.O. Alpar, S. Brocchini
Presented at the 5th European Workshop on Particulate Systems, London, July 2004.
- 104) Estimation of glass transition of amorphous lactose by inverse gas chromatography.
A.V. Ambarkhane, K. Pincitt and G Buckton.
AAPS, Baltimore 2004.
- 105) In vitro deposition from a dry powder inhaler and its correlation with surface energy of amorphous fine particle surfaces
A.C. Oliveira, G. Buckton, E. Collins (need to check rest of names). (2006) J. Pharm. Pharmacol., 58, (1): A24-A24
- 106) A calorimetric investigation of hydrogel swelling and drug release
L. He, S. Gaisford, S. Conti (need to check rest of names). (2006) J. Pharm. Pharmacol., 58, (1): A21-A22
- 107) In-situ process monitoring using calorimetry: Assessment of powder and tablet swelling
S. Gaisford, S. Conti and G Buckton. (2006) J. Pharm. Pharmacol., 58, (1): A5-A5
- 108) The characterization and dissolution properties of griseofulvin solid dispersions with HPMCAS
H. Al-Obaidi and G. Buckton. (2006) J. Pharm. Pharmacol. , 58, (1): A18-A19
- 109) Bridging polymeric excipients to stabilise amorphous dispersions
J. Fletcher, N. Wilson, G. Buckton, S. Brochini
Sent to Controlled Release Society Meeting
- 110) Spray dried alkaline phosphatase: variation of particle morphology
A. Khalid, G. Buckton, S. Brocchini
Sent to Controlled Release Society Meeting
- 111) Influence of the spray-drying concentration on the relaxation of an amorphous solid dispersion
H. Al-Obaidi, S. Brocchini, G. Buckton

BPC, 2007

112) Variation of dissolution rate of spray-dried solid dispersions from different solvents
H. Al-Obaidi, S. Brocchini, G. Buckton
BPC, 2007

113) Comparison of particle-particle interactions measured by atomic force microscopy and calculated from Hansen solubility parameters measured by inverse gas chromatography: preliminary report. In proceedings of Drug Delivery to the Lungs 18, Edinburgh, UK, pp. 180-83.
M.D. Jones and G. Buckton
The Aerosol Society, 2007

114) Solution calorimetry: A valuable technique to investigate properties of co-crystals.
M. Majumder, C. Rawlinson, A.C.Williams and G.Buckton. BACG meeting, London July 2011.

115) Producing homogeneous co-crystals in solid state: Can solution calorimetry provide kinetic information?
M.Majumder, C.F.Rawlinson, A.C Williams and G.Buckton UKPharmSci, August 2011.

116) Surface properties and aerosolization behavior of anhydrous and cocrystal forms of theophylline.
A.Alhalaweh, G.Buckton and S.P.Velaga. AAPS Annual Meeting, Washington DC, October 2011.

117) Mannitol as a co-milling agent for the preparation of theophylline inhalable particles.
M Malamatari, S Somavarapu, M Bloxham G. Buckton. Pharmaceutical Technology conference, Croatia. 2015.

118) Understanding nanoscale order in amorphous pharmaceuticals.
K.B.Borisenko, W., Li, G.Buckton, A,Stewart, A.I.Kirkland. ECM29 Croatia, 2015.

119) Conversion of nanosuspensions of dry powders by spray drying: a platform for the preparation of inhalation particles.
M.Malamatari, M.Bloxham, S.Somavarapu and G.Buckton, J Aerosol Med and Pulmonary Del. 28, A11, (2015).

10) Patents

Al-Hadithi, Buckton, Brocchini: Derivatised Particulate Inhalation Carriers: WO 03/094884

Al-Hadithi, Buckton, Brocchini: Particulate Inhalation Carriers: WO 02/45682

Fletcher, Buckton and Brocchini, Solid dispersions for oral drug release (filed January 2005)

(all lapsed)

Columbano, Buckton, Wickeley. Glycosides to stabilize inhalations granted patent

Patents granted from work at Pharmaterials Ltd for IntraCellular Therapeutics (which I mention as I have been named as an inventor. I was involved in the contract work for the company, but was not involved in the subsequent use of the data nor writing the patents) – US 61/838,105 :“Free base crystals” (2013) and WO 2014/205354, USP 9,469,647 “Salt

crystals". European Patent application 20165092.6 "Process for Preparing salts of a known PDE1 Inhibitor"

11) Research Supervision

PhD Research students supervised

T.C.Blair. Some factors influencing the survival of microbial contaminants in solid oral dosage forms. SERC award: 1986-1989.

N.Mitchard. The interactions of proteins and synthetic polymers with model hydrophobic drug carrier systems. Funded by ADDR Ciba-Geigy: 1987-1990.

S.C.Forster. Changes in physical properties of an homologous series of solids. Funded by Glaxo Group Research: 1987- writing up.

S.Russell. Title withheld. Funded by The Wellcome Foundation: 1988-1991.

G.Parsons. The use of surface energies to model the stability of non-aqueous suspensions. SERC / CASE (Lilly Research Centre Ltd.): 1988-1991.

A.MacKellar. Controlled crystallisation. SERC / CASE (Beecham Pharmaceuticals): 1988-1991.

J.H.King. The effects of processing on the structure of ointments and creams. Funded by The Wellcome Foundation: 1988-1991 (did not submit).

P.L.Sheridan. The use of computer modelling to predict the surface energies, and behaviour of powders. SERC / CASE (MSD): 1990-1993.

J.F.A.Pinto. Development of novel controlled release products from pellets. Personal funding: 1990-1993.

S.Mall. Surfactant interactions in solid dosage forms. SERC / CASE (MSD) 1992-1995

D.Carthew. Stabilisation of microfine suspensions. Wellcome Foundation Ltd., 1992- 1995.

H.Ahmed. The influence of processing on material properties. SERC/CASE (MSD), 1993-1996.

P.Darcy. Studies on the amorphous form of lactose. 1994-1998 (part time)

P.Patel. Crystal structure determination and physico-chemical characterisation of salt forms of drugs. SERC/CASE (SB) 1994-1997.

J.Dove. Molecular modelling, crystal structure determination and physico-chemical characterisation of a range of related drugs. Roche Products. 1994-1997.

M.Ah-Fat. Modelling of powder mixing (1995-1998)

R.Patel. Drug - surfactant interactions (1995-1998)

- O.Chidavaenzi. Understanding spray granulation (1995-1998)
- S.Ali, Suspension stabilisation, Glaxo-Wellcome (1996-1999)
- A.Shah, The influence of processing on powder crystallinity, MSD CASE (1997-2000)
- A.Colombano, Physico-chemical characterisation of novel surfactants, Astra, (1998-2001)
- S.Hogan, Stabilising protein formulation, RPSGB, (1998-2001)
- L.Barriocanal, Surfactant-macromolecule interactions, School Millennium Studentship, (1999-2002).
- M.Daifi, Spray drying processing, SB CASE award, (1998-2001)
- C.Galligan, The influence of surface energy on mixing. Pfizer, (1998-2001)
- J.Guaquiere, Novel particles for inhaled delivery of proteins, (1998-2001)
- R. M. Samra, Characterisation of Terfenadine and a model of hydrophobic amorphous Form of a drug and preparation and characterization of some of its derivatives, (part-time 1998-2003)
- R.Viboonkiat, Stabilising amorphous solid dosage forms (1999-2002)
- D. Al-Hadithi, Development of novel inhaled particles, Novartis (1999-2002)
- A. Moran, Solid state stability of macromolecular drugs, BBSRC, (2000-2003)
- E. Beusang, Modification of the surfaces of microparticles for inhalation drug delivery, AsraZeneca (2001-2004)
- L. Schueller, Dry powder inhalation: investigation of physical and chemical modifications of carrier on drug deposition, Novartis, (2001-2004)
- E. Mwesisgwa, The Hygroscopicity of Moisture-Barrier Film Coatings, Commonwealth Scholarship (2001-2004)
- K. Vora, Use of Dynamic Vapour Sorption Technique to Probe Surface Energies and Wettability of Powders, EPSRC CASE/GSK ((2001-2004)
- J. Stapely, The application of inverse gas chromatography (part-time 2003 – 2007) GSK funded.
- J. Fletcher, Studies of dispersion of drugs in polymers (EPSRC 2001-2004)
- A. Khalid, Studies of spray dried particles for stabilising proteins (EPSRC 2002-2005)
- A.Ambarkhane, Investigating into predicting the long term physical stability of amorphous compounds, GSK/SOP (2002-2005)

M. Pollitt, (with Dr Brocchini and Prof Alpar) Nasal delivery of proteins SOP, (2003-2006)

R. Ramos, The effect of milling process on crystalline drugs , Schering Plough, (2003-2006)

C.V. Scaria, (with Dr Gaisford), Use of isothermal microcalorimetry for stability studies. SOP, (2003-2006)

V. Gohil, Micronised/Milled Materials and Wet Granulation, AstraZeneca, (2003-2006)

Z. Ding, Titration calorimetry to study surfactant interactions with drugs (2003-2006)

L. He, Drug loading and release from hydrogels (2003-2006)

A. Matos De Oliveira, Spray dried powders for dry powder inhalers, Pfizer (2004-2007)

H Al-Obaidi, Griseofulvin in Solid Dispersions, (2004-2007)

Peng Ke, self funding (2005-2008) Stability of amorphous dispersions.

K. Barck, Astra Zeneca, studies on pMDI inhalation systems (2005-2008)

WangJing Li self funded (2010-2013). Stability of amorphous dispersions.

M Malamataris (2013-2016) EPSRC DTC grant. Engineering particles from nanoparticle association.

Z Marchant (2014-2017) SoP Funded. Nanoparticle delivery.

Visiting scientists

The following have worked in my laboratories:-

Dr L Zajic, University of Belgrade, Yugoslavia.; Dr M Efentakis, University of Athens, Greece; Dr L Oner, University of Hacettepe, Turkey; Dr M Angberg, University of Uppsala, Sweden; Mr C Tapia, University of Santiago, Chile; Dr S Tamburic, University of Belgrade, Yugoslavia; Dr E Papadimitriou, University of Athens, Greece; Ms T Gregori, University of Pavia, Italy; L Rousseau, University of Grenoble, France; V Ludet, University of Grenoble, France; Dr M Montagno Cappuccinello, Pharmacia Farmitalia, Italy; Dr M Rillosi, University of Pavia, Italy; Professor Ch'ng Hung Seng, Penang, Malaysia; Dr E O Machiste, University of Pavia, Italy; Dr E Yonemochi, Chiba University, Japan; Dr O Planinsek, University of Ljubljana, Slovenia; Dr M Ohta, Meiji Seika Kaisha Ltd, Japan; Dr M Ono, Daiichi Pharmaceutical Co. Ltd., Japan; Dr M Makoto Seiki Pharmaceuticals Japan, Dr Susumu Hasegawa, Sankyo Co. Ltd., Japan.

12) Invited and external lectures SINCE 2001

1) Plenary lecture at Krka award ceremony, Slovenia, January 2001

2) Research seminar Vectura Ltd, March 2001

- 3) Lecture at Swedish APS 4th International Symposium on Solid Dosage Forms, May 2001
- 4) Plenary lecture EUFEPS meeting on solid dosage forms, May 2001
- 5) Presentation at 29th Interpharm Research Conference, May 2001
- 6) RPSGB meeting - Physical stability testing lecture, May 2001
- 7) Seminar Petra University Jordan, May 2001
- 8) Management Forum speaker - Dry powder inhalers, powder properties, June 2001
- 9) Plenary lecture 1st World Conference on Inverse Phase Gas Chromatography, September 2001
- 10) Plenary speaker EUFEPS 10th Anniversary conference, September, 2001
- 11) Invited lecture at Technology Showcase, BPC, September 2001
- 12) Invited speaker, Drug delivery symposium, Edinburgh (Quintiles), September 2001
- 13) Management Forum - Physical form of excipients with regard registration, September 2001
- 14) Invited presentation at AAPS - Denver USA, October 2001
- 15) Invited seminar Bristol MS - New Jersey USA, October 2001
- 16) Six lectures to RPSGB Tableting Course, November 2001
- 17) RPSGB stability testing, April 2002
- 18) Seminar Strathclyde University, May 2002
- 19) Seminar Mahidol University, Bangkok, August 2002
- 20) Management Forum – Excipients -regulatory issues, September 2002
- 21) BPC – Presentation on Inverse Phase Gas Chromatography, September 2002.
- 22) Presentation at AAPS “Excipioeconomics” October 2002.
- 23) Schering Plough – New Jersey, Seminar – October 2002
- 24) RPSGB meeting on Tableting Technology. Series of lectures. Cambridge, November 2002.
- 25) IPEC Europe Seminar – Plenary lecture Analytical Characterisation of Excipients, January 2003.
- 26) APS – Inhaled Delivery Symposium, session chair and discussion group leader.

- 27) Materials Department, QMW University of London, seminar - Physical properties of materials of importance for drug delivery, February 2003.
- 28) RPSGB - Stability Testing, Cambridge, April 2003.
- 29) Invited presentation to the London, Oxford and Cambridge joint show case of leading new biotech companies, for Pharmaterials Ltd.
- 30) Swedish APS – Presentation on Characterisation and quantification of amorphous content in excipients, September, 2003.
- 31) BPC – Science Conference Chairman, September 2003.
- 32) Management Forum Excipients Conference – Presentation on Physical Testing of Excipients to Ensure Functionality, London, September 2003.
- 33) Kings College London – Seminar on Physicochemical Characterisation of Importance for Drug Delivery. October 2003.
- 34) British Crystallographic Association Industrial Group, Invited lecture on Amorphous Materials, November 2003.
- 35) RPSGB – Course Director for meeting on Tableting Technology. Cambridge, November 2003.
- 36) Management Forum – Speaker on Physical impurities and their effect – London, February 2004.
- 37) RPSGB – Stability Testing, Cambridge, February 2004.
- 38) International Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology – Co-Chair and speaker Pharmaceutical materials to underpin Drug Delivery, Nuremberg, March 2004.
- 39) Interpharm Research Conference – IGC to determine the surface Tg of particles. Chester. May 2004
- 40) Seminar at Bepak on Pharmaceutical Materials Science. July 2004
- 41) In-house training course on physical form – Sanofi-Aventis, September 2004
- 42) Hyper DSC and Inverse Gas Chromatography – British Pharmaceutical Conference Manchester, September 2004
- 43) Thermal methods to characterise the solid state – EDQM Quality on the Move: Dynamics of the European Pharmacopoeia. Budapest, October 2004.
- 44) Workshop on the amorphous state (IQWPC) – Frankfurt, October 2004
- 45) Symposium to mark the retirement of Henning Kristenson, Copenhagen, October 2004.
- 46) Web cast organised by Perkin Elmer- Applications of Hyper DSC November 2004
- 47) Seminar – Materials Properties to underpin Drug Delivery, Astra Zeneca, Wilmington USA November 2004.

- 48) RPSGB Tableting Technology, series of lectures, November 2004
- 49) Training conference on Poorly Soluble Drugs – series of lectures, London November 2004
- 50) Physical characterisation of materials and the significance for drug delivery - Plenary lecture to Korean Pharmaceutical Conference November 2004
- 51) Pharmaceutical materials science. Chuncheon University, Korea November 2004
- 52) Physical form and its significance for drug delivery. Active Biotech, Lund Sweden, December 2004
- 53) Surface properties of powders, determination and application (2 lectures) AAPS Arden House, Harriman NY, January 2005.
- 54) Amorphous materials – where are we now and where will we go? APSGB Amorphous Materials, London February 2005.
- 55) Physical impurities. Management Forum, Barcelona, March 2005
- 56) Hyper DSC, Seminar to global Pfizer sites through video conference, March 2005
- 57) Solid dispersions and the amorphous state. Arden House Conference, London, March 2005
- 57) Inverse gas chromatography. Arden House Conference, London March 2005
- 58) Inverse gas chromatography. Novartis Pharma, Basle, April 2005
- 59) Respiratory Drug Delivery Europe, Amorphous content control – Feasible test methods and specifications for inhaled drug products. Paris, May 2005 (Plenary)
- 60) Amorphous content control – a review of test methods GSK Ware in house seminar. July 2005.
- 61) Pharmaterials four years on. BPC Technology Showcase, Manchester, September 2005.
- 62) Physical characterization for product development. Dr Reddy's, Hyderabad, India, August 2005.
- 63) Amorphous Materials – detection, quantification removal and stabilization. IRR Optimising Polymorph Selection and Crystallisation Processes. London 22-25th November (also meeting Chairman for the entire event). London, 22-25 November 2005
- 64) RPSGB Tableting Technology – series of lectures. November 2005
- 65) Importance of Physical Form for Product Development and Life Cycle Management – Japan, December 2005
- 66) London Technology Network – London, January 2006

- 67) Stability Testing – Characterising Materials With Respect to Physical Stability – Cambridge, February 2006.
- 68) Management Forum – The Impact of Small Physico-Chemical ‘Impurities’ on Product Performance – Barcelona, March 2006.
- 69) Pharma IQ Polymorphism & Crystallisation 2006 – Amorphous Behaviour Workshop, London, March 2006.
- 70) TAC – Thermal Methods for Process Induced Disorder - London, April 2006.
- 71) IWPPCAS-1 – Presented talk and chaired session – Stamford, May 2006.
- 72) Amorphous Meeting – Ran and delivered programme for 2 day training course, London, 7 June 2006
- 73) European Continuing Education College – Formulation and Development for Poorly Water Soluble Drugs – London, June 2006.
- 73) Impurities Meeting IPC – Effectively Overcoming the Consequences of Polymorphism in the Production of Your APIs – London, June 2006.
- 74) Webcast on the use of Hyper DSC 12 October
- 75) Poorly Soluble Drugs – Ran and delivered a two day course. London 18/19 October 2006
- 76) AAPS Short Course. “Compatability starts at the interface” at AAPS Annual Conference Venue 29 October 2006
- 77) Amorphous materials course. Ran and delivered a 2 day course. Copenhagen 16 / 17 November 2006.
- 78) RPSGB Tabletting Technology. Delivered a series of lectures. 27 November 2006
- 79) JPAG “Functionality testing of excipients and APIs” London 7 December 2006
- 80) 7th Int. Symp. On Drug Delivery. CRS Inidian Chapter, Mumbai, 13 February 2007. Plenary lecture.
- 81) Poorly soluble drugs course, European Continuing Education College, London 19 March 2007 (3 hour lectures)
- 82) JPAG meeting “Characterisation of Amorphous Materials” London, 22 March 2007
- 83) APS Inhalation “Problem solving and decision making in inhaled drug delivery” 27th March 2007 Bath.
- 84) Astra Zeneca symposium on poorly soluble drug substances. Loughborough 29 March 2007. “Advances in amorphous formulations”.
- 85) Management Forum “The impact of small physico-chemical impurities on product performance”. Nice, 27 April 2007.
- 86) NATAS , Michigan, 26/27 August 2007

Presented 2 short courses, one plenary lecture and co-hosted session on Pharmacy:

“Isothermal, solution and titration calorimetry to study pharmaceutical systems” Short course

“Hyper DSC and its potential” Short course

“Characterising the amorphous state” Plenary Lecture

87) Management Forum “The impact of small physico-chemical impurities on product performance”. Nice, 5 October 2007

88) Pharmaceutical Training Services – Amorphous Conference. London, 11/12 October 2007

89) Society for Pharmaceutical Medicine “Changes in drug delivery over 20 years”. London, 25 October 2007

90) RPSGB, Tableting Technology – presented the following courses:

“A review of the reasons for granulation and tableting, the classes of excipients and principles of operation of tableting machines”

“Material Properties of Importance for Tableting (I) and (II)”

“A Brief Introduction to Modified Release”

Cambridge, 19 November 2007

91) Seminar at Boehringer Ingelheim, January 2008

92) 3rd SAB Meeting, Mumbai, 22-25 Feb 2008, ‘Physical Form and its Significance for Drug Delivery’,

93) FMC Florida, 27-29 Feb

94) APS Amorphous Conference, Bath, 18/19 March 2008, ‘The Future of Amorphous Materials’

95) Impurities Conference, - ‘The Impact of Small Physico-Chemical “Impurities” on Product Performance’, Nice, 10/11 April 2008

96) Colourcon, ‘Poorly Soluble Drug Formulation’, 30 April 2008

97) AAIPS, Washington, 8 May 2008

98) Interpharm, ‘New Trends in the Pharmaceutical & Regulatory Sciences’, 3-6 May 2008

99) Cambridge Seminar, 3 June 2008

100) Pharma Event – ASSA International Workshop - ‘Particle Characterisation’ – July 2008

101) Informa Life Sciences meeting - Crystal Form Selection and Crystallisation of API - ‘Choosing an amorphous phase over a crystalline phase’, Brussels, 14 October 2008

- 102) Colorcon Formulation School, Germany, 6 November 2008
- 103) ECEC Course – Formulation and Development of Poorly Water-Soluble Drugs - ‘Solid dose strategies for poorly water soluble drugs’, London, 11 November 2008
- 104) Colorcon Formulation School, Budapest, 12 November 2008
- 105) RPSGB, Tableting Technology – series of lectures. 24 November 2008
- 106) Drug Delivery to the Lungs – ‘Academic/Industry/Spin out Interactions – Drivers for Inhalation Innovation’, Edinburgh, 11 December 2008
- 107) 4TH Scientific Advisory Board Meeting – seminar given on ‘Amorphous Pharmaceuticals’, Mumbai, 23 February 2009.
- 108) Controlled Release Society (CRS) Indian Chapter – lecture given on ‘Amorphous Pharmaceuticals’, Mumbai, 25 February 2009.
- 109) Interpharm (Chairman of meeting) The challenges facing pharmaceutical science in the UK. Careys Manor 13-15 May 2009.
- 110) Management Forum Impurities meeting, Series of lectures, Nice, 25-26 June 2009.
- 111) Workshop on Inhalation, Informa Life Sciences, London 21 Sept 2009.
- 112) Compiling a physic-chemical profile (for inhalation products) Informa, London, 22 Sept 2009.
- 113) Short course in poorly soluble drug formulation, Teva, Israel, 25-26 November 2009.
- 114) Solid dispersions: Ideal if the formulation and process are right. APS Amorphous 2010. Nottingham 14th April 2010.
- 115) Interpharm 2010 (Chairman of Meeting), talk “Ordered Chaos”. Careys Manor, Hampshire, May 2010.
- 116) Characterisation of amorphous dispersions. Informa Meeting Slovenia, 18th May 2010.
- 117) Finding the optimum polymorph strategy. Bio2Business, Copenhagen, 17th June 2010.
- 118) Amorphous pharmaceuticals. Visiongain. London. 24th January 2011.
- 119) Series of 3 lectures on physical form, testing methodology and excipient compatibility. Impurities. Management Forum, London 10th June 2011.
- 120) Early formulations: selecting a strategy to achieve fast to man. Bio2Business London, 20th Sept 2011.
- 121) A strategy for formulation of poorly soluble APIs. AAPS Annual Meeting., Washington DC. 25th Oct 2011.
- 122) RPSGB Tableting Technology – series of 5 lectures, November 2011 London
- 123) RPSGB Tableting Technology – series of 5 lectures, November 2012 London

124) Poorly soluble drug delivery – Society for Medicines Research, London, October 2012.

125) Thermal studies of physical form – Thermal Methods Conference, Hertfordshire, November 2012.

126) Update on physical form. Allergan, California, June 21013.

127) RPSGB Tableting Technology – series of 5 lectures, November 2013 London

128) Interpharm conference – Overview presentation – May 2014, Midlands, UK

129) Update on poorly soluble drug delivery. Allergan, California, June 2014

130) RPSGB Tableting Technology – series of 5 lectures, November 2014 London

131) RPSGB Tableting Technology – series of 5 lectures, November 2015 London

132) RPSGB Tableting Technology – series of 5 lectures, November 2016, London

133) RPSGB Tableting Technology – series of 5 lectures, November 2017, London

13) Expert witness

I list below the cases which have progressed to trial or public hearing in which I have assisted as an expert witness. I have underlined the company for which I was retained.

1) Deposition USA – GSK v Teva. Rosiglitazone maleate salt form. [2007]

2) Dublin, court testimony. GSK v Norton Healthcare (Teva). Seretide inhalation formulation patent. [2009] IEHC 277 – Dublin.

3) UK court testimony. Schering Plough v Norbrook. Sustained release veterinary product [2005] EWHC 2532 (Ch) – London

4) Deposition USA – December 2009. Duramed v Paddock. Sustained release tablet formulation.

5) Sweden 2010 – written declaration. Cephalon v Orifarm. Modafinil formulation (particle size). Odense, Denmark, December 2010. Infringement hearing. Cephalon v Orifarm. Modafinil formulation patent. UK report – preliminary injunction. 2011. Cephalon v Orifarm / Orchid / Mylan (Generics UK). Modafinil formulation patent. Danish Appeal Court testimony - September 2011, Cephalon v Orifarm. Modafinil formulation patent.

UK court testimony – May 2011. Cephalon v Mylan(Generics UK) / Orchid. Modafinil formulation patent.

6) UK court testimony – February 2011. Schering (Bayer) v Gedeon Richter. Oral contraceptive (drospirenone and ethinyl estradiol) tablet formulation.

7) US court testimony – June 2011 Valeant v Watson. Bupropion HBr salt patent (deposition in December 2010)

8) Deposition USA – October 2011, Warner Chilcott v Mylan. Doryx formulation. Court testimony February 2012, Warner Chilcott v Mylan. Doryx formulation (stabilizing coat patent). Newark, New Jersey.

9) Deposition May 2013, Par v Novartis, Rivastigmine transdermal patch. New York. And also Deposition in same case in August 2013 and April 2014. Trial testimony in the same case May 2014 in Wilmington Delaware.

10) Deposition Oct 2013, Mylan (Lupin) v Janssen, Darunavir tablets. Chicago. USA.

11) Deposition August 2014, Watson (Actavis) v Sepracor (Sunovion), Levalbuterol tartrate MDI. Washington DC. Trial in same case November 2014 Willmington Dellaware.

12) UK Court testimony. Teva v Boehringer Ingelheim. Tiotropium bromide inhalation capsules. July 2015. Norway court testimony on the same case March 2016. February 2017 testimony in Dublin for Irish version of the same case. Testimony in Oslo appeal court November 2017. Stockholm court testimony March 2018. Testimony in Lisbon, Portugal, November 2021.

13) Deposition July 2015. Apotex (consolidated with Sandoz, Alembic, Zydus, Intas and Hetero) v Otsuka Aripiprazole low hygroscopicity forms. Follow up deposition Washington DC, Sept 2015, same case. Testimony at the Markman hearing in Camden New Jersey, October 2015. Further deposition September 2016.

14) Deposition July 2015 Rufinamide polymorphs. Roxane, Mylan, Lupin v Novartis. Deposition.

15) Deposition October 2015 Perrigo v AstraZeneca, Esomeprazole trihydrate claim construction.

16) Trial testimony, February 2016, Bayer v Cobalt. Drospirenone / ethinyl estradiol tablet. Toronto, Canada.

17) UK Court testimony, June 2016, Actavis / Teva / Mylan / Actelion v ICOS / Lilly. Tadalafil particle size formulation patent. Same case in Norway and Dublin.

18) Deposition July 2016, Mylan v Noven, Methylphenadate transdermal patch claim construction.

19) Deposition July 2017, Mylan / Par v Indivior / Monosol. Buprenorphine oral film. IPR action. San Diego, California. Depositions August 2017 on non-infringement and invalidity for court case, Washington DC.

20) Deposition January 2018, Bionpharma v Silvergate. Enalapril powder. San Diego, California.

21) Deposition June 2018, Apotex v Lilly. Pemetrexed formulation claim construction. Chicago. Deposition June 2019 in the same case.

22) Deposition October 2018, Aurobindo, DRL, Lupin, Sun, Accord, Amneal, Invagen, Torrent, Zydus v Sumitomo. Invalidity of tablet formulation of lurasidone with pregelatinized starch.

23) UK Trial November 2018, GSK v Vectura. Dry powder inhaler with a ternary blend.

- 24) Deposition June 2019, Aurobindo, Sigmapharm, Unichem and Zydus v BMS/Pfizer. Invalidity of claim to an apixaban salt. Trial in same case Wilmington De, October 2019
- 25) Deposition November 2020, Amneal v Silvergate. Validity/Infringement of enalapril maleate oral solution. (Virtual) Trial in same case, Wilmington De, February 2021.
- 26) Deposition March 2021, Apotex and Accord v Astellas. Non-infringement/validity regadenoson monohydrate form.
- 27) UK Trial May 2021, Teva v Bayer. Sorafenib tosylate salt form. Nov 5th 2021 attended (virtual) NL trial in the same case. 16th February 2022 testified (virtual) in Portuguese PI trial, and actual trial in March 2023. Trial Barcelona July 2023.
- 28) Deposition July 2021, Sandoz, Apotex, Sun, Mylan, Aurobindo, DRL, Ajanta v Merck. Sitagliptin dihydrogenphosphate monohydrate form. Trial, Virginia, Mylan v Merck December 2021.
- 29) Deposition August 2021, Alvogen v Indivior. Non-infringement of oral film patent of buprenorphine/naloxone.
- 30) Deposition March 2022, Lupin v Takeda. Non-infringement / invalidity Azilsartan Kamedoxomil.
- 31) Deposition September 2022, Glenmark v Pfizer. Non-infringement axitinib tablets.
- 32) Deposition January 2023, Lupin v Astellas, Non-infringement of mirabegron tablets. Trial February 2023 Wilmington DE.
- 33) Deposition on claim construction January 2023. Bausch/Salix v Mylan Plecanatide tablets.
- 34) Deposition on PTAB case. September 2023. Pharmion v Apotex. Azacitidine non-enteric coated tablets.
- 35) Deposition October 2023, Galderma v Lupin. Non-infringement of Doxycycline IR/DR capsules. Trial of same case January 2024, Wilmington DE (held in Philadelphia).
- 36) Deposition December 2023, Exeltis v Lupin. Invalidity and non-infringement, Slynd Progesterone only pill. Trial in same case, Wilmington Delaware, February 2024.
- 37) Deposition December 2023. Gilead/Janssen v Lupin. Invalidity, Cobicistat on silica. Deposition regarding a 4 drug fixed dose tablet (Darunavir, Tenofovir alafenamide hemifumarate, emtricitabine and cobicistat. Washington DC January 2024.