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Señor

DIRECTOR DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente No. 08.088.449- solicitud de patente de invención a favor de **MEDICIS PHARMACEUTICAL CORPORATION**. Título **FORMULACIONES DEL MODIFICADOR DE INMUNORESPUESTA QUE CONTIENEN ÁCIDO OLEICO Y MÉTODOS**.

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante, manifiesto a usted que debidamente notificado de la Resolución No. 58093 del 28 de septiembre de 2012, interpongo contra ella en debido término, **RECURSO DE REPOSICIÓN**, para que sea revocada en su totalidad, y en su lugar se conceda el Privilegio de Patente, para el objeto de la solicitud en referencia

Respaldo el RECURSO en los siguientes

HECHOS:

1. La resolución arriba citada No. 58093 niega el Privilegio exclusivo de Patente de Invención para el objeto de la solicitud de la referencia considerando que el capítulo reivindicatorio carece de nivel inventivo. Lo anterior, de acuerdo con las siguientes consideraciones:

i. Determinación del Estado de la Técnica

Consultadas las fuentes de información con que se cuenta se encontraron los siguientes documentos, anteriores a la fecha de prioridad invocada y relacionados con la materia de la solicitud en estudio.

N°	Documento	Título	Fecha de Publicación
D1	US2003199538	Pharmaceutical formulation comprising an immune response modifier	23/10/2003
D2	US20040089855	High oleic acid oil compositions and methods of making and electrical insulation fluids and devices comprising the same	13/05/2004
D3	US20020058674	Systems and methods for treating a mucosal surface	16/05/2002

Nivel Inventivo

El examinador considera que las características técnicas esenciales de las composiciones reivindicadas se derivan de manera obvia a partir de las enseñanzas combinadas de D1 y D2, mientras que el método reivindicado se deriva de manera obvia a partir de D3, por lo que la materia reivindicada carece de nivel inventivo.

RESUELVE:

ARTÍCULO SEGUNDO: Denegar la patente de invención a la creación titulada **FORMULACIONES DEL MODIFICADOR DE INMUNORESPUESTA QUE CONTIENEN ÁCIDO OLÉICO Y MÉTODOS.**

FUNDAMENTOS:

En primer lugar, consideramos necesario discutir el problema técnico de la presente invención y la solución aportada, incluyendo los beneficios asociados con la misma.

Tal y como se puede observar en D1, el ácido oleico se puede utilizar para solubilizar diversos modificadores de la inmunorespuesta inclusive aquellos altamente insolubles y difíciles de formular. Sin embargo, estas formulaciones sufren de una estabilidad deteriorada, lo que constituye un grave problema en el campo farmacéutico ya que la vida útil del producto se disminuye considerablemente.

Para solucionar este problema, la presente invención se dirige a formulaciones farmacéuticas que comprenden 1-(2-metilpropil)-1H imidazo [4,5-c]quinolin-4-amina (*imiquimod*) y un componente de ácido oleico, y en donde dicho componente de ácido oleico contienen al menos alrededor de 80% por peso de ácido oleico como ácido graso y con un índice de peróxidos de no más de alrededor de 5 miliequivalentes de oxígeno por kilogramo y contiene menos de alrededor de 1% por peso de impurezas polares en o antes de la formulación de dicha crema farmacéutica, así como al método para preparar y estabilizar la formulación.

Dicho ácido oleico es comúnmente denominado Ácido Oleico Súper Refinado NF (*Super Refined oleic acid NF*) (reivindicaciones 19, 39 y 49). Esta combinación ha demostrado una mejora significativa en la estabilidad de la composición, manteniendo un nivel bajo de impurezas en las formulaciones después de periodos extendidos de tiempo y bajo condiciones severas.

Los ejemplos presentados evidencian este efecto. Particularmente, la tabla 2 muestra la evolución de las impurezas en el tiempo para cuatro composiciones; las composiciones A y B contienen ácido oleico de pureza estándar (como aquel de D1) mientras que las composiciones C y D contienen Ácido Oleico Súper Refinado NF (como en la presente invención). Adicionalmente, las composiciones B y D contienen un antioxidante utilizado comúnmente en la industria (BHA), mientras que las composiciones A y C no lo contienen. Por demás, las composiciones A, B, C y D son iguales. Las composiciones se almacenaron bajo condiciones severas: temperatura de 40°C y una humedad relativa de 75%. Los resultados obtenidos¹ se reproducen a continuación:

Tabla 2				
Punto de Tiempo	Impurezas (%p/p)			
	A	B	C	D
Inicial - parte superior	0,09	0,08	0,02	0,03
2 meses - parte superior	0,25	0,32	0,07	0,09
2 meses - fondo	0,33	0,30	0,04	0,15
4 meses - parte superior	0,42	0,76	0,18	0,15
4 meses - fondo	0,46	0,56	0,04	0,29
6 meses - parte superior	0,81	0,30	0,07	0,14
6 meses - fondo	0,49	0,29	0,04	0,07

Se puede observar que la composición A, formulada con ácido oleico de pureza estándar, degrada progresivamente el componente activo imiquimod durante el almacenamiento de la composición. Una solución obvia, como sería por ejemplo añadir un antioxidante a la composición no tiene ningún efecto sobre la estabilidad del imiquimod tal y como se aprecia en la columna B; de hecho esta adición parece ser una desventaja. Contrario a lo anterior y de acuerdo a la columna C, formular la composición con Ácido Oleico Súper Refinado NF (como en la reivindicación 1 de la presente solicitud) muestra una mejora significativa en la estabilidad de la composición.

¹ De acuerdo a la publicación PCT

Finalmente, la columna D demuestra que la adición del antioxidante a composiciones que contienen Ácido Oleico Súper Refinado NF no produce ningún efecto adicional. En este orden de ideas, se puede concluir que la degradación del imiquimod no está relacionada con la oxidación sino que es un problema directamente atribuible al ácido oleico.

Antes de comparar la solución anteriormente referida con el estado de la técnica, manifestamos una vez más nuestro fuerte desacuerdo en la selección de documentos del estado de la técnica, particularmente en lo que se refiere a D2. El uso de dicho documento es completamente inapropiado y arbitrario, considerando que comprende estado de la técnica no análogo a la solicitud evaluada.

En efecto, la anterioridad D2 se dirige a **fluidos de aislamiento eléctrico** y claramente no se refiere en ningún momento a **composiciones farmacéuticas**, como la presente invención. El empleo de un documento perteneciente a un campo tan marcadamente disímil es inaceptable bajo los modelos empleados a nivel mundial para evaluar la patentabilidad de una solicitud. Por ejemplo, en el caso Colombiano el Instructivo de Examen de Solicitudes de Patentes de Invención y Modelo de Utilidad de su Oficina establece lo siguiente al respecto:

La búsqueda debe hacerse sobre la base de la invención definida por las reivindicaciones y soportada por la descripción y dibujos, si es el caso, ya que las reivindicaciones son las que determinan el alcance de protección.

El examinador debe tomar como objeto de búsqueda, la solución técnica definida en la reivindicación independiente. La búsqueda debe estar enfocada en el concepto inventivo de la reivindicación independiente, y no en la redacción literal de la reivindicación independiente. Sin embargo, la búsqueda no debe ampliarse para incluir cada detalle que puede ser derivado de una consideración de la descripción y de los dibujos. (2.10.4.2 Búsqueda de reivindicaciones independientes; Subrayado fuera de texto)

Considerando que las reivindicaciones establecen claramente en su preámbulo que se refieren a una **crema farmacéutica**, advertimos que es indiscutiblemente inapropiado citar una anterioridad que se refiera a fluidos de aislamiento eléctrico, campo que no se encuentra relacionado con el de la farmacéutica. Otra consideración que se debe tener al respecto es la *motivación* que tendría una persona medianamente versada en el campo de la farmacéutica para buscar componentes de formulaciones para tratar complicaciones de la piel en un documento de fluidos de aislamiento eléctrico, en donde –sobra decir– existen consideraciones completamente diferentes a la hora de seleccionar componentes. Por ejemplo, D2 enseña lo siguiente sobre el ácido oleico de alta pureza:

"La purificación del aceite descrito designado aceite RBD [refinado, blanqueado y desodorizado] es necesaria porque los restos de compuestos polares y materiales ácidos permanecen en el aceite, lo que hace que no sea apto como fluido eléctrico" (página 3, párrafo 37, D2; subrayado fuera de texto)

A pesar de esto, dice el examinador que el anterior argumento "*no es relevante*" porque el uso de ácido oleico súper refinado en los campos de alimentos, farmacéutico y de cuidado personal o cosmética ya era conocido y cita, como pie de página, una industria que produce ácido oleico. Si el examinador ha encontrado una referencia que anticipe el uso de ácido oleico en cremas farmacéuticas como se propone en la presente invención, no entendemos por qué no presenta dicha referencia como estado de la técnica, indicando claramente la fecha de publicación de tales enseñanzas. En cualquier caso, notamos que la búsqueda debe estar enfocada en el concepto inventivo de la solución y en ningún caso debe limitarse a una identificación de los elementos reivindicados en cualquier parte, por lo que una referencia a una industria que produce un componente es bastante arbitraria.

Volviendo al análisis de nivel inventivo de la reivindicación 1, se ha determinado que el documento D1 es el estado de la técnica más cercano a la invención en cuanto revela una formulación farmacéutica que comprende imiquimod y que puede incluir adicionalmente un ácido graso. La referencia específica al ácido oleico se hace en el párrafo [00148], como una lista de posibles ácidos grasos:

"...Ejemplos no limitantes de tales ácidos grasos incluyen ácido isoesteárico, ácido oleico, y ácidos carboxílicos lineales o ramificados con cadena de 6 a 18 átomos de carbono..."

No hay ninguna otra referencia al ácido oleico, lo que da a entender que este no es un componente fundamental de las composiciones de D1, a diferencia de la presente invención. De hecho, como reconoce el señor Examinador, esta anterioridad no menciona ni sugiere el uso de un ácido oleico de alta pureza, como se requiere en la reivindicación 1. En este orden de ideas, no existe ninguna motivación en el estado de la técnica para incluir dicho componente en las composiciones de D1.

Sin embargo, propone el examinador emplear las enseñanzas de D2, particularmente el uso de Ácido Oleico Súper Refinado NF, para complementar las enseñanzas de D1 y que a falta de un efecto técnico inesperado la crema farmacéutica de la presente reivindicación se considera obvia.

Solo con el propósito de establecer que una persona versada en la materia no tendría ninguna motivación para realizar tal combinación pasaremos por alto el hecho de que D2 se refiere a **fluidos de aislamiento eléctrico** (campo técnico completamente diferente al de la presente invención), y nos referimos únicamente a una posible combinación de ácido oleico súper refinado con imiquimod. Para sustentar lo anterior, nos referimos a la Declaración de Marc B. Brown, Ph. D., presentada en casos correspondientes de solicitudes en los Estados Unidos, la cual adjuntamos en su totalidad como evidencia adicional del nivel inventivo de la presente solicitud, y que resumimos en los siguientes puntos.

1. Como quedo establecido en el problema técnico de la presente invención, el ácido oleico no se usa comúnmente en formulaciones farmacéuticas debido a su estabilidad inherente, lo que se puede apreciar con la falta de especificación sobre este componente en D1. El ácido oleico, ya sea purificado o no, contiene un enlace doble en sus moléculas y como resultado es bastante propenso a la oxidación, llevando a la rancidez (decoloración y mal olor). Adicionalmente, la oxidación de ácido oleico puede afectar negativamente la estabilidad de los ingredientes activos y excipientes de la formulación, razón por la cual muy pocos productos farmacéuticos contienen ácido oleico. De hecho, el doctor Brown establece que en todos sus años de experiencia *"nunca ha seleccionado voluntariamente ácido oleico, ya sea de grado estándar o súper refinado, para formulación de medicinas tópicas"*.
2. A pesar de que el ácido oleico súper refinado tiene un nivel más bajo de impurezas polares (como peróxidos) que el ácido oleico de pureza estándar, este es ineludiblemente propenso a la oxidación; a nivel comercial el ácido oleico súper refinado se empaca en tambores revestidos sellados y con un volumen de nitrógeno para protegerlo de la oxidación. En este sentido, cualquier ventaja que se pueda percibir del producto más puro será anulado en el producto final debido a la inclusión de oxidantes, como agua y oxígeno, en la formulación final como resultado de (i) adición de excipientes, (ii) condiciones y operaciones de procesamiento para producir la crema (calentamientos, mezclados, etc.) y (iii) condiciones ambientales de almacenamiento del producto final.
3. Al momento de la presente invención, el ácido oleico súper refinado era un producto relativamente nuevo, por lo que no existía ninguna indicación de si comportamiento en formulaciones farmacéuticas. Esto queda demostrado con la búsqueda de anterioridades relacionadas.

4. Basados en lo anterior, no es posible asegurar que la inclusión de ácido oleico súper refinado en una formulación farmacéutica incrementara de manera evidente la estabilidad de la misma. Así las cosas, una persona versada en la materia en el momento de la invención no hubiera esperado que una formulación con ácido oleico súper refinado tuviera estabilidad aceptable. Más relevante para la presente invención (de acuerdo con la materia reivindicada) no hay ninguna sugerencia en el estado de la técnica que las formulaciones con imiquimod y ácido oleico súper refinado tuvieran una estabilidad aceptable. En palabras del doctor Brown *"no hay ninguna razón científica para creer que el Ácido Oleico Súper Refinado NF le hubiera conferido alguna propiedad estabilizante al imiquimod o que uno pudiera creer razonablemente, mucho menos asegurar, que la estabilidad del imiquimod pudiera ser mejorada por el Ácido Oleico Súper Refinado NF, en comparación con el ácido oleico de pureza estándar"*.
5. Adicionalmente un técnico versado en la materia, al momento de la invención, no habría tenido ninguna expectativa razonable de éxito, en términos de estabilidad mejorada, al formular composiciones con imiquimod y Ácido Oleico Súper Refinado NF porque el ácido oleico súper refinado contiene otros aditivos que podrían afectar negativamente la composición. Por ejemplo, este ácido contiene BHT que ocasiona problemas significativos a la composición final de imiquimod, especialmente si hay una concentración elevada de BHT en éste.
6. Finalmente, a partir de las enseñanzas del estado de la técnica no hay ninguna certeza de que las presencia o ausencia de impurezas en el ácido oleico súper refinado NF fuera relevante para la estabilidad de una formulación de imiquimod, ya que dicho principio activo no es propenso a la oxidación y por tanto no hay razón científica para pensar que un ácido más refinado pudiese incrementar significativamente la estabilidad del imiquimod, como en la presente invención.

En conclusión ninguna de las anterioridades citadas en el análisis de patentabilidad proporciona suficientes enseñanzas para obtener la presente invención de manera obvia.

Además, no hay ninguna base para concluir a partir del estado de la técnica que la estabilidad de las composiciones de imiquimod se aumentara significativamente con la adición de ácido oleico de alta pureza, por lo que el efecto de la presente invención debe ser considerado como un resultado inesperado.

Asimismo, solicitamos no perder de vista el campo técnico de D2, que es completamente diferente al de la presente invención, por lo que no debiese ser considerado para analizar el nivel inventivo de la misma. Estas son razones de sobra para afirmar que la crema farmacéutica de la reivindicación 1 cumple satisfactoriamente con el requisito de nivel inventivo.

Ahora en cuanto, a los métodos reivindicados manifestamos nuestro desacuerdo con el análisis efectuado por el señor Examinador, dado que simplemente se limita a comparar el método de la presente invención con el de D3 y a establecer las diferencias entre los mismos. No hay ningún documento adicional que complemente las enseñanzas de D3 para obtener el método de las reivindicaciones 32 y 40 sin emplear actividad inventiva. De acuerdo al análisis anterior sobre las composiciones reivindicadas, es claro que la adición del ácido oleico súper refinado es una etapa esencial de los métodos y no hay ninguna enseñanza en D3 que permita derivar dicha etapa. Además, el señor Examinador se equivoca nuevamente al afirmar que no existe un efecto técnico inesperado al emplear el ácido oleico de alta pureza, ya la adición de dicho ácido proporciona un efecto de estabilización inesperado, como ya se explicó anteriormente.

En resumen, los métodos de la presente invención no pueden ser derivados a partir de las enseñanzas de D3 y adicionalmente resultan en efectos técnicos inesperados relacionados con la estabilidad de la formulación. Por lo tanto, estos cumplen satisfactoriamente con el requisito de nivel inventivo.

Finalmente deseamos mencionar que la Oficina de Patentes de Estados Unidos ha expedido 29 patentes relacionadas directamente con la materia divulgada y reivindicada en la presente solicitud, las que listamos a continuación lo cual es un claro indicio de la patentabilidad de la presente invención:

- US8,080,560 Immune response modifier formulations containing oleic acid and methods
- US7,939,555 Method of preparing a pharmaceutical cream and minimizing imiquimod impurity formation
- US7,928,118 Reduction of imiquimod impurities in pharmaceutical creams
- US7,928,117 Method of inducing cytokine biosynthesis
- US7,928,116 Method of treating actinic keratosis
- US7,923,463 Methods for stabilizing imiquimod for two months, four months, and six months
- US7,919,501 Method of controlling formation of imiquimod impurities
- US7,915,279 Method of treating mollescum contagiosum

- US7,915,278 Method of treating basal cell carcinoma
- US7,915,277 Method of treating genital or peri-anal warts
- US7,906,543 Method of reducing imiquimod impurity formation
- US7,906,527 Reduction of imiquimod impurities using refined oleic acid
- US7,906,526 Method of treating a dermal and/or mucosal associated condition
- US7,906,525 Reduction of imiquimod impurities at four months using refined oleic acid
- US7,906,524 Pharmaceutical cream having similar or less levels of imiquimod impurity formation as cream with BHA (comparator)
- US7,902,246 Methods for controlling formation of imiquimod impurities for two months, four months, and six months
- US 7,902,245 Methods for reducing imiquimod impurities for two months, four months, and six months
- US7,902,244 Method of preparing a pharmaceutical cream and minimizing imiquimod impurity formation (at least four months storage)
- US7,902,243 Methods for improving imiquimod availability at two months, four months and six months between refined and compendial
- US7,902,242 Method of stabilizing imiquimod
- US7,902,216 Pharmaceutical creams with refined oleic acid
- US7,902,215 Pharmaceutical creams with reduced imiquimod impurities
- US7,902,214 Method of treating a mucosal and/or dermal associated condition
- US7,902,213 Pharmaceutical cream with reduced imiquimod impurities at four months using refined oleic acid
- US7,902,212 Reduction of imiquimod impurities at six months using refined oleic acid
- US7,902,211 Method of inducing interferon biosynthesis
- US7,902,210 Reduction of IMIQUIMOD impurities at two months using refined oleic acid
- US7,902,209 Method of preparing a pharmaceutical cream and minimizing imiquimod impurity formation
- US7,655,672 Immune response modifier formulations containing oleic acid and methods

Por las razones anteriormente expuestas, solicito a ese despacho REVOCAR la decisión tomada mediante la Resolución No. 58093 del 28 de septiembre de 2012, y tendiente a obtener la concesión del Privilegio de Patente de conformidad con los artículos 14 y 48 de la Decisión 486 de la comunidad Andina, arriba citados.

NOTIFICACIONES

Recibiré notificaciones en la Secretaria General de la Superintendencia de Industria y Comercio, o en su defecto, en mi Oficina de Abogado, situada en la Calle 70A No. 4-41 de esta ciudad de Bogotá.

Del Señor Director



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.S.J.

C.C. 80.410.337 de Usaquén

Calle 70 A No. 4 - 41

Application of A.S. Statham et al.
U.S.S.N.: 12/334,255
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Docket No.: 67064C2 (54610)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Alexis S. Statham et al.

Application No.: 12/334,255

Confirmation No.: 7883

Filed: December 12, 2008

Art Unit: 1617

For: IMMUNE RESPONSE MODIFIER
FORMULATIONS CONTAINING OLEIC
ACID AND METHODS

Examiner: D. Claytor

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR §1.132

The undersigned, **Marc B. Brown**, hereby declares as follows:

1. I received my Ph.D. in *Pharmaceutical analysis* from Loughborough University of Technology in 1993, and I received my B.Sc. honours in medicinal and pharmaceutical chemistry from Loughborough University in 1990.

2. I am the Chair in Pharmaceutics at the School of Pharmacy, University of Hertfordshire. I am also presently the Chief Scientific Officer and a Director of MedPharm Ltd, a company I founded, which specialises in the formulation of topical drug delivery systems for application to the skin, nail, and wounds. Before joining MedPharm Ltd., I was employed as Director of Pharmaceutical Development at Hyal Pharmaceutical Corp for 3 years. Prior to and during my employment with Hyal

Pharmaceutical, I was a Lecturer and Senior Lecturer in pharmaceuticals, at the School of Pharmacy, Kings College London, for 13 years. I have about 20 years of experience in the fields of pharmaceuticals and drug development in both academia and industry. I have published over 80 papers and 11 patents and/or patent applications in the pharmaceutical field. My curriculum vitae is attached hereto as Appendix A.

3. I have reviewed and am familiar with the above-identified application for U.S. patent. In particular, I am familiar with rejected claims 29-46 thereof, directed to pharmaceutical formulations, as well as now pending claims 29-48, as amended and added in a paper being submitted on even date herewith. I understand that, in an Office Action issued from the U.S. Patent Office on March 6, 2009 (the "Office Action"), the Examiner has rejected previous claims 29-46 as allegedly unpatentable under 35 U.S.C. §103(a) over Wick et al., U.S. Patent No. 5,238,944 ("Wick"), in view of CRODA, Super-refined Oleic Acid NF ("CRODA") and/or over Purcell, U.S. Patent No. 6,559,182 ("Purcell") in view of CRODA.

4. The Office Action states that Wick discloses "compositions comprising the imiquimod compound with an oleic acid component." The Office Action also states that CRODA discloses Super Refined Oleic Acid NF. The Office Action then states on page 3 thereof that:

...it would be obvious to a person of ordinary skill in the art to provide the Super Refined Oleic Acid NF as taught by CRODA in the invention of Wick et al. with a reasonable expectation of success. One would be motivated to include the Super refined Oleic Acid because it is known to have less polar impurities, including low peroxide amounts, which will aid in providing longer storage of the overall product and it is a known emulsifying and solubilizing agent (as shown under Pharmaceutical

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Application of A.S. Statham et al.
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and Healthcare Uses on page 2). Therefore, if one skilled in the art wanted to obtain a composition that is known to have oleic acid as a vehicle and wanted to ensure that there was a low amount of polar impurities and high stability of the overall product would occur, one would be led to use Super Refined Oleic Acid NF because of the properties of the compound to have low polar impurity amounts.

5. I do not agree with the Examiner's conclusions, these Examiner statements or the Examiner's line of reasoning, as set forth in the Office Action, based on my knowledge of imiquimod, oleic acid, Super Refined Oleic Acid NF, pharmaceuticals and drug and formulation development and my experience in the fields of pharmaceuticals and formulation development for the reasons described herein.

6. In the literature, oleic acid is proposed as a dermal penetration enhancer; however it is not widely used due to its inherent instability. For perspective, oleic acid, whether purified or not, comprises a double bond in the molecule and is very prone to oxidation, resulting in rancidity (discolouration, bad smell). In addition, the oxidation of oleic acid can affect the stability of other formulation ingredients (active as well as excipients). Only a few products are on the market containing oleic acid. In these products, the instability is often addressed by other means, e.g., storage in a container or packaging with no oxygen access (e.g. aerosol) or addition of antioxidants. Examples comprise Tostran® gel (a testosterone gel which contains the antioxidant BHT and is presented in a metered dispenser) and a couple of transdermal gels for hormone delivery (e.g. Estalis®, and Combipatch®). In addition, the usage levels are generally quite low. For example, Calamine oily lotion (BP 1980) contains 0.5% oleic acid.

7. While it is my understanding that Super Refined Oleic Acid NF has a lower level of peroxides and polar impurities than standard compendial grade oleic acid, it nevertheless is not without stability issues. For example, Super Refined Oleic Acid NF

is packaged in lined tight-head steel drums with a nitrogen head space to protect the product from oxidation. In addition, CRODA recommends maintenance of the nitrogen blanket after the containers have been opened.

8. In my opinion, it is unlikely that anybody formulating a topical product would choose oleic acid, Super Refined or not, as a suitable solubiliser/solvent due to the inherent instability problem of this raw material and its very limited shelf life as described above; especially at levels of 28%. In all my years of development experience, I have never by choice selected oleic acid, whether standard compendial or Super Refined grade, for formulation in a topical medicine for all of these reasons.

9. It is understood that CRODA Super Refined Oleic Acid NF has been developed in order to address the rancidity problem of oleic acid itself and to reduce its impact on the formulation in which it is contained. The term "polar impurities" and "substantially free from polar impurities" in the patent summary and detailed description refers to impurities in the oleic acid which have been reduced in order to mitigate the risk of oxidation of oleic acid. There is no reason to believe that Super Refined Oleic Acid NF would confer any stabilising properties to any API other than those prone to oxidation.

10. For clarification, Table 1 in the above-identified application for U.S. patent describes a series of formulations with either standard compendial grade oleic acid or Super Refined Oleic Acid NF with or without an antioxidant BHT. Table 2 describes the imiquimod related impurities (assayed at 308 nm for this reason) that are observed as a result of these differing compositions. The impurities described in Table 2 refer to imiquimod degradants and related imiquimod substances, as detected at 308 nm, and not polar impurities associated with oleic acid decomposition.

11. Imiquimod is a very stable molecule, in fact one of the most stable molecules

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that I have ever come across in all my years of experience in pharmaceutical development. In my opinion, imiquimod is not susceptible to oxidative degradation. However, Table 2 in the above-identified application for U.S. patent shows that the presence of standard compendial grade oleic acid leads to formation of imiquimod degradation products over time as detailed in Column A. Adding an antioxidant to the formulation has no effect on the stability of imiquimod and, if anything, makes it worse (seen at the 6 months time point, see Table 2 Column B). In contrast, using Super Refined Oleic Acid NF leads to an unexpected improvement of stability (Column C). Adding an antioxidant on top of Super Refined Oleic Acid NF again does not make any further difference (Column D). This further supports my opinion that imiquimod is not subject to oxidative degradation as anti-oxidants have no effect on its stability. In addition, the presence of Super Refined Oleic Acid NF prevents degradation which is not, in my opinion, directly linked to oxidation. This is completely surprising and unexpected and I have no logical explanation for this phenomenon.

12. The key parameter which is expected to play a role in the improved stability of Super Refined Oleic Acid NF (not the active ingredient) vs a standard compendial grade oleic acid is thought to be the low peroxide value. However, in reviewing the specification for Super Refined Oleic Acid NF, it becomes clear that Super Refined Oleic Acid NF is tested for a number of additional parameters which are not required in the Ph. Eur. and USP/NF. These parameters comprise e.g. unsaponifiable matter, heavy metals such as lead and mercury and also a lower iodine value than required by Ph. Eur. and USP/NF. As such, it is my opinion that it is impossible to predict which, if any, of these defined parameters and/or combinations thereof are responsible for the improved stability of imiquimod. This is not something that could have been anticipated or predicted when using this novel grade of oleic acid. As such, in my opinion, nobody skilled in the art would be able to predict that the Super Refined Oleic Acid NF as taught by CRODA in the invention of Wick et al. would confer the enhanced imiquimod

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stability with a reasonable predictability of success.

13. In my opinion, imiquimod is not prone to oxidation. Thus, there is no scientific reason to believe that Super Refined Oleic Acid NF would confer any stabilising properties to imiquimod or that one could reasonably believe, nevermind ensure, that the stability of imiquimod could be significantly improved by Super Refined Oleic Acid NF, as compared with standard compendial grade oleic acid. Given the fact that imiquimod is not prone to oxidation, and there is nothing in the specification sheet for Super Refined Oleic Acid NF that would remotely suggest that Super Refined Oleic Acid NF could possibly enhance imiquimod stability, it is my opinion that the Examiner's conclusions, statements and line of reasoning, as quoted above and set forth in the Office Action, are misplaced and in error.

14. Moreover, and as discussed above, it is my opinion that one skilled in the art would not formulate or even be motivated to formulate imiquimod with Super Refined Oleic Acid NF at the time the invention, as claimed in now pending claims 29-48, was made, because:

(a) it was and still is generally understood by those of skill in the art that standard compendial grade oleic acid is inherently highly unstable and notorious for degrading and turning rancid;

(b) Super Refined Oleic Acid NF at the time the invention was made, was a relatively undefined and unproven new material with no track record that was introduced into the market as I understand in about late 2002;

(c) To the extent there are any perceived stability advantages with Super Refined Oleic Acid NF over standard compendial grade oleic acid, those advantages

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would most likely be negated or disappear in a final formulated product due to a number of reasons, including the introduction of oxidants, such as water and oxygen, into the final formulated product as a result of: (i) the addition of formulation excipients to make the final formulated product; (ii) processing conditions and techniques, such as heat, stirring, shearing and mixing, used to make the final formulated product, during which oxidation reactions detrimental to the final formulated product can be catalysed; and (iii) ambient conditions at which the final formulated products is stored.

(d) Super Refined Oleic Acid NF contains the antioxidant BHT, which can add significant complication and potential problems to a final formulated product, especially if too much BHT is in the final formulated product, such as when formulating an imiquimod product; in my view, an unusually high amount of BHT would be introduced into an imiquimod product due to the amount of oleic acid required to solubilise imiquimod;

(e) BHT, which is included in Super Refined Oleic Acid NF, is a known antiviral which could negatively bias any clinical evaluation by causing false positives when final formulated products, such as imiquimod formulations, are used to treat viral infections;

(f) Super Refined Oleic Acid NF is packaged in lined tight-head steel drums with a nitrogen head space to protect the product from oxidation and CRODA recommends maintenance of a nitrogen blanket after the containers have been opened. As such it is highly unlikely that any final formulated product containing Super Refined Oleic Acid NF will remain stable under commercially viable storage conditions;

(g) Super Refined Oleic Acid NF, even today, is not considered to offer any significant benefit or improvement over standard compendial grade oleic acid as to long

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term stability of final formulation products formulated with oleic acid; and

(h) Wick, which issued approximately 11 years prior to the filing date of the above-identified application for U.S. patent, was silent as to the stability of imiquimod formulated with oleic acid.

15. I have also read and am familiar with U.S. Patent No. 6,559,182 ("Purcell"). As I understand, Purcell in its broadest sense is concerned with esters, not free acids. More particularly, as I understand Purcell, it is concerned with jojoba oil esters, not free oleic acid.

16. I am familiar with the oleic acid component as claimed in pending claims 29-48 and jojoba oil esters as discussed in Purcell. The oleic acid component, as claimed in amended claims 29-48, contain oleic acid in an amount of at least about 80% w/w. Jojoba oil esters, on the other hand, as taught by Purcell, are mixtures of bound fatty acids and fatty alcohols, of which oleic acid, if even present in free acid form, is present only in a minor amount of no more than about 4-8% w/w. In my view, Purcell relates to esters, not free oleic acid, in their true form and has no relevance to claims 29-48, as now pending.

17. In conclusion, it is my opinion that, at the time the invention was made, as claimed in pending claims 29-48, the cited prior art, including Wick, Purcell, CRODA and/or the Croda references, neither taught nor even remotely suggested, either alone or in any appropriate combination, that Super Refined Oleic Acid NF could be used in any manner to stabilise imiquimod. Wick does not discuss imiquimod stability and there is no evidence from Wick that the stability of imiquimod was tested or that the imiquimod in the disclosed oleic acid compositions would have been stable. In addition, none of these issues are addressed in the Declaration submitted during the prosecution

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of Wick and cited in the above-identified application for U.S. patent. Thus, it is my opinion that, at the time the invention was made, as claimed in pending claims 29-48, there was no motivation to even try to stabilise imiquimod with Super Refined Oleic Acid NF, because there was no scientific justification at that time to believe that the stability of imiquimod could be improved with Super Refined Oleic Acid NF, as compared to standard compendial grade oleic acid. In also my opinion, I do not believe that one could predict that Super Refined Oleic Acid NF would improve the stability of imiquimod without trying it first. In addition, I cannot imagine anyone skilled in the art presuming anything else.

18. Accordingly, it is my opinion that there would be no probability, never mind a reasonable probability, that the teachings of Wick or Purcell could be modified as suggested by the Examiner to successfully enhance the stability of imiquimod, at the time the invention was made as claimed in pending claims 29-48, and the stability results for imiquimod, as reported in Table 2 of the above-identified application for U.S. patent, are very surprising, unexpected and unpredictable.

19. I hereby further 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 are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. 1001), and that such willful false statements may jeopardize the validity of the above-identified Application or any patent issued thereon.

Date: 1st April 2009

M.B. Brown
Marc B. Brown

CURRICULUM VITAE

NAME Professor Marc B. Brown B.Sc.(Hons), Ph.D., CChem MRSC.

E MAIL marc.brown@medpharm.co.uk

EDUCATION AND QUALIFICATIONS

1986 - 1990 Loughborough University of Technology
B.Sc.(Hons) in Medicinal and Pharmaceutical Chemistry;
Class 2.1 with a Diploma in Industrial Studies

1990 - 1993 Loughborough University of Technology
Ph.D. entitled 'The use of long wavelength fluorescence in the
study of ligand-protein interactions.'

PRESENT POSITIONS

1999-present Chief Scientific Officer and Director, MedPharm Ltd

My industrial experience and the subsequent success of my collaborations with industry led to me co-founding a spin-out company named MedPharm Ltd. The company is a contract research organisation which specialises in the formulation of topical drug delivery systems for application to the skin, nail and wounds. The company has a 600 m² GLP accredited laboratory in Guildford, Surrey along with a GMP facility in Hampshire and business offices in Oxford and France. This rapidly expanding venture currently employs 35 people and has recently announced collaborations with companies in the US, Australia, Japan, Asia and Europe. MedPharm also owns intellectual property in the area of drug delivery which it is currently commercialising, with four products due to enter the clinic in the next 2 years. I have acted as Chief Scientific Officer and Director for MedPharm since its initiation in 1999. Recently, MedPharm was selected to present at the 'Ones-to-watch' Conference, Genesis 2003 and has been awarded a DTI Smart award, an SBRI award and a SEEDA development award for its drug delivery inventions.

2006- present Chair in Pharmaceutics, School of Pharmacy, University of Hertfordshire

I was appointed as Chair in Pharmaceutics in the School of Pharmacy, University of Herts., in July 2006.

Research

During my early career I received funding from a Toronto based company, Hyal, for the study of the use of hyaluronan in localising the delivery of drugs to the skin thereby reducing systemic absorption. Hyal owned many patents in this area and employed me to further develop their

understanding of the mode of action of hyaluronan. In addition, I was asked to manage the pharmaceutical development of many hyaluronan based formulations which were undergoing clinical investigation, including their lead product (Solaraze) which is a topical hyaluronan-based formulation developed for the treatment of actinic keratosis. My research led to the production of a patent (WO9813024, Hyaluronan in drug delivery) and a more fundamental understanding of the dermal drug delivery properties of hyaluronan. During this time, my research and expertise were fundamental in Hyal (now SkyePharma) receiving regulatory approval in Europe and the USA for Solaraze. This initial success encouraged me continue research in drug delivery and at present my key areas of interest can be defined as follows:

Transdermal/dermal drug delivery. The transdermal and dermal delivery of drugs serves as a suitable alternative for overcoming problems associated with other more conventional means of drug administration such as oral therapy. However, the barrier nature of human skin imposes physicochemical limitations to the type of permeant that can traverse the barrier, which has limited the amount of commercially available products based on this route of administration. My research in this area is focused on the development of systems to enhance drug permeation across the stratum corneum for either systemic or localised drug delivery. The latter treatment is of potential benefit for psoriasis, eczema and various skin cancers where systemic absorption of a topically applied drug such as an immunosuppressant or a cytotoxic is likely to cause considerable adverse side effects. Solaraze was one of the first regulatory approved formulations of this type. I have been responsible for several patent/patent applications in this area.

Topical formulations for the prevention/treatment of parasitic infection. Bilharzia is a parasitic infection associated with the skin. It is endemic in 74 countries and infects 200 million people annually, with a further 500-600 million at risk. My research, in collaboration with Phil Whitfield on bilharzia has resulted in the successful design of the first ever *in vitro* model of the cercarial infection of human skin. The model has rendered it possible to study the temporal dynamics of this penetration and to gain a greater understanding of the processes involved in the infection. We have also developed a topical formulation that acts as a barrier to the parasite and is highly effective in preventing its penetration of the skin. The formulation is receiving considerable attention from the 'travel community' as a means of reducing the risk of infection. The PhD student who performed this work was nominated as 'Young Investigator of the Year' at the 50th Anniversary Conference of the American Society of Tropical Medicine (Atlanta, Georgia, USA). As a direct result of the development of this new concept we have been invited to contribute articles to the New Scientist and various travel magazines in Europe and the USA. A development, which is linked to our bilharzia treatment, is the design of one of the first topical formulations for the treatment of cutaneous leishmaniasis. This work is being undertaken in collaboration with Dr. Simon Croft of the London School of Hygiene and Tropical Medicine and it is planned for the formulation to enter field trials within 2 years.

Drug delivery via the airway. The advances in biotechnology over recent years have led to the identification and production of a range of peptides and proteins, which have potential to be employed as therapeutic agents. Formulating such proteins in a state that provides chemical and physical stability up to the point of delivery, is a more difficult process than formulating traditional small molecular weight drugs. My research in this area involves the formulation of particulate dosage forms for delivery to the nose and lung. Proprietary technology has been developed that not only helps to stabilise biopharmaceuticals in the final dosage form but also significantly increases the amount delivered to the deep lung when compared to other more conventional formulations. This research recently resulted in one of my PhD students, Sian Lim, receiving the 'EMI Outstanding Manuscript Award in Pharmaceutical Technology' from the American Association of Pharmaceutical Scientists (AAPS) in 2001.

Mucoadhesive drug delivery. The ability to retain pharmacologically active agents for extended periods of time on any mucosal epithelia, including those of the eye, nose, mouth, rectum or vagina confers a number of potential therapeutic advantages. All of these epithelia are coated with a layer of mucus. My current research involves the development and optimisation of mucoadhesive

particulate and gel formulations. Particulate formulations are being produced with controlled solid state surface properties in order to enhance mucoadhesion and drug dissolution (see above). In addition, the process of coacervation, freeze drying and spray drying are also being optimised and the mucoadhesive function of the resultant microparticles determined using physical, *in vitro* and *in vivo* techniques. Other research involves the development of gel formulations for oral and buccal retention and drug delivery.

Development of analytical methods and in vitro models. In order to further the development of the formulations described above my research group has become heavily involved in the development and validation of both analytical methods and *in vitro* models specifically designed to study and optimise such systems. Along with the first *in vitro* model of the infection of human skin by cercariae, I have co-developed *in vitro* skin, wound and nail models of bacterial and fungal infections. In addition, various cell culture, tissue culture and *in vivo* models have been developed to study formulation factors on the delivery and absorption of drugs into and across the nail, skin, wounds, arthritic joints, nose, lung and mucosal epithelia. As a direct result of these new ideas I was invited to become a member of the DTI funded VAM Postgraduate working group, which was initiated by the Laboratory of the Government Chemists. The role of the group is to ensure that any research performed in an academic environment is 'fit for purpose'. The group produced a guideline document for all postgraduate students on the validation of analytical methods in academe and I am a co-author of this work.

Other responsibilities include:

- Chair of the Research Executive, School of Pharmacy
- Member of the Research Board, University of Hertfordshire

Teaching

Teaching responsibilities include:

- Lectures, tutorials and laboratory classes on drug formulation and design, physical pharmacy, pharmaceutical analysis, mathematics, microbiology, mucoadhesion, polymers, modified release injections, solubilisation, gene delivery, skin physiology, transdermal and dermal drug delivery, carbohydrates, biological membranes and drug absorption and drug delivery via the lymphatic system.
- The supervision of many undergraduate projects.
- Member of the School Management Executive

The supervision of the following research students for a PhD:

- PD1. Zhoujing Zhou (Completed August. 2000; Chinese Government funded) *Spray-dried peptide formulations for transdermal powdered delivery*
- PD2. Manita Hanpanitcharoen (Completed Sept. 2000; Thailand Government funded) *Hyaluronan induced targeting of drugs to the epidermis*
- PD3. Tahir Nazir (P/T, Completed Aug.. 2004; Industrially funded). *The dermal delivery and localisation of drugs*
- PD4. Shahira Amr (Completed May. 2002; Self funded). *An investigation of novel vesicle type formulations for intradermal drug delivery*

- PD5. Sian Lim (Completed Feb. 2001; Self funded) - Winner of the EMI Graduate Student Outstanding Manuscript Award at AAPS 2001. *An investigation of novel microparticulate mucoadhesive formulations for nasal drug delivery*
- PD6. Francesca Rytlewski (completed Sept 2002, EPSRC funded). *Pharmaceutically engineered systems for transdermal absorption.*
- PD7. Yong-Hong Liao (Completed Nov 2002; Industrially and ORS funded). *Pharmaceutical development of protein/peptide powder formulations*
- PD8. Rebecca Ingram (Completed March 2003; KCLA studentship). *A novel topical approach for the treatment of schistosomiasis*
- PD9. Abdul Quadir (completed October 2004; EPSRC studentship. *Spray dried formulations for the pulmonary delivery of peptides and proteins*
- PD10. Tracey Garnier (completed Sept 2004, Sir Halley Stewart Trust funded). *Novel approaches to the topical treatment of cutaneous leishmoniasis*
- PD11. Stuart Jones (completed April 2005, MedPharm and KCL funded). *Protein/peptide formulations for pulmonary delivery*
- PD12. Weijiang He (completed October 2005, KCL funded). *An investigation into the mode of action of hyaluronan in topical formulations*
- PD13. Franklyn Akomeah (Completed October 2005, Industrially funded). *Development of novel transdermal drug delivery devices*
- PD14. Barbara Jff (Completed Sept. 2005, EPSRC funded). *Investigating the dissolution of amorphous and semi-amorphous particles in simulated lung fluid*
- PD15. Fergus Manford (completed February. 2006, Industrially funded). *Drug targeting to the lung*
- PD16. Emily Cooper (completed Nov 2005, Sir Halley Stewart funded). *The use of imaging technology to investigate the inhibition of schistosome cercarial penetration of human skin*
- PD17. Gilhan Nananyakkara (completed March 2006, MedPharm and KCL funded). *Development of novel topical penetration enhancers*
- PD18. Marlise Santos (completed Feb. 2006, Brazilian Space Agency funded). *Nasal drug delivery in zero gravity*
- PD19. See Wah Tang (Completed July. 2008, EPSRC/RSC funded). *The use of dynamic mechanical analysis for the detection and quantification of amorphous content in pharmaceutical powders*
- PD20. Maria Prapadopolou (P/T expected to complete Sept 2009, self funded). *Mathematical modelling of drug absorption across the skin*
- PD21. David Potter (P/T expected to complete Sept 2009, self funded). *The development of cannabis based medicinal products*
- PD22. Mark Lakeram (Completed March. 2007). *Novel topical formulations for drug delivery to the skin*
- PD23. Rajeshree Khengar (expected to complete, Sept. 2007, self-funded). *Novel topical formulations for ungual drug delivery*
- PD24. Mojgan Moddaresi (expected to complete Sept 2007, Institute of Cosmetic Science funded). *The assessment of some cosmetic formulations*
- PD25. Monica Reid (expected to complete January. 2009, Industrially funded). *The development of novel MDA systems for topical drug delivery..*

- PD26. Yanjun Zhao (expected to complete January. 2009, Dorothy Hodgkin funded). *Novel nanoformulations.*
- PD27. Hadjer Nacer (expected to complete Oct. 2008, Algerian Government funded). *Nanoparticulate nasal formulations.*
- PD28. Kirsten Staff (expected to complete March. 2009, Industrially funded). *The development of novel topical formulations for wound healing.*
- PD29. Sarah Fila (expected to complete March. 2009, Algerian Government funded). *Eutectic topical formulation development.*
- PD30. Charles Evans (P/T expected to complete Feb.2012, Industrially funded). *Ungual formulation development for the treatment of nail disease.*
- PD31. Daniel Wood (expected to complete September 2009, EPSRC funded). *Development of thermoregulating topical drug delivery systems.*
- PD32. Iris Palmer (expected to complete September 2009 SoP funded). *Novel particulate formulations for the treatment of skin infection.*
- PD33. Faiza Benouda (expected to complete September 2009, Algerian Government funded). *Dermal formulations and supersaturated residual drug activity*

The supervision of the following postdoctoral workers/research fellows:

- PF1. Dr. Suki Klair (November 1995 - March 1996). *The development of a synthetic route for the radiolabelling of diclofenac.*
- PF2. Dr. Rohanah Hussain (July. 1996 -December 1996). *The study of ligand interactions with HA*
- PF3. Dr. Fiona Bennett (Sept. 1995 - October 1998). *The targeting potential of hyaluronan and other possible drug delivery systems*
- PF4. Dr. Larissa Gould (June 1996 - February 1998). *The development of cyclosporin formulations*
- PF5. Dr. David Riley (January 1997- March 1997). *The formulation of Taxol*
- PF6. Dr. Paul Laidler (August 1997 - July 1998). *The development and validation of a cyclosporin assay in blood and skin*
- PF7. Dr. David Riley (January 1998- June 1998). *The formulation of calcitonin for TPD*
- PF8. Dr. Lisa Sanderson (August 1998- July 1999). *Development of novel foam formulations for the treatment of varicose veins*
- PF9. Dr. Zehing Zhu (November 1998 –June 1999). *The effect of liposome fluidity on the topical delivery of drugs*
- PF10. Dr. Ann Bartlett (April 1999 – present). *The use of Franz cell technology to investigate a novel approach to the control of schistosomiasis*
- PF11. Dr. Michael Donaldson (July 2000 –Nov. 2002). *The development of HA based dermal formulations*
- PF12. Dr. Nilesh Patel on a project entitled (Nov. 2000- Nov.2001). *Development of novel particulate drug delivery systems*
- PF13. Dr. Nilesh Patel (Jan. 2004- Oct 2004). *Cell Culture studies*
- PF14. Dr. Lewis Lee (March 2004-present). *Isolation and characterisation of synovial specific microvascular determinants using defined peptides identified by in vivo phage display'*

- PF15. Dr. Stuart Jones (September 2004-August 2005). *Nanotechnology and drug delivery*
- PF16. Dr Cynthia Bousquet (Oct. 2004-Sept. 2005). *Cell culture Studies*
- PF17. Darragh Murnane (Sept. 2005 – June 2006). *The development of novel airway formulations*
- PF18. Dr. Matt Traynor (Nov.2006-) *Novel dermal formulations*

PREVIOUS POSITIONS

2002-2006 Senior Lecturer in Pharmaceutics, Department of Pharmacy, KCL
(1993-2002, Lecturer in Pharmaceutics, Department of Pharmacy, KCL)

I was appointed to the academic staff as a Lecturer in the Pharmacy Department at King's College London in 1995 having spent approximately 18 months as a research fellow working under the guidance of Chris Marriott and Gary Martin. The Lectureship was industrially funded and consequently I divided my time between the College and working as Director of Pharmaceutical Development for Hyal Pharmaceutical Corporation who were based in Toronto, Canada. In 1997, I took up a position as a full-time member of academic staff and developed other areas of interest in the field of drug delivery.

Teaching responsibilities included:

- Lectures, tutorials and laboratory classes on drug formulation and design, physical pharmacy, pharmaceutical analysis, mathematics, microbiology, mucoadhesion, polymers, modified release injections, solubilisation, gene delivery, skin physiology, transdermal and dermal drug delivery, biological membranes and drug absorption and drug delivery via the lymphatic system.
- The supervision of many undergraduate and MSc projects.
- Examiner on MPharm and MSc courses
- Course leader for MPharm IV electives Drug Delivery and Science of Dosage Form Design
- Member of Departmental Executive
- Member of the School Executive
- Former Postgraduate Tutor

Other responsibilities included:

- Member of the Pharmaceutical Sciences Research Division Executive
- Member of the Centre for Ultrastructural Imaging Executive

2003-2006 Academic Business Fellow, KCL Enterprises

In May 2003 I was appointed to the position of Academic Business Fellow at KCL. My role was to use the experience I have gained in industry and my entrepreneurial skills to identify spin-out opportunities within KCL, prepare a business plan, secure funding and ensure that they have the best chance of success. To achieve these objectives I work closely with IP2IPO and other venture capitalists, business angels and funding institutions.

2003 - 2004 London Technology Network Business Fellow

I was appointed as a London Technology Network (LTN) Business Fellow in January of 2003. The aim of the LTN is to help technology-intensive companies be more effective and efficient in their knowledge acquisition from London's universities. The network has the support of the Department of Trade and Industry (DTI); Invest UK; Business Link London; Government Office for London, and the London Development Agency. Specifically, LTN's four main objectives are to:

- work with its network of large and small companies to map their short-, medium- and long-term technology needs.
- help universities respond to industry's need for technology-related knowledge acquisition.
- match the technology needs of client companies to London's world-class researchers and teachers.
- support technology-focused special interest groups and encourage better and more frequent interaction between companies and universities.

1995 - 1997 Director of Pharmaceutical Development, Hyal Pharmaceutical Corporation, (now SkyePharma) Toronto, Canada.

The position involved the management of all pharmaceutical and product development projects in the company. One such formulation has recently received a Product Licence from the FDA, MCA, HPB and various European regulatory authorities. I also ensured that the laboratory, comprising 15 people, was run according to GLP and GMP.

Work performed in the facility was divided into four main areas:

- In house pharmaceutical development and study of novel topical formulations for the targeting of xenobiotics to the pathological site.
- Development of validated and stability indicating assays for the testing and study of these formulations.
- Raw material analysis, product manufacture and QA/QC testing of finished product prior to release for use in Phase I, II & III clinical trials and as EDR.
- To ensure all data is acceptable for submission to the relevant Regulatory Authority for licensing approval.

1988 - 1989 Chemist, Goodyear Tyre and Technical Centre, Luxembourg**PRESENTATION OF WORK****Invited Lectures**

- IL1. 5th International Symposium on Quantitative Luminescence Spectrometry in Biomedical Sciences. University of Ghent, Belgium (May 1993) *Long wavelength fluorescence and its biomedical applications.*
- IL2. 2nd International Workshop on Hyaluronan in Drug Delivery. Toronto, Canada (May 1994). *A study of the mechanism of the drug delivery properties of hyaluronan.*

- IL3. 6th Interscience World Conference on Inflammation, Antirheumatics, Analgesia and Immunomodulators 1995. Geneva, Switzerland (March 1995). *The effect of hyaluronan on the in vitro deposition of diclofenac within the skin.*
- IL4. 3rd International Workshop on Hyaluronan in Drug Delivery. Nyon, Switzerland (April 1995). 1) *A study of the transdermal drug delivery properties of hyaluronan;* 2) *An in vitro investigation of the mode of action of hyaluronan as drug delivery vehicle using circular dichroism;* 3) *A preliminary study of the effect of hyaluronan on the deposition of diclofenac within human skin using autoradiography.*
- IL5. Dermatology Update 1995. Montreal, Canada (Oct. 1995). *Topical formulations of drugs-How to penetrate the skin barrier.*
- IL6. 7th International Seminar on the Treatment of Rheumatic Diseases. Tel Aviv, Israel (Dec. 1995). *Hyaluronan, A transdermal drug delivery system: An in vitro investigation.*
- IL7. International Society for Rheumatic Therapy. 5th Biennial Congress, Paris, France (May 1996). *Referred analgesia: Topical Hyanalges-D. Delivery to the skin.*
- IL8. 4th International Workshop on Hyaluronan in Drug Delivery. Paris, France (May 1996). 1) *The diffusion of diclofenac from hyaluronan and other polysaccharide formulations through human skin in vitro;* 2) *The determination of the viscosity-average molecular weight of hyaluronan by capillary viscometry;* 3) *An in vitro study of the effect of hyaluronan on diclofenac binding to human serum albumin;* 4) *Hyaluronan delivery of cyclosporin'.*
- IL9. Clinical Dermatology 2000 - Improving Drug Delivery Technology, University of British Columbia, Vancouver, Canada (June 1996). *Hyaluronan: A targeting agent for diclofenac.*
- IL10. Cancer Drug Development. Hannover, Germany (March 1997). *The use of the glycosaminoglycan hyaluronan to target chemotherapeutic drugs to breast carcinoma.*
- IL11. 6th International Symposium on Hyaluronan. Toronto, Canada (June 1997).. *Hyaluronan Improved Liposome Technology.*
- IL12. Hyaluronan 2000, Wrexham, UK (Sept. 2000). *The use of hyaluronan in topical drug delivery.*
- IL13. London Technology Network launch meeting, London UK (Dec. 2002). *Technology vs biology – what does the industry need?*
- IL14. London, School of Pharmacy, London UK (Jan. 2003). *Academic parasites II.*
- IL15. Pfizer, Ann Arbor, USA (Feb. 2003). *Formulation optimisation for percutaneous and perungual delivery.*
- IL16. St. Thomas' Hospital, Dept of Dermatology, London, UK (Feb. 2003). *Skin delivery systems: Getting under your skin.*
- IL17. BBSRC sponsored 'Intellectual Property Masterclass', London UK (April 2003). *MedPharm, a daydream, a dalliance or a dilemma.*
- IL18. SYMPHONEC sponsored 'Entrepreneurship and Innovation', London UK (May 2003). *Winning with the entrepreneurial venture.*
- IL19. British Pharmaceutical Conference 2003. Harrogate (Sept 2003). *Spinning-out in academia: MedPharm.*
- IL20. Thermal analysis and skin, TMG, London (Nov. 2003). *Skin deep'*
- IL21. BBSRC sponsored 'Practical Issues for Commercialising Research Masterclass', London UK (April 2004). *Mind to market: Commercialisation from a researchers perspective.*

- IL22. RSC Analytical Sciences meeting 'Advances in Bioanalysis', (May 2004). *The Application of Analytical Methods in Drug Delivery and Deposition.*
- IL23. 5th Annual Meeting of Skin Forum, Portsmouth, UK, (July 2004) Academic parasites: topical inhibition or enhancement.
- IL24. American Chemical Society 228th National Meeting, Philadelphia, USA. (August 2004). *Investigations into the mode of action of hyaluronan as a topical drug delivery system.*
- IL25. UK Podiatric Dermatology Conference, Coventry, UK. (September 2005). *Topical pharmacology: localised drug delivery.*
- IL26. British Pharmaceutical Conference 2005. Manchester, UK. (September 2005). *Does involvement in start-up companies dilute academic research?*
- IL27. 2nd EUFEPS Conference on Optimising Drug Delivery and Formulation. Palais de Congres, Versailles, France. (November 2005). *Evaluation models for dermal and ungual drug delivery*
- IL28. 3rd Annual Drug Delivery Systems Conference, London, UK (November 2006). *Ungual and dermal drug delivery: In vitro models in formulation development.*
- IL29. Inaugural Nail Forum, London, UK (April 2007). *In vitro modelling of ungual drug delivery: As hard as nails.*
- IL30. Diabetes UK Satellite Symposium, St. Albans, UK (October 2007). *From pig to powder: Developments in the delivery of insulin.*
- IL31. DTI/EEDA/EEI Life Sciences in the East of England Conference, Cambridge, UK (October 2007). *A new presentation for topical drug delivery.*
- IL32. 14th UKICRS Conference on Predicting Drug Delivery: Opportunities and Challenges, London, UK (January 2008). *In vitro models for optimising ungual drug delivery*
- IL33. 11th International Perspectives in Percutaneous Penetration, La Grande Mott, France (March 2008). *Thermoenhancement of dermal drug delivery.*
- IL34. 9th Annual Meeting of Skin Forum, London UK (June 2008) *Ungual formulation development: Can it be nailed.*
- IL35. Drug Delivery to the Lung XIX, Edinburgh, UK (December 2008) *Contract research and academia: Symbiotic or parasitic*

Lectures

- L1. Third International Symposium on Pharmaceutical and Biomedical Analysis. Boston, Massachusetts, USA (April 1991). *Biomedical applications of very near infra-red fluorescence spectrometry.*
- L2. Royal Society of Chemistry Autumn Meeting and Pre-Doctoral Chemistry Symposium. Trinity College, Dublin (Sept. 1992). *Novel instrumentation and biomedical applications of very near infra-red fluorescence.*
- L3. Euroanalysis VII. University of Edinburgh, Scotland (Sept. 1993). *Novel developments in instrumentation for long wavelength fluorescence.*

- L4. British Pharmaceutical Conference 1994, University College, London (Sept. 1994). *An in vitro investigation of the interaction of diclofenac with hyaluronan.*
- L5. Second British Society of Rheology Young rheologists Day, University of Coventry (Sept. 1996). *Rheological and viscosity average molecular weight studies of hyaluronan.*
- L6. Aerosol Society: Drug Delivery to the Lungs IX, London, UK (Dec. 98). *The effect of chirality on the fine particle fractions of DPI formulations of mandelic acid and lactose monohydrate mixtures.*
- L7. Phorum 23, Stratford, UK (April 99). *Hyaluronan.*
- L8. SOCRATES 2000 – Drug Delivery and Development, Santiago, Spain (Feb.2000). *Development of an analytical method for passive diffusion drug transport system suitability testing.*
- L9. 50th Anniversary Conference of the American Society of Tropical Medicine and Hygiene, Atlanta, USA (Nov. 2001). *A topical prophylaxis for the Schistosomiasis (Nominated for entry into Young Investigator Award Competition).*
- L10. British Society for Parasitology, Spring Meeting, Salford UK (April 2002). *A topical prophylaxis for the Schistosomiasis in travellers.*
- L11. Thermal Analysis Conference, Chatham UK (Aug. 2002). *The use of thermal methods to characterize the influence of production parameters on spray dried particles.*
- L12. Aerosol Society: Drug Delivery to the Lungs XIII, London, UK (Dec. 2002). *An in vitro investigation of the aerodynamic performance of spray-dried stabilized protein particles.*
- L13. Australian Society of Cosmetic Scientists 39th Annual Conference Dermal delivery Down under- Delivering the Dream, Melbourne, Australia, (May 2005). *1) Transdermal drug delivery: the impact of schistosome cercarial secretions on skin permeability; 2) A comparison of topical formulations for the prevention of human schistosomiasis.*
- L14. British Pharmaceutical Conference 2005, Manchester, UK. (September 2005). *The analysis of amorphous material in pharmaceutical powders by solution calorimetry and dynamic mechanical analysis*
- L15. 8th Annual meeting of Skin Forum, London UK (April 2007). *The influence of lidocaine and prilocaine partitioning on their permeation across silicone membrane*
- L16. Australian Society of Cosmetic Chemists 2007, Melbourne, Australia (March 2007) *Deviations from Fick's law of diffusion when modeling corticosteroid permeation using cellulose membrane.*
- L17. 11th International Perspectives in Percutaneous Penetration, La Grande Mott, France (March 2008). *A novel permeation enhancer designed to increase the permeation of currently marketed nail lacquers through human nail.*
- L18. 8th IEEE International Conference on Data Mining Pisa, Italy (November 2008) *Predictions of Skin Penetration Using Machine Learning Methods*

Posters

- P1. Research and Development Topics in Analytical Chemistry, Royal Society of Chemistry (RSC) University of Aberdeen, Scotland . (July 1991). *Near infra-red fluorescence spectrometry - a novel method for probing and analysing molecules.*
- P2. Research and Development Topics in Analytical Chemistry, Royal Society of Chemistry (RSC). University of Birmingham, Scotland (July 1992). *Biomedical applications of near IR fluorescence spectrometry.*
- P3. Royal Society of Chemistry Autumn Meeting and Pre-Doctoral Chemistry Symposium. Trinity College, Dublin (Sept. 1992). *Novel instrumentation and biomedical applications of very near infra-red fluorescence.*
- P4. The Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, World Conference Centre, Atlanta, USA (March 1993). *Very near infra-red fluorescence: instrumentation and application.*
- P5. Research and Development Topics in Analytical Chemistry, Royal Society of Chemistry (RSC). University of Bradford, England (July 1993). *Biomedical applications of long wavelength fluorescence.*
- P6. British Pharmaceutical Conference 1995. Warwick University, Warwick (Sept. 1995). 1) *An in vitro investigation of the transdermal drug delivery properties of hyaluronan;* 2) *A study of the effect of hyaluronan on the binding of diclofenac to serum albumin using circular dichroism.*
- P7. Dermatology Update 1995. Montreal, Canada (Oct. 1995). *An in vitro study of hyaluronan as a transdermal drug delivery agent.*
- P8. 2nd UK Controlled Release Society Symposium on Controlled Drug Delivery. School of Pharmacy, University of London, UK (Jan 1996). *The intradermal localisation of diclofenac using hyaluronan.*
- P9. 3rd European Congress of Pharmaceutical Sciences. Edinburgh (Sept. 1996). 1) *Rheological and molecular weight studies of hyaluronan;* 2) *Investigation of the effect of hyaluronan on drug-protein binding using circular dichroism.*
- P10. 10th AAPS Annual Meeting. Seattle, USA (Oct. 1996). 1) *The effect of hyaluronan on diclofenac binding to albumin;* 2) *Franz cell studies of hyaluronan as a drug delivery agent.*
- P11. British Pharmaceutical Conference 1997. Scarborough, UK (Sept 1997). *Improved chromatography of Cyclosporin A using a porous graphitic carbon stationary phase.*
- P12. 11th AAPS Annual Meeting. Boston, USA (Nov. 1997). 1) *Hyaluronan antioxidant activity within liposomal systems;* 2) *A rheological study, including the effect of heat, on the viscosity average molecular weight of the drug targeting agent hyaluronan;* 3) *Intradermal localisation of diclofenac using a hyaluronan-containing topical vehicle;* 4) *Improved chromatography of cyclosporin analogues using a highly temperature stable porous graphitic carbon stationary phase.*
- P13. British Pharmaceutical Conference 1998. Eastbourne, UK (Sept. 1998). 1) *The role of glycosaminoglycans in the skin partitioning of ibuprofen;* 2) *The effect of hyaluronan on the binding of diclofenac to human albumin using equilibrium dialysis.*
- P14. 4th European Congress of Pharmaceutical Sciences, Milan University,, Italy (Sept. 1998). 1) *The role of glycosaminoglycans in the skin partitioning of diclofenac;* 2) *The effect of hyaluronan on the binding of diclofenac to human albumin: Equilibrium dialysis studies.*
- P15. 12th AAPS Annual Meeting. San Francisco, USA (Nov. 1998). *The influence of glycosaminoglycans on dermal partitioning of NSAIDs.*
- P16. British Pharmaceutical Conference 1999. Cardiff (Sept. 99). 1) *Evaluation of the mucociliary clearance of microspheres;* 2) *Activity of clindamycin phosphate and clindamycin against organisms of the skin microflora and pilosebaceous isolates* 3) *The effect of liposome composition and size on the skin partitioning of cyclosporin A.*

- P17. Millennial World Congress of Pharmaceutical Sciences, San Francisco, USA (April 2000). 1) *The mucoadhesive potential of novel hyaluronan and chitosan microspheres*; 2) *The effect of homogenised skin on the activity of lincosamide antibiotics*.
- P18. British Pharmaceutical Conference 2000, Birmingham (Sept. 2000). *Biological and chemical assays for the determination of formulated lysozyme activity*.
- P19. UKICRS 2001, London (Jan 2001). *Nasal delivery of gentamycin: In vivo evaluation of novel microparticulates*.
- P20. British Pharmaceutical Conference 2001, Glasgow (Sept 2001). 1) *Nasal delivery of gentamycin: in vivo evaluation of novel microparticles*; 2) *The effects of hyaluronan and other polymers on the dermal diffusion in vitro of NSAID drugs*.
- P21. 14th AAPS Annual Meeting, Denver, USA (Oct 2001). 1) *Dermal delivery of cyclosporin A entrapped liposomal gels – preformulation Franz cell diffusion studies using silastic membranes*; 2) *The effect of hyaluronan and other glycosaminoglycans on the biodisposition of diclofenac and ibuprofen when applied*; 3) *A novel method to deliver dry powdered formulations onto cell monolayers*; 4) *Protective mechanism of stabilising excipients in the freeze-drying of proteins*; 5) *Localisation of tight junction proteins in human skin and LSE*; 6) *Loop interaction of the tight junction protein occludin*.
- P22. 50th Anniversary Conference of the American Society of Tropical Medicine and Hygiene, Atlanta, USA (Nov. 2001). *Investigation of the temporal dynamics of S. Mansoni penetration of different skin layers*.
- P23. Thermal Analysis Conference, Chatham UK (Aug. 2002). 1) *Investigation of lysozyme denaturation upon spray-drying by DSC*; 2) *Thermal analysis of a spray-dried model protein: catalase*.
- P24. British Pharmaceutical Conference 2002, Birmingham (Sept 2002). 1) *An in vitro investigation of a topical prophylaxis for Schistosomiasis*; 2) *Investigation of protein denaturation upon spray-drying by differential scanning calorimetry* 3) *Temperature and modulated differential scanning calorimetry of a spray-dried model protein: catalase*.
- P25. 15th AAPS Annual Meeting, Toronto, Canada (Nov 2002). 1) *Racial differences in the temporal dynamics of Schistosoma Mansoni cercarial skin penetration*; 2) *Thermal analysis of spray-dried protein formulations*; 3) *The effects of excipients on the stabilisation of spray-dried proteins*; 4) *An in vitro investigation of a topical prophylaxis for schistosomiasis*.
- P26. Skin Forum, University of Newcastle, Newcastle, UK (July 2003). 1) *Heat and percutaneous absorption: In vitro evaluation using 3 model penetrants* 2) *An in vitro investigation of a topical prophylaxis of Schistosomiasis*.
- P27. Biological function of mammalian skin, Gordon Research Conference, Roger Williams University, Bristol, RI, USA (Aug. 2003). *Topical treatment of cutaneous Leishmaniasis*.
- P28. British Pharmaceutical Conference 2003, Harrogate (Sept 2003). 1) *An in-vitro study of the effect of heat on the percutaneous absorption of three model penetrants*; 2) *Test materials for solution calorimeters*.
- P29. Skin and formulation, Association de Pharmacie Galenique Industrielle (APGI), Paris, France (Oct. 2003). *Heat and percutaneous absorption: An in vitro study using 3 model penetrants*.
- P30. 16th AAPS Annual Meeting, Salt Lake City, USA (Nov 2003). *The effect of heat on the percutaneous absorption and epidermal retention of methyl paraben, butyl paraben and caffeine: An in vitro study*.
- P31. 5th Annual Meeting of Skin Forum, Portsmouth, UK, July 2004. 1) *A comparison of topical formulations for the prevention of human schistosomiasis*; 2) *Transdermal drug delivery: the impact of schistosome cercarial secretions and related chemical penetration enhancers on skin permeability*.

- P32. British Pharmaceutical Conference 2004, Manchester (Sept 2004). *Effect of molecular weight and concentration of hyaluronan on the in vitro release characteristics of diclofenac and ibuprofen across cellulose membrane.*
- P33. 17th AAPS Annual Meeting, Baltimore, USA (Nov 2004). 1) *Stabilisation and delivery of deoxyribonuclease within pressurised hydrofluoroalkane metered dose inhaler formulations;* 2) *An evaluation of simulated lung fluids using solute partitioning.*
- P34. British Pharmaceutical Conference 2005, Manchester, UK. (September 2005). *The development of powder pocket dynamic mechanical analysis for the detection of amorphous content in salbutamol sulphate: a feasibility study.*
- P35. British Pharmaceutical Conference 2006, Manchester, UK. (September 2006). 1) *In vitro efficacy of a non-alcoholic antibacterial cleansing lotion as a potential routine hand disinfectant;* 2) *Vitamin E nanoparticles for dermal application.*
- P36. European Society for Dermatological Research, Paris (November 2006), *Schistosome cercarial interactions with human keratinocytes and langerhan*
- P37. Focus on fungal infections 17, San Diego, USA (March 2007) *A multi-model approach for the evaluation of topical antifungal agents and formulations for the treatment of onychomycosis*
- P38. Set for Britain R&D Road show, House of Commons, UK (March 2007). *The development of a novel dynamic self-assembling topical patch for the treatment of psoriasis*
- P39. 8th Annual meeting of Skin Forum, London UK (April 2007). 1) *In situ formation of supersaturated metered dose aerosols for topical drug delivery* 2) *A comparison of pig and human skin as an in vitro model for the diffusion of highly lipophilic drugs* 3) *An investigation of thioglycolic acid effectiveness as a nail penetration enhancer in aqueous and non-aqueous based vehicles* 4) *An investigation of the enhancing effect of a novel permeation enhancer on two nail lacquers.*
- P40. Pharmaceutical Sciences World Congress, Amsterdam, Netherlands (April 2007) 1) *In-situ supersaturation using a topically applied metered dose aerosol to enhance topical drug delivery* 2) *Nail swelling as a pre-formulation screen for the selection and optimisation of ungual penetration enhancers* 3) *The effect of a simple solvent on the drug release from a eutectic composition.*
- P41. European Academy of Dermatology and Venereology Vienna, Austria (April 2007) 1) *The development of a novel metered dose aerosol spray for the topical administration of corticosteroids* 2) *Thioglycolic acid and urea hydrogen peroxide as novel ungual penetration enhancers* 3) *Development of an effective, cosmetically acceptable vitamin E topical formulation* 4) *An investigation into the influence of a simple solvent upon the rate of diffusion from a eutectic composition*
- P42. 11th International Perspectives in Percutaneous Penetration, La Grande Mott, France (March 2008). *A novel permeation enhancer designed to increase the permeation of currently marketed nail lacquers through human nail.* 2) *The use of statistical design to optimise a heat generating topical formulation.* 3) *A novel franz cell method to assess the permeation of benzoyl peroxide across silicone membrane.* 4) *Prediction of skin penetration using machine learning methods.* 5) *The development of a eutectic lidocaine-prilocaine spray formulation.* 6) *An investigation into the mechanism by which thioglycolic acid and urea-hydrogen peroxide enhance terbinafine permeation through human nail plate.* 7) *Novel powder formulation for topical delivery of miconazole nitrate and clotrimazole.* 8) *The use of residual solvents to delay dose depletion in novel metered dose aerosols for topical drug delivery.*
- P43. PBB, Barcelona 2008. The influence of delivery vehicle on the permeation of lidocaine and prilocaine through silicone membrane. Fiala, M.B. Brown, S.A. Jones.
- P44. BPC. Manchester 2008. K. Staff, M.B. Brown, H. Nacer, R.C. Hider, P. Friden, S.A. Jones. The effect of complex coordination on gallium determination using ion chromatography.

- P45. BPC. Manchester 2008 D.G Wood, M.B. Brown. S.A. Jones. The effect of temperature on the diffusion of lidocaine base.
- P46. BPC. Manchester 2008. F. Benouda, S. A. Jones, M. B. Brown, G. P. Martin. Effect of propylene glycol on in vitro membrane transport of ionised diclofenac diethylamine from saturated binary cosolvent mixtures.

PUBLICATION OF WORK

Refereed Papers in Scientific Journals.

- M1. *Biomedical applications of near infra-red fluorescence spectrometry.* M.B.Brown, J.N.Miller, D.P.Riley & N.J.Seare. Anal. Proc., (1993), 30 (3):157-161.
- M2. *Novel instrumentation and biomedical applications of very near infra-red fluorescence.* M.B.Brown, J.N.Miller, D.P.Riley & N.J.Seare. Analyst, (1993), 118 (4):407-410.
- M3. *An investigation of the use of Nile red as a long wave-length fluorescent probe for the study of α -acid glycoprotein:drug interactions.* M.B.Brown, J.N.Miller, & N.J.Seare. J. Pharm. Biomed. Anal., (1995), 13: 1011-1117.
- M4. *The effect of hyaluronan on the in vitro deposition of diclofenac within the skin.* M.B.Brown, C. Marriott and G.P. Martin. Int. J. Tissue Reac., (1995), XVII: 133-140.
- M5. *An in vitro study of the effect of hydrocolloid patch occlusion on the penetration of triamcinolone acetonide through human skin.* D. Ladenheim, C. Marriott, G.P. Martin, D.A. Hollingsbee and M.B.Brown. J. Pharm. Pharmacol., (1996), 48:806-811
- M6. *Hyaluronan: a transdermal drug delivery system* M.B.Brown, F. Bennett, C. Marriott and G.P. Martin. Prog. Rheumatol., (1996), VI:59-66.
- M7. *High performance liquid chromatography of a cyclosporin formulation on a porous graphitic carbon column.* T. Nazir, L.A. Gould, C.Marriott, G.P. Martin and M.B. Brown. Chromatographia. (1997), 46: 628-636.
- M8. *The effect of chirality on the fine particle fractions of DPI formulations of mandelic acid and lactose monohydrate mixtures* S. Nowaseb, M.B.Brown and C.Marriott (1998) Drug Delivery to the Lung, IX:76-80
- M9. *An in vitro study of the diclofenac delivery properties of hyaluronan in human skin.* F.C.Bennett, M.B.Brown, C.Marriott and G.P.Martin, (1999), Drug Del., 6:39-43.
- M10. *The influence on hydrocolloid patch composition on the bioavailability of triamcinolone acetonide in humans.* G.P. Martin, D. Ladenheim, C. Marriott, D.A. Hollingsbee and M.B.Brown. Ind. Pharm. Drug Devel., (2000), 26:35-43.
- M11. *The infection of human skin by schistosome cercariae: Studies using Franz cells.* Bartlett, M.B.Brown, C.Marriott, and P.J. Whitfield. Parasitology (2000), 121:49-54.
- M12. *Preparation and evaluation of mucoadhesive and in vitro drug release properties of novel microspheres of hyaluronan and chitosan.* S.T.Lim, G.P.Martin, D.J.Berry and M.B.Brown, J. Control. Rel. (2000), 66:281-292.
- M13. *Mitigation of surfactant erythrocyte toxicity by egg phosphatidylcholine* L.A. Gould, A.B. Lansley, G.P.Martin B. Forbes and M.B.Brown, J. Pharm. Pharmacol., (2000), 52:1203-1209.

- M14. *Activation of clindamycin phosphate by human skin* S. K. Amr, M. B. Brown, G.P. Martin and B. Forbes, J. Appl. Micro., (2001), 90:550-554.
- M15. *Turbidimetric and HPLC assays for the determination of formulated lysozyme activity.* Y-H. Liao, M. B. Brown, G.P. Martin, J. Pharm. Pharmacol., (2001), 53:549-554.
- M16. *Comparison of the effect of hyaluronan and other polysaccharides on drug skin partitioning.* M.B.Brown and G.P.Martin, Int. J. Pharm., (2001), 225:113-121.
- M17. *Dimethicone barrier cream prevents infection of human skin by schistosome cercariae: evidence from Franz cell studies.* R.J.Ingram, A. Bartlett, M.B.Brown, C.Marriott, and P.J. Whitfield. J. Parasitol., (2002), 88:399-402.
- M18. *Evaluation of microparticulate delivery systems for the nasal delivery of gentamycin in rabbits.* S.T.Lim, G.P.Martin, D.J.Berry and M.B.Brown, Int. J. Pharm. (2002), 231: 73-82.
- M19. *In vivo and in vitro characterisation of novel microparticulates based on hyaluronan and chitosan.* S.T.Lim, G.P.Martin, B.J.Forbes and M.B.Brown, PharmSciTech. (2001), 2:1-14.
- M20. *An in vitro technique for evaluating inhaled nasal delivery systems.* B.Forbes, S.T.Lim, G.P.Martin, M.B.Brown, , S.T.P. Pharma Sciences (2002) 12:75-79.
- M21. *Protective mechanism of stabilising excipients against dehydration in the freeze-drying of proteins* Y-H. Liao, M. B. Brown, G.P. Martin, Pharm Res. (2002), 19:1854-1861.
- M22. *Effects of sucrose and trehalose on the preservation of the native structure of spray-dried lysozyme.* Y. Liao, M.B. Brown and G.P. Martin. Pharm Res (2002), 19:1862-1866.
- M23. *An in vitro investigation of the aerodynamic performance of spray-dried stabilized protein particles.* Y.H Liao,, M.B Brown,, A Quader and G.P Martin. Drug Delivery to the Lungs (2002), 13: 244-247.
- M24. *Delayed tail loss during skin invasion by schistosome cercariae.* P.J.Whitfield, A. Bartlett, N.Khammo, M.B.Brown, C.Marriott and R. Clothier. Parasitology (2003), 126:135-140.
- M25. *Penetration of human skin by the cercariae of Schistosoma mansoni: An Investigation of the Effect of Multiple Cercarial Applications.* R.J.Ingram, A. Bartlett, M.B.Brown, C.Marriott, and P.J. Whitfield, J. Helminthology (2003), 77:27-31.
- M26. *Skin invasion by schistosome cercariae: insights gained from studies with human skin explants.* P. J. Whitfield, A. Bartlett, M.B.Brown and C. Marriott Trends in Parasitology , (2003), 19:339-340.
- M27. *Investigation of the physical properties of spray-dried stabilised protein particles.* Y.H Liao, M.B Brown,, A Quader and G.P Martin. J. Pharm. Pharmacol. (2003), 55:1213-1221.
- M28. *Simulated Lung Fluid to investigate the biopharmaceutics of inhaled drugs.* B.T.S. Yff, P. G. Royall, B. Forbes, M.B. Brown and G.P.Martin, Drug Delivery to the Lungs (2003), 14: 156-159.
- M29. *An investigation of calibration methods for solution calorimetry.* B.T.S. Yff, P. G. Royall, M.B. Brown and G.P.Martin. Int. J. Pharm., (2004), 269:361-372.
- M30. *Effect of heat on the percutaneous penetration and epidermal retention of three model penetrants.* F. K. Akomeah, G.P. Martin and M. B. Brown, Eur. J. Pharm Sci.(2004), 21: 337-345.
- M31. *Determination of polyvinyl alcohol using gel filtration liquid chromatography.* S. Jones, M.B.Brown and G.P. Martin, Chromatographia, (2004), 59:43-46.
- M32. *Determination of polyvinylpyrrolidone using high performance liquid chromatography.* S. Jones, M.B.Brown and G.P. Martin. J.Pharm. Biomed. Anal., (2004), 35:621-624
- M33. *Investigation of the stabilisation of freeze-dried lysozyme and the physical properties of the formulations.* Y.H Liao, M.B Brown and G.P Martin. Eur. J. Pharm. Biopharm.(2004), 58:15-24

- M34. *Development of a rapid preformulation screen for suspension metered dose inhalers.* S. Jones, G.P. Martin and M.B.Brown, *Respiratory Drug Delivery*, (2004), IX:529-532.
- M35. *A comparison of topical formulations for the prevention of human schistosomiasis.* E Cooper, A Iqbal, A Bartlett, C Marriott, P J Whitfield & M B Brown. *J.Pharm. Pharmacol.*, (2004), 56:1-6
- M36. *Hyaluronic acid: a unique topical vehicle for the localised delivery of drugs to the skin.* M.B. Brown and S.A. Jones, *J. Eur. Acad. Derm. Vener.*, (2005), 19:308-318
- M37. *Inter-laboratory variation of in vitro diffusion cell measurements: An international multi-centre study using quasi-standardised methods and materials.* R.Chilcott, M.B. Brown et al, *J. Pharm. Sci.*, (2005), 94:632-638
- M38. *High-pressure aerosol suspensions– a novel laser diffraction particle sizing system for hydrofluoroalkane metered dose inhalers.* S. Jones, G.P. Martin and M.B.Brown, *Int. J. Pharm.*, (2005), 302:154-165
- M39. *Hyaluronan: pharmaceutical characterisation and drug delivery.* Y.H Liao, S.A. Jones, B. Forbes, G.P Martin and M.B Brown. *Drug Delivery*, (2005), 12:1-16
- M40. *The effects of polyvinyl alcohol on the physical stability of spray-dried protein particles within surfactant-free HFA 134a based metered dose formulations* Y.H Liao, M.B Brown, S.A. Jones, T. Nazir and G.P Martin. *Int. J. Pharm.*, (2005), 304:29-39
- M41. *Biocompatible polymer blends: the effects of physical processing on the molecular interaction of polyvinyl alcohol and polyvinylpyrrolidone* S.A.Jones, G.P.Martin, P.G. Royall and M.B.Brown. *J. Appl. Polymer Sci.*, (2005), 98:2290-2299
- M42. *The effect of unsaturated fatty acids in benzyl alcohol on the percutaneous permeation of three model penetrants.* G. R. Nanayakkara, A. Bartlett, B. Forbes, C. Marriott, P. J. Whitfield, M. B. Brown. *Int. J. Pharm.*, (2005), 301:129-139
- M43. *Transdermal drug delivery systems.* M. B. Brown, S. A. Jones, F. K. Akomeah and Gary P. Martin. *Drug Delivery*, (2005), 12:327-42
- M44. *The development of DMA for the detection of amorphous content in pharmaceutical powdered materials.* P. G. Royall, C-Y. Huang, S-W. J. Tang, J. Duncan, G. Van-de-Velde and M. B. Brown. *Int. J. Pharm.*, (2005), 301:181-191
- M45. *Stabilisation of deoxyribonuclease in hydrofluoroalkane using miscible vinyl polymers.* S. Jones, G.P. Martin and M.B.Brown, *J. Cont. Rel., J. Cont. Rel.*, (2006), 115, 1-8
- M46. *In vitro & in vivo studies on a topical formulation of sitamaquine for cutaneous leishmaniasis* T. Garnier, M.B.Brown, J. Lawrence and Simon Croft. *J. Pharm. Pharmacol.*, (2006), 58:1043-1054
- M47. *Manipulation of beclomethasone-hydrofluoroalkane interactions using biocompatible macromolecules.* S. Jones, G.P. Martin and M.B.Brown, *J. Pharm. Sci.*, (2006), 95:1060-1074
- M48. *Applicability of a novel dynamic rheological technique as an indicator of stability for a milled respiratory drug.* S-W. J. Tang, J. Duncan, G. Van-de-Velde, M. B. Brown and P. G. Royall, *Respiratory Drug Delivery*, (2006), X:634-649
- M49. *Variability in human skin permeability in vitro: comparing penetrants with different physicochemical properties.* F. K. Akomeah, G.P. Martin and M. B. Brown. *J. Pharm. Sci.*, (2007) 96:824-834
- M50. *In vivo studies on the antileishmanial activity of buparvaquone and its prodrugs.* T.Garnier, A. Mäntylä, T. Järvinen, J. Lawrence, M. B. Brown and S. Croft, *J. Antimicrobial. Chemo.*, (2007), 60: 802–810

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- M52. *Nail swelling as a pre-formulation screen for the selection and optimisation of ungual penetration enhancers.* R.Khengar, S.A.Jones, R.B.Turner, B.Forbes and M.B.Brown. *Pharm. Res.*, (2007), 24:2207-2212.
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- D9. UK patent application 'Therapeutic compositions' M.B.Brown, T. Nazir, M. Crothers and P Welburn (0525680.5) PCT/GB2006/004739
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- D11. UK patent application ' Use of pyrroloquinolone compounds to kill cinically latent organisms' P.B. Beck, M.B Brown, D.E. Clark, A. Coates, H.J, Dyke, Y. Hu, D.J. Londesborough, K. Mills, T.D. Pallin, G.P. Reid, G. Stoddart , (0522715.2)
- D12. US patent application 'Pharmaceutical Formulations for Iontophoretic Delivery of Gallium'. P.M. Friden, H. Kim, K. Staff, M. B. Brown and S.A. Jones. (4035.3007 US)

GRANTS AWARDED

Available on request

MEMBERSHIP OF PROFESSIONAL BODIES AND SOCIETIES

CChem MRSC Membership of the Royal Society of Chemistry (1993)
 Member of the American Association of Pharmaceutical Scientists
 Member of the Academy of Pharmaceutical Scientists
 Member of the Controlled Release Society
 Member of the Royal Pharmaceutical Society of Great Britain Academic Pharmacy Group
 Member of the Joint Pharmaceutical Analysis Group

ADDITIONAL INFORMATION

- Examiner for PhD viva voce examinations (at least 2 a year for the last 5 years).
- Editorial Board Member for Current Drug Discovery Technologies since 2007
- Referee for manuscripts submitted to Nature Reviews, the Journal of Pharmacy and Pharmacology, International Journal of Pharmaceutics, Journal of Controlled Release, Pharmaceutical research, Spectroscopy Letters, Journal of Drug Targeting, International Journal of Pharmaceutical Medicine, International Journal of Cancer, Drug Development Research, European Journal of Pharmaceutics and Biopharmaceutics, Biomacromolecules, Pulmonary Pharmacology and Therapeutics, American Journal of Clinical Dermatology, Archives of Dermatological Research, Current Drug Delivery and Journal of Dermatological Treatment
- Visiting Professor of Drug Delivery at King's College London

- Member of the EPSRC Peer Review College 2006-2009.
- Founding member and committee member of the EPSRC Drug Delivery Research Network.
- Member of numerous scientific advisory boards
- Member of the executive organising committee of the international meeting Perspectives in Percutaneous Permeation that occurs biennially in France.
- Grant referee for the Research and Development Office of Northern Ireland, Austrian Science Fund, the Scottish Research and Development Office and STW, the Dutch Technology Foundation
- Intercollegiate examiner for the London School of Pharmacy.
- Former member of the DTI funded VAM Postgraduate working group
- One of my former students (Sian Lim) was awarded the EMI Graduate Student Outstanding Manuscript Award in Pharmaceutical Technology at AAPS 2001.
- Awarded the EMI faculty supervisor of the year in Pharmaceutical Technology at AAPS 2001.
- Invitations to speak at International and National Conferences including American Chemical Society 228th Annual meeting 2004, Dermatology Update and Clinical Dermatology 2000, Canada; Hyaluronan 2000, UK; World Conference in Inflammation, Switzerland; 7th International Seminar on the Treatment of Rheumatic Disease, Israel; Cancer Drug Development, Germany; International Society for Rheumatic Therapy, France, the 3rd Annual Drug Delivery Systems Conference 2006, 2nd EUFEPS Conference on Optimising Drug Delivery and Formulation, British and European Pharmaceutical Conferences and various Hyaluronan in Drug Delivery meetings in France, Canada, Switzerland and the UK.
- Invitations to visit and work at the Hospital for Sick children, Toronto Canada and the Lyons Eye Institute, Perth, Australia

REFEREES

Available on request