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89

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-073857- -00007-0000
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Evento : 379
Actuación : 444

Referencia : Expediente No. 06073857
Asunto : Solicitud de patente para: "ARTICULO MULTICAPA IMPERMEABLE Y PERMEABLE AL CALOR"
Solicitante : GEOX S.P.A.
Fecha de solicitud: Julio 27 de 2006.

1. Yo, Emilio FERRERO, *obrando como apoderado del solicitante* en el asunto antes identificado, me refiero al Oficio **No. 0748** notificado por fijación en lista del **23 de Enero de 2009. Mediante memorial radicado el 20 de abril de 2009 solicité un plazo de treinta (30) días para dar respuesta a este oficio.**

2. Mediante el Oficio **No. 0748** se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la siguiente manera:

3. De la solicitud de patente:

Su Despacho concluye que el capítulo reivindicatorio y descriptivo no cumplen con los requisitos de claridad y concisión de acuerdo con los artículos 30 y 28 respectivamente.

Con respecto a lo señalado por su Despacho mi representada desea señalar lo siguiente:

Con el fin de atender las anteriores observaciones y de acuerdo al artículo 34 de la Decisión 486, se presentan nuevos capítulos reivindicatorio y descriptivo como sustitutos de los anteriormente presentados. En los nuevos capítulos *reivindicatorio y descriptivo*, se ha revisado la redacción de los mismos con el fin de hacer

claridad sobre la materia que se solicita proteger y sobre el alcance de la misma. De tal manera que, las objeciones formuladas a este respecto quedan superadas respectivamente con las modificaciones realizadas de la siguiente manera:

3.1 Descripción.

- La expresión "por lo menos parcialmente" ha sido eliminada del nuevo pliego descriptivo.
- La expresión "según el "aspecto"" ha sido sustituida por "según la "apariencia"".
- Con respecto a la objeción formulada al término "solución de extensión" mi representada desea poner de presente que dicha expresión hace referencia a las soluciones que son aplicadas por extensión, es decir, aquellas soluciones que contienen la mezcla polimérica básica y son usadas para formar la primera capa 11. En efecto, la primera capa se forma extendiendo la "solución de extensión" sobre la superficie de la segunda capa 12. Como se menciona en el capítulo descriptivo, se puede aplicar la solución del polímero al soporte, utilizando técnicas estándares de extensión ampliamente conocidas en el estado de la técnica, tales como la extensión por rodillo o la extensión por pulverización. Con la anterior aclaración, consideramos que la objeción formulada al respecto se debe tener por superada.

3.2 Reivindicaciones.

- Se ha incluido en la reivindicación 1, la característica técnica anteriormente divulgada en la reivindicación 17 y esta última ha sido eliminada.
- La expresión "según una o varias reivindicaciones anteriores" ha sido sustituida por "de acuerdo con cualquiera de las reivindicaciones anteriores".
- La expresión "por lo menos parcialmente" ha sido eliminada del capítulo reivindicatorio.
- La expresión "por lo menos" ha sido eliminada de la reivindicación 3.
- En las reivindicaciones 7, 29 y 30 el término "substancialmente" ha sido eliminado.
- La reivindicación 4 ahora depende de la reivindicación 2.
- Las reivindicaciones 19 y 36 han sido eliminadas. De tal manera que el nuevo pliego reivindicatorio esta constituido por 35 reivindicaciones.
- La expresión: "fabricada por la empresa DARAMIC Inc. Y conocida comercialmente bajo el nombre DARAMIC®" ha sido eliminada de la reivindicación 14.
- Con respecto a la objeción formulada a las reivindicaciones 34-36 por cuanto de acuerdo con el Señor Examinador en dichas reivindicaciones se repite el alcance de las reivindicaciones

18 y 19, mi representada desea aclarar a su Despacho que la segunda capa de la reivindicación 18 es adherida a la primera capa extendiendo o sumergiendo dicha primera capa en un baño de dicho polímero mientras que la segunda capa de las reivindicaciones 34-35 es depositada en la primera capa por deposición de plasma. De tal manera que, la materia de invención divulgada en las reivindicaciones 34 y 35 difiere de la divulgada en las reivindicaciones 18-19 y por tanto, la objeción formulada a este respecto se debe tener por superada.

Así entonces, con las modificaciones realizadas al capítulo reivindicatorio y descriptivo se contribuye a mejorar la claridad y concisión de la presente solicitud de patente y por tanto, las objeciones formuladas a este respecto se deben tener por superadas.

Sin embargo, en el evento que el Despacho considere que una modificación adicional sea necesaria, respetuosamente le solicito hacer uso de la facultad que le otorga el artículo 45 inciso 2 de la Decisión 486 de la Comisión de la Comunidad Andina a efecto de requerir nuevamente de nuestra parte cualquier complementación o aclaración.

4. Nivel inventivo.

Su Despacho concluye que los documentos US5032450 (D1), WO9530793 (D2), US4686135(D3), ES2219922(D4) afectan el nivel inventivo de la presente invención y enuncia lo siguiente:

4.1 Con respecto a la reivindicación 1.

- "La reivindicación 1 de las solicitud colombiana se diferencia en D2, porque la primera capa no es higroscópica".

- "El problema técnico objetivo de esta solicitud es absorber toda la humedad que no puede ser expulsada de las prendas de vestir, del calzado u otros artículos, evitando el efecto "húmedo" desagradable".

- "El anterior problema técnico objetivo es solucionado en la anterioridad D1, ya que describe que la primera capa de material microporoso esta compuesto entre otros por un relleno de partículas finamente divididas insolubles en agua, como por ejemplo el dióxido de silicona (COL 4 linea 1-5), siendo este compuesto similar al utilizado en la solicitud, el cual da el carácter de higroscopicidad a esta capa.

- "La anterioridad D1 da solución al problema técnico objetivo de la reivindicación 1, por lo tanto al combinar D1 y D2 se afecta el nivel inventivo de la reivindicación 1 y sus dependientes".

4.2 Con respecto a la reivindicación 20.

- "D2 relaciona el método para fabricar una lamina formada por dos capas, donde los polímeros de la primera capa se polimerizan sobre la segunda capa formando un revestimiento".

- "La reivindicación 20 de la solicitud colombiana se diferencia en D2, por el paso de evaporar los componentes volátiles. Esta diferencia no parece darle un efecto técnico sorprendente ya que como es conocido por cualquier experto del arte este resultado también se obtiene al secar la lamina en la cual ocurre la polimerización de reticulación con compuestos volátiles, como se describe en el ultimo paso en el proceso D2".

4.3 Con respecto al a reivindicación 37.

- "El estado de la técnica mas cercano es D4, porque describe los pasos característicos en la deposición por plasma frío de un polímero sobre una superficie".

- "La reivindicación 37 se diferencia en D4, por el paso de cargar dicha primera capa a revestir en la cámara de reacción. Esta diferencia no parece darle un efecto técnico sorprendente porque este es un paso obvio dentro del proceso de deposición por plasma ya que siempre se debe disponer de una superficie en la cual ocurrirá la deposición o sino el proceso no se lleva a cabo. Es así como en la anterioridad D3 se describe una hoja precursora (superficie a depositar) que es colocada en el aparato de plasma frío para iniciar el proceso de deposición".

Con respecto a lo señalado por su Despacho mi representada desea señalar lo siguiente:

Inicialmente, se pone de presente a su Despacho lo que indica el Manual para el Examen de Solicitudes de Patentes de invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina con respecto a la evaluación del nivel inventivo:

"*La pregunta a contestar es si teniendo en cuenta el estado de la técnica en su conjunto existe alguna* ***indicación que lleve a la persona versada en la materia a modificar o adaptar el estado de la técnica más cercano para resolver el problema técnico,*** *de tal forma que llegue a un resultado que estuviera incluido en el tenor de la(s) reivindicación(es)*". (Negrita fuera del texto).

De esta manera, este Manual indica que los documentos citados deben revelar sugerencias y enseñanzas claras para el técnico en la materia que lo lleven a obtener la presente invención.

A este respecto, el mismo Manual señala que el primer paso del método problema-solución es establecer cuál es el estado del arte

más cercano, es decir, frente al cual se debe comparar la invención, documentos que no pueden exceder de dos (2) y que deben estar dirigidos a la solución del mismo problema técnico.

Ahora bien, teniendo en cuenta lo anterior y las modificaciones realizadas al capítulo reivindicatorio, procederemos a continuación a exponer los argumentos por los cuales la presente invención es inventiva frente a las anterioridades citadas.

4.4 Reivindicación 1.

El Examinador afirma que el documento D1 divulga la primera capa del artículo multicapa reivindicado en la reivindicación 1 y que el documento D2 la segunda capa. Sin embargo, se aclara a su Despacho que en la presente reivindicación 1 se especifica que la segunda capa además de ser impermeable al vapor y permeable al vapor de agua, es hidrofóbica. En contraste, D2 divulga una capa que es impermeable al agua y permeable al vapor de agua que esta compuesta por polímeros hidrofílicos (Ver paginas 5-6 D2). Por lo tanto, es claro que este documento no revela o enseña las características técnicas esenciales relacionadas con la segunda capa del artículo multicapa de la presente invención, tal como acá es reivindicado. En efecto, antes que tener una enseñanza o sugerencia que permitiera a un técnico medio obtener la presente invención, lo alejaría de la misma ya que enseña que la capa impermeable al agua y permeable al vapor debería ser hidrofílica.

A este respecto, es importante resaltar que la ventaja de la presente invención sobre el artículo resultante de la combinación de D1 y D2, es la velocidad mayor de liberación de vapor de agua, por cuanto un artículo comprendiendo la capa higroscopica de D1 y la capa hidrofílica de D2 tendería a retener el vapor de agua por un tiempo mas prolongado que el artículo de la presente solicitud de patente ya que en ésta la segunda capa es hidrofóbica.

Así entonces, es claro que a partir de la lectura de estos documentos un técnico versado en la materia no llegaría al artículo multicapa reivindicado por la presente solicitud, ya que dentro de estos no se encuentra ninguna enseñanza o sugerencia que lo lleve a obtener específicamente el artículo multicapas reclamado a partir de las enseñanzas allí reveladas y por ende, no resultan relevantes para efectos de estudiar su patentabilidad.

4.5 Reivindicación 20 (Nueva reivindicación 18).

La reivindicación 20, tal como se encuentra ahora reivindicada se relaciona a un método de fabricación de un artículo multicapas con 2 capas donde una de las capas es hidrofóbica. Sin embargo, como se mencionó anteriormente, a diferencia de la presente solicitud, D2 no divulga un artículo multicapa, donde la capa impermeable al agua y permeable al vapor sea hidrofóbica.

De tal manera que, D2 no divulga el paso de aplicar la solución preparada en el paso anterior en una segunda capa que es hidrofóbica o el paso de "evaporar los componentes volátiles" tal como lo hace la presente solicitud. Consecuentemente, este documento no anticipa ni hace evidente la materia reivindicada en la presente solicitud ya que las enseñanzas divulgadas en este documento no llevan a un técnico versado en la materia a obtener el articulo multicapa de la presente invención y o su método de obtención, tal como acá son reivindicados.

Así entonces, teniendo en cuenta que las enseñanzas de las anterioridades citadas no llevan a un técnico versado en la materia a obtener la presente invención ya que no revelan o enseñan implícita o explícitamente las características técnicas esenciales (capas) relacionadas con la misma tal como acá es reivindicada, estos documentos **no** son anterioridades válidas que pueda afectar su nivel inventivo. Lo anterior si se tiene en cuenta que para el estudio de nivel inventivo el Examinador no puede adoptar la posición de un inventor y que además no puede partir de la solución dada sino simplemente de lo que expresamente revelen el o los documentos más cercanos del estado del arte, que en el presente caso son D1 y D2.

4.6 Reivindicación 37 (Nueva reivindicación 34).

A diferencia de la reivindicación 37, la cual esta relacionada con un método para producir una articulo multicapas impermeable al agua y permeable al vapor de agua, ninguno de los documentos D3 o D4 citados por su Despacho tiene en cuenta la impermeabilidad o la capacidad de transpiración del producto final. De hecho, el problema técnico planteado en D3 es la necesidad de un material compuesto que sea resistente a elevadas temperaturas y el de D4 es la necesidad de un tratamiento de un substrato de polímero con una deposición de plasma para obtener una capa hidrofóbica.

En contraste, el método divulgado en la reivindicación 37 permite la producción de una capa ultradelgada de material de soporte que provee características de impermeabilidad al agua sin alterar las características generales, y en particular sus propiedades de permeabilidad.

Así entonces, teniendo en cuenta que las enseñanzas de esta anterioridad no llevan a un técnico versado en la materia a obtener la presente invención ya que no revelan o enseñan las características técnicas esenciales relacionadas con la misma, tal como acá es reivindicada, estos documentos no resultan relevantes para efectos de estudiar su patentabilidad.

En efecto, los documentos D3 y D4 citados por su Despacho no hacen parte del estado del arte más cercano porque no resuelven el mismo problema técnico que resuelve la presente invención, ya que tal y como lo señala el **Manual Andino de Patentes**: "Normalmente el estado de la

técnica más cercano se encuentra en el mismo campo de la invención o trata de solucionar el mismo problema o uno semejante"[1].

Teniendo en cuenta lo anterior, se debe concluir que los documentos D3 y D4 citados por su Despacho no son anterioridades válidas capaces de afectar el nivel inventivo de la presente invención dado que a diferencia de la presente solicitud de patente, no abordan el problema de la necesidad de un articulo permeable al vapor de agua e impermeable al agua. De tal manera que, aunque estos documentos se refieren en general a articulos multicapas, dichos documentos no enseñan ni sugieren especificamente el uso de una capa impermeable al agua, permeable al vapor de agua e hidrofóbica. Por tanto, a partir de las enseñanzas ya sea de D3 o D4, o incluso la combinación de estos documentos, no seria obvio u evidente obtener la materia de invención reivindicada en la presente reivindicación 34.

Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

5. Anexos:

- Nuevo pliego reivindicatorio conformado por 35 reivindicaciones.
- Nuevo pliego descriptivo.
- Recibo por 20 reivindicaciones adicionales a la décimo quinta reivindicación ($500.000).
- Formulario para modificaciones.

Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO-13377-841-005-9
MGM\MGM\ID-150861\WPC13377
No. M-2009-150861\MGM

[1] IEPI, BID. "*MANUAL PARA EL EXAMEN DE SOLICITUDES DE PATENTES DE INVENCIÓN EN LAS OFICINAS DE PROPIEDAD INDUSTRIAL DE LOS PAÍSES DE LA COMUNIDAD ANDINA*". Quito, Ecuador 2004. Página 77.

96

Industria y Comercio
SUPERINTENDENCIA

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FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1 SOLICITUD DE:

☐ Corrección de Error Material ☒ Modificación a una solicitud

2 SOLICITANTE

Nombre: GEOX S.P.A.
Sociedad constituida y existente bajo las leyes de Italia.

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IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐

Número: _____

3 REPRESENTANTE O APODERADO

Nombre: Emilio FERRERO
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Teléfono: 347 36 11 **Fax:** 217 92 11
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IDENTIFICACION

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C.E. ☐ Otro ☐

Número: 438.019 TP 31.929

4 Número de expediente: 06.073.857

5 Descripción de la corrección o modificación solicitada:

Presento nuevos capitulos descriptivo y reivindicatorio compuesto por 35 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.

6 Comprobante de pago No. 09-34.459 **Fecha:** 11 de mayo de 2009
09-36.561 18 de mayo de 2009

7 Anexos

☐ Comprobante de pago de la tasa por $111.000, por concepto de modificaciones.

☒ Comprobante de pago por 20 reivindicaciones adicionales después de la decimoquinta reivindicación por $500.000.oo.

☐ Poderes, si fuere el caso

☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

ARTICULO MULTICAPA IMPERMEABLE y PERMEABLE AL VAPOR

La presente invención se refiere a un artículo multicapa impermeable y permeable al vapor.

Los artículos multicapa, impermeables y permeables al vapor, constituidos en la práctica por una membrana basada en el politetrafluoroetileno, son conocidos actualmente, sobre todo en el campo del calzado y de la ropa.

Una membrana de este tipo está acoplada a las telas que componen la prenda de vestir con el fin de permitir una permeación correcta del vapor al agua que se genera debido a la transpiración que desprende el cuerpo hacia el ambiente delimitado por la prenda de vestir.

Al mismo tiempo, la prenda de vestir debe permitir una impermeabilización correcta, con el mismo propósito de mantener el cuerpo seco.

Ocurre lo mismo con el calzado: unas membranas de este tipo están asociadas con la pala y con la suela del calzado; en este sentido, debería observarse que la mayoría de la transpiración podal se genera en la interfaz entre la suela del pie y la suela del calzado.

Unas membranas conocidas actualmente, aunque se utilizan desde hace varios años y son reconocidas unánimemente como capaces de asegurar una impermeabilización apropiada y una permeabilidad óptima al vapor de agua y al aire, presentan, no obstante, algunos aspectos mejorables.

Dichas membranas son apenas resistentes y, de hecho, pueden desgarrarse fácilmente: para hacerlas resistentes, son acopladas por lo tanto, generalmente por laminado, a una malla de soporte de material plástico, 16 que reduce inevitablemente su permeabilidad al vapor de agua o al aire.

De todas formas, el acoplamiento a la malla no es suficiente para conseguir unas características de resistencia aceptables.

Dada la consistencia limitada de dichas membranas, resulta evidente que no son capaces de soportarse a sí mismas.

Por lo tanto, por ejemplo en las suelas, la membrana (integrada con la malla) debe acoplarse a unos soportes que son capaces de soportarla apropiadamente.

Además, debería observarse que cuando, por alguna razón en concreto, se condensa la transpiración en el ambiente que debería mantenerse seco, que está delimitado por dichas membranas, dicha transpiración ya no puede ser expulsada, lo que produce un efecto "húmedo" desagradable.

El propósito de la presente invención consiste en proporcionar un artículo multicapa impermeable y permeable al vapor que supere los inconvenientes observados en los tipos conocidos.

Dentro de dicho propósito, un objetivo de la presente invención consiste en proporcionar un artículo multicapa impermeable y permeable al vapor que sea estructuralmente resistente.

Otro objetivo de la presente invención consiste en proporcionar un artículo multicapa impermeable y permeable al vapor que sea particularmente permeable al vapor o al aire.

Otro objetivo de la presente invención consiste en proporcionar un artículo multicapa impermeable y permeable al vapor que sea capaz de ser soportada por sí misma.

Otro objetivo de la presente invención consiste en proporcionar un artículo multicapa impermeable y permeable al vapor que pueda fabricarse con unos sistemas y tecnologías conocidos.

Dicho propósito y estos y otros objetivos de la presente invención que se pondrán de manifiesto más claramente a continuación, se alcanzan mediante un artículo multicapa impermeable y permeable al vapor, caracterizado porque comprende por lo menos una primera capa de un material permeable al vapor y microporoso e higroscópico o que puede adoptar unas propiedades higroscópicas con el tiempo, y por lo menos una segunda capa impermeable y permeable al vapor.

Otras características y ventajas de la invención se pondrán de manifiesto a partir de la descripción de dos formas de realización preferidas pero no exclusivas, ilustradas a continuación a título de ejemplo no limitativo en los dibujos adjuntos, en los que:

la Figura 1 representa una vista en sección de una primera forma de realización de un artículo multicapa según la invención;

la Figura 2 representa una vista en sección de una variante del artículo multicapa de la Figura 1;

la Figura 3 representa una vista en sección de una segunda forma de realización de un artículo multicapa según la invención; y

la Figura 4 representa una vista en sección de una variante del artículo multicapa de la Figura 3.

Haciendo referencia a la primera forma de realización, ilustrada en la Figura 1, un artículo multicapa. impermeable y permeable al vapor según la invención está designado en general con la referencia numérica 10.

El artículo multicapa 10 comprende una primera capa 11, de un material permeable al vapor, microporoso e higroscópico, y una segunda capa 12, impermeable y permeable al vapor.

La primera capa 11 está constituida por ejemplo por un material higroscópico basado en poliolefina y partículas de carga.

Dichas partículas de carga están diseñadas para crear los microporos que permiten la permeabilidad al vapor o al aire.

La poliolefina que se utiliza en el ejemplo descrito presenta un peso molecular muy alto; por lo tanto, preferentemente dicha poliolefina es un polietileno de UHMW (de peso molecular ultra alto).

Las características de una poliolefina de UHMW se refieren a una poliolefina con un peso molecular medio de por lo menos 500.000 g/mol.

Preferentemente, el peso molecular medio está comprendido entre $4x10^6$ g/mol y $7x10^6$ g/mol.

La carga preferida consiste en el silicio finamente triturado (dióxido de silicona, SiO_2).

El silicio presenta una capacidad higroscópica importante, lo que favorece totalmente las propiedades higroscópicas de la primera capa 11.

El diámetro medio óptimo de las partículas de carga de dióxido de silicona SiO_2 está comprendido entre 0,01 y 20 µm, mientras que el área superficial media de dichas partículas de carga está comprendida entre $30m^2/g$ y $950m^2/g$.

Preferentemente, el área superficial media de las partículas de carga es por lo menos $100m^2/g$.

La primera capa 11 que se ha descrito, presenta un tamaño de poros inferior a 1 µm de diámetro.

Preferentemente, más del 50% de los poros presentan un diámetro inferior a

0,5 µm.

La porosidad entendida como:

Porosidad =[1- (densidad aparente de membrana / densidad de resina)]x100

es preferentemente por lo menos el 50%.

Se trata la primera capa 11, por ejemplo, con unos agentes antibacterianos y/o fungicidas.

La forma definitiva preferida consiste en una hoja de grosor predeterminado, comprendido substancialmente entre 200 µm y 1,5 cm; en particular, entre 200 y 600 µm.

Una membrana microporosa conocida por su nombre comercial DARAMIC® y fabricada por DARAMIC Inc. (Norderstedt, Alemania) presenta las características descritas anteriormente para la primera capa 11 y por lo tanto se puede utilizar para formar un artículo multicapa según la invención.

Dicha membrana microporosa es conocida por sí misma y se utiliza actualmente a modo de división en acumuladores y pilas y se proporciona en forma laminar.

Las características de la membrana se dan a conocer en la patente US n° 3.351.495 (a nombre de W R GRACE & CO.) y la patente US n° 6.139.759 (en nombre de Daramic Inc.).

La versión que presenta un grosor de 600 µm de dicha membrana DARAMI® presenta una resistencia a la tracción definitiva de substancialmente 5,8 MPa y una elongación de rotura máxima del 505% (según ISO 37): como consecuencia, presenta unas excelentes características de resistencia.

En esta primera forma de realización que se ha descrito, la segunda capa 12, impermeable y permeable al vapor, está constituida por un material hidrófobo y microporoso basado en polipropileno (donde se utiliza el término "polipropileno" para designar cualquier polímero, homopolímero o copolímero procedente de monómeros de propileno).

Preferentemente, el polipropileno de la segunda capa 12 consiste en un homopolímero isotáctico con una afinidad baja para la absorción de proteínas y grasas.

Una membrana hidrófoba conocida bajo el nombre comercial CELGARD® de la empresa CELGARD Inc. presenta las características que se han descrito anteriormente con respecto a la segunda capa 12, y por lo tanto se puede utilizar para formar un artículo multicapa según la invención.

El acoplamiento entre la primera capa 11 y la segunda capa 12 se realiza según la "apariencia" que presentan dichas capas en el momento del acoplamiento.

Por ejemplo, si tanto la primera capa 11 como la segunda capa 12 están en forma laminar, se pueden acoplar aplicando unos puntos de adhesivo, para evitar crear una capa compacta, o utilizando unas tecnologías de alta frecuencia o de ultrasonido, evitando así la sustracción de superficie respirable.

Una alternativa consiste, por ejemplo, en extender o laminar una capa encima de la otra, lo que se denomina "soportado".

En este caso, la capa que se ha extendido debe adherirse de forma resistente al soporte dispuesto abajo para evitar su separación.

Además, debe resultar fácil formar o colocar dicha capa sobre la capa dispuesta abajo, utilizando unas técnicas de extensión y de laminado a gran escala.

La capa polimérica de polietileno de la membrana DARAMIC® puede ser apta para la extensión, dado que su peso molecular es lo

suficientemente alto para impedir que penetre en los poros del soporte microporoso, o se puede dispersar en agregados de mayor tamaño que los poros de la membrana de polipropileno de CELGARD®.

Por ejemplo, un procedimiento para fabricar un artículo multicapa según la invención comprende las siguientes etapas:

- preparar una solución o dispersión de la mezcla polimérica básica para la primera capa 11 en un líquido orgánico volátil con una tensión superficial baja, con el fin de producir una solución de extensión con cierta viscosidad;
- aplicar la solución extendiéndola sobre la superficie de la lámina de la segunda capa 12 que actúa como soporte, para formar una capa de revestimiento en su superficie;
- hacer que los componentes volátiles de la solución extendida se evaporen para fomentar la reacción de reticulación de la superficie extendida; y
- secar el revestimiento con el fin de eliminar la humedad residual y producir el artículo laminado.

Resulta evidente que pueden aplicarse una o varias capas adicionales del polímero de la misma manera y secarse hasta alcanzar el grosor deseado.

Se puede aplicar la solución del polímero al soporte compuesto por una membrana higroscópica y microporosa, utilizando unas técnicas estándares de extensión conocidas en la técnica anterior, por ejemplo la extensión por rodillo o la extensión por pulverización.

Se ilustra en la Figura 2 una variante de la configuración básica del artículo multicapa 10 compuesto por dos capas individuales.

En esta variante, el artículo multicapa según la invención, designado en general con la referencia numérica 100, está compuesto por una primera capa 111 de material permeable al vapor, higroscópico y microporoso, delimitada a modo de sándwich por dos segundas capas 112 impermeables y permeables al vapor.

Resulta evidente que la primera capa 111 y las segundas capas 112 respectivamente presentan las mismas características que se han descrito anteriormente con respecto a la primera capa 11 y a la segunda capa 12.

Además, resulta evidente que otras variantes pueden incluir unas superposiciones de una o varias de dichas primera y segunda capas, combinadas según las necesidades.

Asimismo, se puede proporcionar una segunda capa 12 (ó 112) extendiendo un fluoropolímero sobre una primera capa microporosa 11 (ó 111) u opcionalmente un polisiloxano.

Por ejemplo, dicho fluoropolímero es el conocido comercialmente bajo el nombre Zonyl® y fabricado por DuPont.

Asimismo, se puede proporcionar la segunda capa 12 (ó 112) sumergiendo la primera capa 11 (ó 111) en un baño de fluoropolímero (por ejemplo Zonyl®) o de un polisiloxano.

Una segunda forma de realización (véase la Figura 3) de un artículo multicapa según la invención, designada en general con la referencia numérica 200, comprende una primera capa 211 tal como la que se ha descrito en los ejemplos anteriores y comprende, como su segunda capa, designada en este caso con la referencia numérica 212, una película obtenida mediante un tratamiento por deposición de plasma.

La idea de la película obtenida mediante la deposición de plasma surge del sorprendente descubrimiento de que se puede utilizar un vapor

de un compuesto orgánico de siloxano para producir una capa ultrafina sobre un material microporoso de soporte mediante la polimerización de "plasma frío" bajo un vacío alto a temperatura ambiente, proporcionando unas características de impermeabilización sin alterar las características generales y en particular las características de permeabilidad del material de soporte.

De hecho, se puede proporcionar una capa hidrófoba impermeable y respirable mediante la polimerización por plasma de, por ejemplo, un monómero basado en siloxano, depositando una capa de polímero (polisiloxano) sobre un material microporoso de soporte (por ejemplo de polietileno o poliestireno).

Asimismo, se puede llevar a cabo dicha deposición utilizando unos fluoropolímeros repelentes al aceite y al agua, tales como los que .producen DuPont y que están registrados bajo el nombre comercial Zonyl®.

El plasma está dividido entre unos tipos calientes y fríos en función de las temperaturas que llega a alcanzar; asimismo está dividido entre el plasma de presión de ambiente y el plasma al vacío.

En un proceso de plasma frío para obtener una película según la presente invención, se introduce un compuesto precursor gaseoso o vaporizado en una cámara de reacción a una presión muy baja (bajo condiciones de vacío).

Se genera una condición de plasma excitando el precursor en el interior de la cámara de reacción mediante la generación de un campo eléctrico.

El resultado consiste en una capa ultrafina del polímero, que se adhiere a, y está depositada en, toda la superficie de cualquier material de substrato introducido en la cámara de reacción.

El proceso de polimerización por plasma se inicia y se lleva a cabo mediante un campo eléctrico para conseguir la descomposición del precursor de la capa de deposición en el interior de la cámara de reacción.

Una vez se ha descompuesto, se forman unos iones y unas especies reactivas que inician y realizan las reacciones atómicas y moleculares que finalmente forman unas películas delgadas.

Las capas generadas por la polimerización por plasma pueden utilizar distintas configuraciones de campos eléctricos y diferentes parámetros de reacción.

Se controla el grosor de la capa seleccionando el material de partida polimerizable y las condiciones de reacción, tal como el tiempo de deposición del monómero, el tiempo de tratamiento, la frecuencia eléctrica de la reacción, y la potencia empleada.

En la presente invención, la polimerización por plasma se realiza bajo vacío.

El intervalo típico de presiones está comprendido entre 10^{-1} y 10^{-5} mbar.

Se hace reaccionar el precursor en estado puro, utilizando un gas inerte no polimerizable, tal como por ejemplo argón; dicho gas inerte se utiliza tanto como diluyente inerte como gas portador que asiste en la polimerización del precursor.

Otros gases que se pueden utilizar son cualesquiera de entre oxígeno, helio, nitrógeno, neón, xenón y amoniaco.

El precursor debe presentar una presión de vapor suficiente como para permitir la vaporización en un vacío moderado.

Se inicia el proceso de deposición de plasma cargando el material de soporte a revestir (en este caso, la primera capa 212) en la cámara de reacción y posteriormente llevando dicha cámara a la presión de vacío deseada.

Una vez alcanzada la presión de vacío, puede iniciarse la reacción de polimerización por plasma o una reacción de tratamiento previo.

Se realiza la reacción de polimerización por plasma provocando la descarga que genera el plasma e inyectando el monómero precursor vaporizado en la cámara de reacción.

Se precisa una reacción de tratamiento previo cuando sea necesario limpiar la superficie de la primera capa, sometiéndola a un gas inerte tal como argón o nitrógeno para limpiar la superficie o fomentar la adhesión de la película de polímero.

Durante la descarga que genera el plasma, la colisión del monómero con los iones y los electrones del plasma permite la polimerización del monómero.

El polímero resultante se deposita en las superficies expuestas en el interior de la cámara.

Las propiedades de la película no son únicamente una función de la estructura del monómero, sino también una función de la frecuencia de descarga, de la potencia empleada, del caudal del monómero y de la presión.

La porosidad, la morfología superficial y la permeabilidad pueden variar según las condiciones de reacción.

Se acaba el proceso de deposición cuando se alcanza el grosor deseado del material depositado.

Gracias al hecho de que la primera capa superior 212 está realizada en material aislante (por ejemplo, el polietileno es uno de los materiales más aislantes conocidos), con el fin de mantener las condiciones de plasma, resulta necesario aplicar al proceso un generador de radiofrecuencias, para que el campo eléctrico en el tratamiento oscile según una frecuencia substancial mente del orden de 13,56 MHz, con una potencia aplicada de campo eléctrico de 50-700 vatios y un nivel de vacío comprendido entre 10^{-1} y 10^{-5} mbar.

En cuanto a la duración del tratamiento, se ha observado que con respecto a un precursor tal como un monómero de siloxano, el tiempo óptimo está comprendido substancialmente entre 160 y 600 segundos; particularmente se ha descubierto una duración óptima de substancialmente 420 segundos.

Se ilustra en la Figura 4 una variante de la configuración básica del artículo multicapa 200 compuesto por dos capas individuales.

En esta variante, el artículo multicapa según la invención, designado en general con la referencia numérica 300, está compuesto por una primera capa 311 de material permeable al vapor, higroscópico y microporoso, delimitada a modo de sándwich por dos segundas capas 312, impermeables y permeables al vapor.

Resulta evidente que la primera capa 311 y las segundas capas 312 respectivamente presentan las mismas características que se han descrito anteriormente con respecto a la primera capa 211 y la segunda capa 212.

Además, resulta evidente que otras variantes pueden comprender unas superposiciones de una o varias de las primera y segunda capas, combinadas según las necesidades.

En la práctica, se ha observado que la invención así descrita supera los problemas observados en los tipos conocidos de artículos multicapa impermeables y permeables al vapor.

De hecho se ha proporcionado un artículo multicapa que asocia una primera capa microporosa e higroscópica con una segunda capa hidrófoba, impidiendo dichas capas el flujo hacia el interior de cualesquiera

fases líquidas, a la vez que permite la transferencia de vapor de agua y otros componentes volátiles.

La carga a base de silicona provista en el interior de la primera capa para generar la estructura microporosa consiste en un material con una gran capacidad higroscópica y que demuestra una marcada tendencia a absorber agua; como consecuencia, la primera capa no resulta apta individualmente como capa impermeable, sino que resulta útil para alejar la transpiración y la humedad del cuerpo (el torso o las piernas, en el caso de prendas de vestir, y los pies en el caso de un calzado).

Además, dado que la primera capa higroscópica y la segunda capa hidrófoba son ambas más resistentes estructuralmente que las membranas que se emplean hoy en día, y asimismo son más gruesas, se pueden utilizar de forma combinada sin los soportes que tienden a reducir su permeabilidad al vapor y al aire.

En este sentido, dado que el artículo multicapa (10, 100, 200, 300 etc.) presenta unas características estructurales, se puede utilizar a modo de estructura de soporte en un calzado; por ejemplo, de forma combinada con una banda de rodadura con unas aberturas orientadas hacia arriba, se puede utilizar el artículo multicapa como elemento de soporte para una suela respirable e impermeable.

Se pueden acoplar dichas capas, según las necesidades, mediante la aplicación de unos puntos de adhesivo para evitar crear una capa compacta, o mediante unas tecnologías conocidas de alta frecuencia o ultrasonidos, evitando la sustracción de superficie respirable, o extendiendo o laminando una capa encima de la otra.

En este sentido, dado que la primera capa es la que alcanza un mayor grosor sin comprometer la permeabilidad al vapor y al aire, cuando se utiliza como soporte para la deposición por plasma de una película impermeable y respirable, se puede conseguir el mismo propósito y objetivos que los que se han mencionado anteriormente, formando una pareja entre las dos capas por extensión, laminado o unión por adhesivo.

Debería observarse que la aplicación de la deposición de plasma supera los problemas de conformidad y de adhesión entre la primera y la segunda capa, porque el polímero depositado por plasma se adhiere a la capa de soporte durante más tiempo que, por ejemplo, una extensión convencional.

Además, dado que se deposita la película impermeable bajo unas condiciones parciales de vacío, y dado que se puede limpiar el material de soporte en la cámara de reacción previamente utilizando argón con un grado elevado de pureza, se evitan totalmente cualesquiera impurezas que podrían ocasionar fisuras, interrupciones o distorsiones en la película impermeable.

La invención así concebida es susceptible de numerosas modificaciones y variantes, todas las cuales están comprendidas en el alcance de las reivindicaciones adjuntas; además todos los detalles pueden ser sustituidos por otros elementos técnicamente equivalentes.

En la práctica, los materiales que se emplean, siempre que sean compatibles con el uso específico, así como las dimensiones, pueden ser cualesquiera según las necesidades y la técnica anterior.

Las divulgaciones en la solicitud de patente italiana n°PD2003A000314 de la cual la presente solicitud reivindica prioridad, se incorporan en la presente memoria como referencia.

153
105

REIVINDICACIONES

1. Artículo multicapa impermeable y permeable al vapor, caracterizado porque comprende por lo menos una primera capa (11, 111, 211, 311) realizada en un material permeable al vapor, microporoso e higroscópico o que puede adoptar unas características higroscópicas con el tiempo, y por lo menos una segunda capa (12, 112, 212, 312) impermeable, permeable al vapor e hidrofobica.

2. Artículo multicapa de acuerdo con la reivindicación 1, caracterizado porque dicha por lo menos una primera capa (11. 111, 211, 311) comprende una base compuesta por poliolefina y partículas de carga.

3. Artículo multicapa de acuerdo con la reivindicación 2. caracterizado porque el peso molecular de dicha poliolefina es 500.000 g/mol.

4. Artículo multicapa de acuerdo con la reivindicación 2, caracterizado porque el peso molecular de dicha poliolefina está comprendido preferentemente entre $4x10^6$ g/mol y $7x10^6$ g/mol.

5. Artículo multicapa de acuerdo con una de las reivindicaciones 2 a 4 caracterizado porque dicha poliolefina está constituida por polipropileno o polietileno isotáctico.

6. Artículo multicapa de acuerdo con una de las reivindicaciones 2 a 5, caracterizado porque dicha carga es preferentemente el dióxido de silicona SiO_2.

7. Artículo multicapa de acuerdo con la reivindicación 6, caracterizado porque el diámetro medio de las partículas de carga de di óxido de silicona Si02 está comprendido entre 0,01 µm y 20 µm, mientras que el área superficial media de dichas cargas está comprendida entre $30m^2/g$ y $950m^2/g$.

8. Artículo multicapa de acuerdo con la reivindicación 6 ó 7, caracterizado porque el área superficial media de dichas partículas de carga es preferentemente por lo menos $100m^2/g$.

9. Artículo multicapa de acuerdo con cualquiera de las reivindicaciones anteriores, caracterizado porque dicha por lo menos una primera capa (11, 111, 211, 311) de material microporoso presenta un tamaño de poros inferior a 1 µm de diámetro.

10. Artículo multicapa de acuerdo con cualquiera de las reivindicaciones anteriores, caracterizado porque preferentemente más del 50% de los poros de dicha por lo menos una primera capa (11, 111, 211, 311) de material microporoso presentan un diámetro inferior a 0,5 µm.

11. Artículo multicapa de acuerdo con cualquiera de las reivindicaciones anteriores, caracterizado porque la porosidad de dicha por lo menos una primera capa (11, 111, 211,311) de material microporoso es preferentemente por lo menos el 50%.

12. Artículo multicapa de acuerdo con cualquiera de las reivindicaciones anteriores, caracterizado porque dicha por lo menos una primera capa (11, 111, 211, 311) de material microporoso presenta un grosor comprendido entre 200 µm y 1,5 cm.

13. Artículo multicapa de acuerdo con la reivindicación 12, caracterizado porque dicha por lo menos una primera capa (11, 111, 211, 311) de material microporoso presenta un grosor comprendido preferentemente entre 200 µm y 600 µm.

14. Artículo multicapa de acuerdo con la reivindicación 1, caracterizado porque dicha por lo menos una primera capa (11, 111, 211, 311) está constituida por una membrana microporosa.

15. Artículo multicapa de acuerdo con cualquiera de las reivindicaciones anteriores, caracterizado porque dicha por lo menos una segunda capa impermeable y permeable al vapor (12, 112) está constituida por un material microporoso e hidrófobo, a base de polipropileno.

16. Artículo multicapa de acuerdo con la reivindicación 15, caracterizado porque el polipropileno de dicho material microporoso e hidrófobo es un homopolímero isotáctico.

17. Artículo multicapa de acuerdo con la reivindicación 1, caracterizado porque dicha por lo menos una segunda capa (12, 112) está compuesta por un polímero a base de fluoropolímero o polisiloxano, adhiriéndose dicha por lo menos una segunda capa (12, 112) a dicha primera capa (11, 111) extendiendo o sumergiendo dicha primera capa (11, 111) en un baño de dicho polímero.

18. Procedimiento para fabricar un artículo multicapa de acuerdo con cualquiera de las reivindicaciones anteriores, que consiste en:

- preparar una solución o dispersión de la mezcla polimérica básica para dicha primera capa (11, 111) en un líquido orgánico volátil con una tensión superficial baja, para producir una solución de extensión que presenta cierta viscosidad;
- aplicar dicha solución extendiéndola sobre la superficie de dicha segunda capa (12, 112), que actúa como soporte, para formar una capa de revestimiento en su superficie; y
- evaporar los componentes volátiles de la solución de extensión con el fin de fomentar la reacción de reticulación de la superficie extendida;
- secar el revestimiento para eliminar la humedad residual.

19. Procedimiento para fabricar un artículo multicapa de acuerdo con una de las reivindicaciones 1 a 16, que consiste en acoplar dicha primera capa (11, 111) y dicha segunda capa (12, 112) laminando una de dichas capas encima de la otra.

20. Procedimiento para fabricar un artículo multicapa de acuerdo con una de las reivindicaciones 1 a 16, que consiste en acoplar dicha primera capa (11, 111) en forma laminar a dicha segunda capa (12, 112), asimismo en forma laminar, aplicando unos puntos de adhesivo o utilizando ultrasonidos o mediante soldadura por alta frecuencia.

21. Artículo multicapa de acuerdo con una o más de las reivindicaciones 1 a 14, caracterizado porque dicha por lo menos una segunda capa (212, 312) está compuesta por una película obtenida mediante un tratamiento por deposición de plasma.

22. Artículo multicapa de acuerdo con la reivindicación 21, caracterizado porque dicho tratamiento por deposición de plasma se obtiene trabajando en unas condiciones de vacío alto y plasma frío.

23. Artículo multicapa de acuerdo con la reivindicación 21 ó 22, caracterizado porque dicho tratamiento por deposición de plasma se obtiene utilizando un generador de radiofrecuencia de modo que el campo eléctrico del tratamiento oscila con una frecuencia comprendida substancialmente entre 13 MHz y 14 MHz.

24. Artículo multicapa de acuerdo con la reivindicación 23, caracterizado porque dicho tratamiento por deposición de plasma utilizando un generador de radiofrecuencia de modo que el campo eléctrico del tratamiento oscila con una frecuencia preferentemente del orden de 13,56 MHz.

25. Artículo multicapa de acuerdo con una de las reivindicaciones 21 a 24, caracterizado porque dicho tratamiento por deposición de plasma se obtiene utilizando una potencia de campo eléctrico aplicada en el tratamiento comprendida substancialmente entre 50 vatios y 700 vatios.

26. Artículo multicapa de acuerdo con una de las reivindicaciones 21 a 25, caracterizado porque la duración de dicho tratamiento por deposición de plasma para un monómero a base de siloxano está comprendida entre 160 y 600 segundos.

27. Artículo multicapa de acuerdo con la reivindicación 26, caracterizado porque la duración de dicho tratamiento por deposición de plasma para un monómero a base de siloxano es equivalente a 420 segundos.

28. Artículo multicapa de acuerdo con una de las reivindicaciones 21 a 27, caracterizado porque el nivel de vacío en dicho tratamiento por deposición de plasma está comprendido entre 10^{-1} mbar y 10^{-5} mbar.

29. Artículo multicapa de acuerdo con la reivindicación 21, caracterizado porque dicho tratamiento por deposición de plasma se obtiene trabajando en condiciones de vacío alto y plasma fría y utilizando un generador de radiofrecuencias para que el campo eléctrico del tratamiento oscila con una frecuencia del orden de 13,75 MHz, con una potencia de campo eléctrico aplicada de 300-500 vatios, y un nivel de vacío comprendido entre 10^{-1} mbar y 10^{-3} mbar.

30. Artículo multicapa de acuerdo con una de las reivindicaciones 21 a 29, caracterizado porque el material precursor de la deposición de plasma consiste en un monómero a base de siloxano.

31. Artículo multicapa de acuerdo con una de las reivindicaciones 21 a 29, caracterizado porque el material precursor de la deposición de plasma consiste en un fluoropolímero repelente al aceite y al agua.

32. Artículo multicapa de acuerdo con una de las reivindicaciones 21 a 29, caracterizado porque el material de dicha por lo menos una segunda capa (212, 312) consiste en un polisiloxano.

33. Artículo multicapa de acuerdo con una de las reivindicaciones 21 a 29, caracterizado porque el material de dicha por lo menos una segunda capa (212, 312) consiste en un fluoropolímero repelente al aceite y al agua.

34. Procedimiento para fabricar un artículo multicapa de acuerdo con cualquiera de las reivindicaciones anteriores 21 a 32, que comprende las siguientes etapas:

- cargar dicha primera capa (211, 311) a revestir en la cámara de reacción,
- llevar dicha cámara de reacción a una presión de vacío predeterminada;
- iniciar dicha descarga eléctrica que genera el plasma;
- inyectar el monómero precursor vaporizado en dicha cámara de reacción; y
- esperar un tiempo de deposición predeterminado.

35. Procedimiento de fabricación de acuerdo con la reivindicación 34, caracterizado porque comprende una etapa de tratamiento previo que consiste en limpiar la superficie de dicha primera capa (211, 311) sometiéndola a un gas inerte que se inyecta en dicha cámara de reacción.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 06-073857- -00007-0000

Fecha: 2009-06-01 17:30:57 Dep: 2020 NUEVACREACION
Tra: 11 PATENTES Eve: 378 PATENACIONALES
Act: 444 RESPUESTA REQUE Folios: 22

13377-891-005-a.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 06-073857- -00007-0000

Fecha 2009-06-01 17:30:57 Dep: 2020 NUEVACREACION1
Ins 11 PATENTE1YII Eve. 378 FASENACIONAL1
Act 444 RESPUESTAREQUE Folios 22

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 36,561
FECHA : MAYO 18 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062759387	1056001245	18/05/2009	$9,725,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS	81,000.00
		TOTAL : $	81,000.00

SON: OCHENTA Y UNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cobro: 13377-841-005-9.

United States Patent [19]

Rechlicz et al.

[11] **Patent Number: 5,032,450**

[45] **Date of Patent: Jul. 16, 1991**

[54] **MICROPOROUS MATERIAL HAVING A COATING OF HYDROPHOBIC POLYMER**

[75] Inventors: **Thomas Rechlicz**, Clinton, Ohio; **Dennis D. Leatherman**, Pittsburgh, Pa.

[73] Assignee: **PPG Industries, Inc.**, Pittsburgh, Pa.

[21] Appl. No.: **473,769**

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[51] Int. Cl.[5] **B32B 3/00; B32B 27/14**

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[58] Field of Search 428/224, 196, 225, 245, 428/253, 254, 255, 280, 281, 283, 290, 315.5, 315.7, 315.9, 316.6, 317.9, 910

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,751,314	6/1956	Keil	117/72
4,194,041	3/1980	Gore et al.	428/315
4,226,926	10/1980	Goldberg et al.	429/252
4,443,511	4/1984	Worden et al.	428/198
4,613,544	9/1986	Burleigh	428/315.5
4,616,049	10/1986	Thompson et al.	523/212
4,764,560	8/1988	Mitchell	524/506
4,791,144	12/1988	Nagou et al.	521/90
4,833,172	5/1989	Schwarz et al.	521/62
4,861,644	8/1989	Young et al.	428/195
4,877,679	10/1989	Leatherman et al.	428/224

FOREIGN PATENT DOCUMENTS

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OTHER PUBLICATIONS

E. Reagan, "Comparing the High-Tech Fabrics", *Outside Business* (Apr. 1989), pp. 41–45 and 47–49.

B. A. Ross et al., "Breathable Coatings-The How and Why" (May 1989).

D. Graiver, "Emulsion Polymerized Polydimethylsiloxane", *Rubber Chemistry and Technology*, vol. 56, No. 5 (Nov.–Dec. 1983), pp. 918–926.

R. S. Ward et al., "Development of Monolithic Breathable Barrier Films for Disposable Products" (1987).

R. S. Ward et al., "The Science and Technology of Breathable Barrier Films and Coatings" (1987).

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[57] **ABSTRACT**

A coated article comprises a substantially continuous, moisture vapor permeable coating of hydrophobic polymer joined to one side of a sheet of microporous material comprises a matrix consisting essentially of linear ultrahigh molecular weight polyolefin, a large proportion of finely divided, water-insoluble siliceous filler, and interconnecting pores.

31 Claims, No Drawings

MICROPOROUS MATERIAL HAVING A COATING OF HYDROPHOBIC POLYMER

[redacted], or [redacted] the present invention are known.

U.S. Pat. No. 4,194,041 discloses a hydrophobic layer which is porous and permeable to gases, joined to one surface of the layer a continuous film of hydrophilic material. Examples of hydrophobic layers include microporous expanded polytetrafluoroethylene film which has been heated above its crystalline melt point after expansion, microporous polypropylene film and tightly woven fabrics or tightly spaced nonwoven webs of fibers of polyethylene, polypropylene, polytetrafluoroethylene, or other fibers treated with hydrophobic agents. Examples of hydrophilic films include films of crosslinked polyoxyethylene-polyurethane and films of a copolymer of tetrafluoroethylene and a monomer such as perfluoro-3,6-dioxa-4-methyl-7-octenesulfonic acid.

U.S. Pat. No. 4,443,511 discloses stretching a composite comprising a layer of hydrophobic material and an elastomeric hydrophilic layer.

Waterproof, moisture vapor permeable, unitary sheet materials are also known.

U.S. Pat. No. [redacted] discloses a material of this type which comprises a microporous polymeric matrix, which is preferably hydrophobic but may be hydrophilic, the pores of which are sufficiently filled with a moisture vapor permeable, water impermeable, hydrophilic material to prevent the passage of water and other liquids while permitting the passage of moisture vapor.

U.S. Pat. No. 4,764,560 discloses porous materials which are impervious to liquid water and pervious to air. The materials are stretched interpenetrating polymer networks of cured silicone and polytetrafluoroethylene.

The disclosures of U.S. Pat. Nos. 4,194,041; 4,443,511; 4,613,544; and 4,764,560 are, in their entireties, incorporated herein by reference.

Contrary to the disclosures of the patents discussed above, a coated article which is substantially impermeable to liquid water and permeable to moisture vapor has been discovered [redacted]. The hydrophobic coating is characterized by a high moisture permeability coefficient. Due to the hydrophobic property of the coating, liquid water beads up on the exposed surface rather than forming an extensive liquid water film. Inasmuch as the primary driving force for transporting moisture vapor molecules through the coating is ultimately a difference in moisture vapor pressure on opposite sides of the coating, the avoidance of such liquid water films is advantageous in promoting efficient moisture vapor transfer.

The microporous material, if initially hydrophobic, becomes hydrophilic upon washing due to the effect of the detergent and/or soap, that is, the surfactant. The hydrophilic microporous material acts as a wicking agent to increase the transport of moisture to the hydrophobic coating.

Accordingly, one embodiment of the invention is a coated article which is substantially impermeable to

liquid water and permeable to moisture vapor, the article comprising: (a) a sheet of microporous material having generally opposing sides, the microporous material comprising: (1) [redacted] linear ultrahigh [redacted]ing an intrinsic viscosity of at least about 18 deciliters/gram, essentially linear ultrahigh molecular weight polypropylene having an intrinsic viscosity of at least about 6 deciliters/gram, or a mixture thereof, the matrix comprising regions of stretch-induced molecularly oriented ultrahigh molecular weight polyolefin distributed throughout the matrix, (2) finely divided particulate substantially water-insoluble filler, of which at least about 50 percent by weight is siliceous, distributed throughout the matrix, the filler constituting from about 50 percent to about 90 percent by weight of the microporous material, and (3) a network of interconnecting pores communicating throughout the microporous material, the pores on a coating-free and impregnant-free basis constituting more than 70 percent by volume of the microporous material; and (b) a substantially continuous, moisture vapor permeable coating of [redacted] polymer joined to one side of the microporous material.

It has surprisingly been found that the moisture vapor transmission rate of the microporous material is much less dependent upon the porosity of the microporous material than would have been expected. Although it is not desired to be bound by any theory, it is believed that the capillary forces within the pores of the siliceous filler provide a strong driving force for transport of liquid water through the microporous material and delivery to the hydrophobic polymeric coating. It is also believed that inasmuch as the hydrophobic polymeric coating is substantially continuous, it is not porous in the sense that there are passageways larger than molecular in size and that the moisture vapor is effectively transported through the layer by diffusion on a molecule by molecule basis. Since coatings are only rarely perfect, pinholes may occasionally be present, but these are few in number and the quantity of moisture vapor transported by them is very small compared with that transported through the continuous coating.

Microporous materials which may be used in the present invention and methods for their production are described in U.S. Pat. Nos. 4,833,172 and 4,877,679, the entire disclosures of which are incorporated herein by reference.

The microporous material may be produced by stretching precursor microporous material in at least one stretching direction above the elastic limit, the precursor microporous material comprising (a) a matrix consisting essentially of essentially linear ultrahigh molecular weight polyolefin which is essentially linear ultrahigh molecular weight polyethylene having an intrinsic viscosity of at least about 18 deciliters/gram, essentially linear ultrahigh molecular weight polypropylene having an intrinsic viscosity of at least about 6 deciliters/gram, or a mixture thereof, (b) finely divided particulate substantially water-insoluble filler, of which at least about 50 percent by weight is siliceous, distributed throughout the matrix, the filler constituting from about 50 percent to about 90 percent by weight of the microporous material, and (c) a network of interconnecting pores communicating throughout the precursor microporous material, the pores constituting from about 35 percent to about 80 percent by volume of the precur-

5,032,450

sor microporous material, to produce stretched microporous material which is dimensionally stable at room temperature and which comprises (d) a matrix consisting essentially of the essentially linear ultrahigh molecular weight polyolefin, the matrix of the stretched microporous material comprising regions of stretch-induced molecularly oriented ultrahigh molecular weight polyolefin distributed throughout the matrix of the stretched microporous material, (e) the filler distributed throughout the matrix of the stretched microporous material, and (f) a network of interconnecting pores communicating throughout the stretched microporous material, the pores of the stretched microporous material constituting more than 70 percent by volume of the stretched microporous material.

It will be appreciated from the above that the stretching both increases the void volume of the material and induces regions of molecular orientation in the ultrahigh molecular weight (UHMW) polyolefin. As is well known in the art, many of the physical properties of molecularly oriented thermoplastic organic polymer, including tensile strength, tensile modulus, Young's modulus, and others, differ considerably from those of the corresponding thermoplastic organic polymer having little or no molecular orientation. Although it is not desired to be bound by any theory, it is believed that the properties of the UHMW polyolefin, the regions of molecular orientation, the high levels of filler loading, and the high degrees of porosity cooperate to provide many of the desirable properties characteristic of the microporous material.

The microporous material is non-isotropic, that is, the pore or microvoid shapes and distributions of pore or microvoid sizes are not the same in planes perpendicular to the surface as in planes parallel to the surface.

The thickness across the microporous material may vary widely, but usually it is in the range of from about 0.03 to about 0.4 millimeter. In many cases, it is in the range of from about 0.05 to about 0.3 millimeter. From about 0.07 to about 0.25 millimeter is preferred.

Inasmuch as UHMW polyolefin is not a thermoset polymer having an infinite molecular weight, it is technically classified as a thermoplastic. However, because the molecules are essentially very long chains, UHMW polyolefin, and especially UHMW polyethylene, softens when heated but does not flow as a molten liquid in a normal thermoplastic manner. The very long chains and the peculiar properties they provide to UHMW polyolefin are believed to contribute in large measure to the desirable properties of the microporous material.

As indicated earlier, the intrinsic viscosity of the UHMW polyethylene is at least about 18 deciliters/gram. In many cases the intrinsic viscosity is at least about 19 deciliters/gram. Although there is no particular restriction on the upper limit of the intrinsic viscosity, the intrinsic viscosity is frequently in the range of from about 18 to about 39 deciliters/gram. An intrinsic viscosity in the range of from about 18 to about 32 deciliters/gram is preferred.

Also as indicated earlier, the intrinsic viscosity of the UHMW polypropylene is at least about 6 deciliters/gram. In many cases the intrinsic viscosity is at least about 7 deciliters/gram. Although there is no particular restriction on the upper limit of the intrinsic viscosity, the intrinsic viscosity is often in the range of from about 6 to about 18 deciliters/gram. An intrinsic viscosity in the range of from about 7 to about 16 deciliters/gram is preferred.

As used herein and in the claims, intrinsic viscosity is determined by extrapolating to zero concentration the reduced viscosities or the inherent viscosities of several dilute solutions of the UHMW polyolefin where the solvent is freshly distilled decahydronaphthalene to which 0.2 percent by weight, 3,5-di-tert-butyl-4-hydroxyhydrocinnamic acid, neopentanetetrayl ester [CAS Registry No. 6683-19-8] has been added. The reduced viscosities or the inherent viscosities of the UHMW polyolefin are ascertained from relative viscosities obtained at 135° C. using an Ubbelohde No. 1 viscometer in accordance with the general procedures of ASTM D 4020-81, except that several dilute solutions of differing concentration are employed. ASTM D 4020-81 is, in its entirety, incorporated herein by reference.

The nominal molecular weight of UHMW polyethylene is empirically related to the intrinsic viscosity of the polymer according to the equation:

$$M=5.37\times10^{4}[\eta]^{1.37}$$

where M is the nominal molecular weight and [η] is the intrinsic viscosity of the UHMW polyethylene expressed in deciliters/gram. Similarly, the nominal molecular weight of UHMW polypropylene is empirically related to the intrinsic viscosity of the polymer according to the equation:

$$M=8.88\times10^{4}[\eta]^{1.25}$$

where M is the nominal molecular weight and [η] is the intrinsic viscosity of the UHMW polypropylene expressed in deciliters/gram.

The essentially linear ultrahigh molecular weight polypropylene is most frequently essentially linear ultrahigh molecular weight [redacted]. Often the degree of isotacticity of such polymer is at least about 95 percent, while preferably it is at least about 98 percent.

[redacted] in the [redacted] to the microporous [redacted]. Other thermoplastic organic polymer may also be present in the matrix so long as its presence does not materially affect the properties of the microporous material in an adverse manner. The amount of the other thermoplastic polymer which may be present depends upon the nature of such polymer. In general, a greater amount of other thermoplastic organic polymer may be used if the molecular structure contains little branching, few long sidechains, and few bulky side groups, than when there is a large amount of branching, many long sidechains, or many bulky side groups. For this reason, the preferred thermoplastic organic polymers which may optionally be present are low density polyethylene, high density polyethylene, poly(tetrafluoroethylene), polypropylene, copolymers of ethylene and propylene, copolymers of ethylene and acrylic acid, and copolymers of ethylene and methacrylic acid. If desired, all or a portion of the carboxyl groups of carboxyl-containing copolymers may be neutralized with sodium, zinc or the like. It is our experience that usually at least about 70 percent UHMW polyolefin, based on the weight of the matrix, will provide the desired properties to the microporous material. Often at least about 70 percent by weight of the matrix is UHMW polyolefin. In many cases the other thermoplastic organic polymer is substantially absent.

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EXRE3

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O/ Ref.: *INS/JG - EP 03 749 520.7*

Paris, December 18, 2008

European Patent Application N° 03 749 520.7 - 2103
Filed on September 8, 2003
In the name of ELAN PHARMACEUTICALS, Inc. et al.

Communication pursuant to Article 94(3) EP

Dear Sirs,

In response to the communication pursuant to Art. 94(3) EPC of August 7, 2008 concerning the patent application in reference, Applicants amend the claims.

Please find attached a marked up version of the amended set of claims.

I. Amendments:

Current Ammendments

Claims 1 to 20 are pending.

In claim 5, the phrase "wherein R_{1-a} and R_{1-b} are - H or C_1-C_6 alkyl" was introduced after "$NR_{1-a}R_{1-b}$".

In claims 7 and 8, the following amendments were carried out:

- regarding the definition of R_5:
  - The optional substitution of the cycloalkyl groups was deleted;
  - The definition C_3-C_7 cycloalkyl was completed so that it now reads "C_3-C_7 cycloalkyl C_1-C_4 alkyl". The addition is supported by claim 1 as originally filed.

18/12/2008

[redacted]ceous. As present in the microporous material, the siliceous filler may be in the form of ultimate particles, aggregates of ultimate particles, or a combination of both. In most cases, at least about 90 percent by weight of the siliceous filler used in preparing the microporous material has gross particle sizes in the range of from about 5 to about 40 micrometers as determined by use of a Model TAII Coulter Counter (Coulter Electronics, Inc.) according to ASTM C 690-80 but modified by stirring the filler for 10 minutes in Isotton II electrolyte (Curtin Matheson Scientific, Inc.) using a four-blade, 4.445 centimeter diameter propeller stirrer. Preferably at least about 90 percent by weight of the siliceous filler has gross particle sizes in the range of from about 10 to about 30 micrometers. It is expected that the sizes of filler agglomerates may be reduced during processing of the ingredients to prepare the microporous material. Accordingly, the distribution of gross particle sizes in the microporous material may be smaller than in the raw siliceous filler itself. ASTM C 690-80 is, in its entirety, incorporated herein by reference.

Examples of suitable siliceous fillers include silica, mica, montmorillonite, kaolinite, asbestos, talc, diatomaceous earth, vermiculite, natural and synthetic zeolites, cement, calcium silicate, aluminum silicate, sodium aluminum silicate, aluminum polysilicate, alumina silica gels, and glass particles. Silica and the glass are the preferred siliceous fillers. Of the silicas, precipitated silica, silica gel, or fumed silica is most often used.

In addition to the siliceous filler, finely divided particulate substantially water-insoluble non-siliceous fillers may also be employed. Examples of such optional non-siliceous fillers include carbon black, charcoal, graphite, titanium oxide, iron oxide, copper oxide, zinc oxide, antimony oxide, zirconia, magnesia, alumina, molybdenum disulfide, zinc sulfide, barium sulfate, strontium sulfate, calcium carbonate, magnesium carbonate, magnesium hydroxide, and finely divided particulate substantially water-insoluble flame resistant filler such as ethylenebis(tetrabromophthalimide), octabromodiphenyl oxide, decabromodiphenyl oxide, and ethylenebis(dibromonorbornane dicarboximide).

The finely divided substantially water-insoluble non-siliceous filler used in the microporous material is particulate. As present in the microporous material, the non-siliceous filler may be in the form of ultimate particles, aggregates of ultimate particles, or a combination of both. In most cases, at least about 75 percent by weight of the non-siliceous filler used in preparing the microporous material has gross particle sizes in the ranges of from about 0.1 to about 40 micrometers as determined by use of a Micromeretics Sedigraph 5000-D (Micromeretics Instrument Corp.) in accordance with the accompanying operating manual. The preferred ranges vary from filler to filler. For example, it is preferred that at least about 75 percent by weight of antimony oxide particles be in the range of from about 0.1 to about 3 micrometers, whereas it is preferred that at least about 75 percent by weight of barium sulfate particles be in the range of from about 1 to about 25 micrometers. It is expected that the sizes of filler agglomerates may be reduced during processing of the ingredients to prepare the microporous material. Therefore, the distribution of gross particle sizes in the microporous material may be smaller than in the raw non-siliceous filler itself.

The particularly preferred finely divided particulate substantially water-insoluble siliceous filler is precipitated silica. Although both are silicas, it is important to distinguish precipitated silica from silica gel inasmuch as these different materials have different properties. Reference in this regard is made to R. K. Iler, *The Chemistry of Silica*, John Wiley & Sons, New York (1979), Library of Congress Catalog No. QD 181.S6I44, the entire disclosure of which is incorporated herein by reference. Note especially pages 15–19, 173–176, 218–233, 364–368, 462–465, 554–564, and 578–579. Silica gel is usually produced commercially at low pH by acidifying an aqueous solution of a soluble metal silicate, typically sodium silicate, with acid. The acid employed is generally a strong mineral acid such as sulfuric acid or hydrochloric acid although carbon dioxide is sometimes used. Inasmuch as there is essentially no difference in density between the gel phase and the surrounding liquid phase while the viscosity is low, the gel phase does not settle out, that is to say, it does not precipitate. Silica gel, then, may be described as a non-precipitated, coherent, rigid, three-dimensional network of contiguous particles of colloidal amorphous silica. The state of subdivision ranges from large, solid masses to submicroscopic particles, and the degree of dehydration from almost anhydrous silica to soft gelatinous masses containing on the order of 100 parts of water per part of silica by weight, although the highly hydrated forms are only rarely used in the microporous material.

Precipitated silica is usually produced commercially by combining an aqueous solution of a soluble metal silicate, ordinarily alkali metal silicate such as sodium silicate, and an acid so that colloidal particles will grow in weakly alkaline solution and be coagulated by the alkali metal ions of the resulting soluble alkali metal salt. Various acids may be used, including the mineral acids and carbon dioxide. In the absence of a coagulant, silica is not precipitated from solution at any pH. The coagulant used to effect precipitation may be the soluble alkali metal salt produced during formation of the colloidal silica particles, it may be added electrolyte such as a soluble inorganic or organic salt, or it may be a combination of both.

Precipitated silica, then, may be described as precipitated aggregates of ultimate particles of colloidal amorphous silica that have not at any point existed as macroscopic gel during the preparation. The sizes of the aggregates and the degree of hydration may vary widely.

Precipitated silica powders differ from silica gels that have been pulverized in ordinarily having a more open structure, that is, a higher specific pore volume. However, the specific surface area of precipitated silica as measured by the Brunauer, Emmett, Teller (BET) method using nitrogen as the adsorbate, is often lower than that of silica gel.

Many different precipitated silicas may be employed in the microporous material, but the preferred precipitated silicas are those obtained by precipitation from an aqueous solution of sodium silicate using a suitable acid such as sulfuric acid, hydrochloric acid, or carbon dioxide. Such precipitated silicas are themselves known and processes for producing them are described in detail in U.S. Pat. No. 2,940,830, and in U.S. Pat. No. 4,681,750, the entire disclosures of which are incorporated herein by reference, including especially the processes for making precipitated silicas and the properties of the products.

In the case of the preferred filler, precipitated silica, the average ultimate particle size (irrespective of whether or not the ultimate particles are agglomerated) is less than about 0.1 micrometer as determined by transmission electron microscopy. Often the average ultimate particle size is less than about 0.05 micrometer. Preferably the average ultimate particle size of the precipitated silica is less than about 0.03 micrometer.

The finely divided particulate substantially water-insoluble filler constitutes from about 50 to 90 percent by weight of the microporous material. Frequently such filler constitutes from about 50 to about 85 percent by weight of the microporous material. From about 60 percent to about 80 percent by weight is preferred.

At least about 50 percent by weight of the finely divided particulate substantially water-insoluble filler is finely divided particulate substantially water-insoluble siliceous filler. In many cases at least about 65 percent by weight of the finely divided particulate substantially water-insoluble filler is siliceous. Often at least about 75 percent by weight of the finely divided particulate substantially water-insoluble filler is siliceous. Frequently at least about 85 percent by weight of the finely divided particulate water-insoluble filler is siliceous. In many instances all of the finely divided particulate water-insoluble filler is siliceous.

Minor amounts, usually less than about 5 percent by weight, of other materials used in processing such as lubricant, processing plasticizer, organic extraction liquid, surfactant, water, and the like, may optionally also be present. Yet other materials introduced for particular purposes may optionally be present in the microporous material in small amounts usually less than about 15 percent by weight. Examples of such materials include antioxidants, ultraviolet light absorbers, dyes, pigments, and the like. The balance of the microporous material, exclusive of filler and any impregnant applied for one or more special purposes is essentially the thermoplastic organic polymer.

On a coating-free and impregnant-free basis, pores constitute more than 70 percent by volume of the microporous material. Frequently the pores constitute at least about 80 percent by volume of the microporous material. In many instances the pores constitute at least about 85 percent by volume of the microporous material. Often the pores constitute from more than 70 percent to about 95 percent by volume of the microporous material. From about 80 percent to about 95 percent by volume is preferred. From about 85 percent to about 95 percent by volume is particularly preferred. As used herein, and in the claims, the porosity (also known as void volume) of the microporous material, expressed as percent by volume, is determined according to the equation:

$$\text{Porosity} = 100\left(1 - \frac{d_1}{d_2}\right)$$

where d_1 is the density of the sample which is determined from the sample weight and the sample volume as ascertained from measurements of the sample dimensions and d_2 is the density of the solid portion of the sample which is determined from the sample weight and the volume of the solid portion of the sample. The volume of the solid portion of the sample is determined using a Quantachrome Stereopycnometer (Quantachrome Corp.) in accordance with the accompanying operating manual.

The volume average diameter of the pores of the microporous material is determined by mercury porosimetry using an Autoscan mercury porosimeter (Quantachrome Corp.) in accordance with the accompanying operating manual. The volume average pore radius for a single scan is automatically determined by the porosimeter. In operating the porosimeter, a scan is made in the high pressure range (from about 138 kilopascals absolute to about 227 megapascals absolute). If about 2 percent or less of the total intruded volume occurs at the low end (from about 138 to about 250 kilopascals absolute) of the high pressure range, the volume average pore diameter is taken as twice the volume average pore radius determined by the porosimeter. Otherwise, an additional scan is made in the low pressure range (from about 7 to about 165 kilopascals absolute) and the volume average pore diameter is calculated according to the equation:

$$d = 2\left(\frac{v_1}{r_1} + \frac{v_2}{r_2}\right) / \left(\frac{v_1}{r_1^2} + \frac{v_2}{r_2^2}\right)$$

where d is the volume average pore diameter, v_1 is the total volume of mercury intruded in the high pressure range, v_2 is the total volume of mercury intruded in the low pressure range, r_1 is the volume average pore radius determined from the high pressure scan, r_2 is the volume average pore radius determined from the low pressure scan, w_1 is the weight of the sample subjected to the high pressure scan, and w_2 is the weight of the sample subjected to the low pressure scan. Generally the volume average diameter of the pores is in the range of from about 0.6 to about 50 micrometers. Very often the volume average diameter of the pores is in the range of from about 1 to about 40 micrometers. From about 2 to about 30 micrometers is preferred.

In the course of determining the volume average pore diameter by the above procedure, the maximum pore radius detected is sometimes noted. This is taken from the low pressure range scan if run; otherwise it is taken from the high pressure range scan. The maximum pore diameter is twice the maximum pore radius.

The microporous sheet may be produced by processing precursor microporous material according to the method described briefly above and in more detail below.

The precursor microporous material may be produced according to the general principles and procedures of U.S. Pat. No. 3,351,495, the entire disclosure of which is incorporated herein by reference, including especially the processes for making microporous materials and the properties of the products.

Preferably filler, thermoplastic organic polymer powder, processing plasticizer and minor amounts of lubricant and antioxidant are mixed until a substantially uniform mixture is obtained. The weight ratio of filler to polymer powder employed in forming the mixture is essentially the same as that of the microporous material to be produced. The mixture, together with additional processing plasticizer, is introduced to the heated barrel of a screw extruder. Attached to the extruder is a sheeting die. A continuous sheet formed by the die is forwarded without drawing to a pair of heated calender rolls acting cooperatively to form continuous sheet of lesser thickness than the continuous sheet exiting from the die. The continuous sheet from the calender then passes to a first extraction zone where the processing plasticizer is substantially removed by extraction with

The examination is based on the following examination documents:
Description, Pages 1-351, as originally published
Claims, Nos. 1-20, *as received on 14.05.08 with letter dated* 07.05.08

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D1: Journal of Medicinal Chemistry, Vol. 38, Nr. 4 1995, pp 581-584
D2: EP-A-0 233,437
D3: WO 98/22287
D4: WO 95/08030
D5: WO 03/006429
D6: WO 02/02512
D7: Database Crosshre Beilstein - Registry Number 8790682
D8: Database Crossfire Beilstein - Registry Number 5463420
D9: WO 03/02505
D10: J. Chem. Soc., Perkin Trans. 1, 2002, pp 577-580

This communication is in response to the letter dated 07.05.08:
Article 123(2) EPC - With letter dated 07.05.08, claim 11 which was a claim dependent on the main compound claim 1, has been redrafted as an independent claim. *Claim 11 is directed to selected compounds and covers more than thousand specific compounds.* The problem with Article 123(2) EPC is actually seen in the present case with regard to claim 20 which is directed to "a pharmaceutical composition comprising a compound *according to any one of the claims* 1-11 and 19, in combination with a physiologically acceptable carrier or excipient". Basis for such composition in the context of each of the specific compounds of claim 11 is not evident in the application *as originally filed.*

Clarity - Inconsistencies are noted between claim 1 and the following claims dependent thereon.

✓ In Claim 5 the expression "-NR_{1}-$_{a}R_{1}$-$_{b}$ should include the definition "wherein R_{1}-$_{a}$ and R_{1}-$_{b}$ are -H or C_1-C_6 alkyl";

✓ In claim 7 the definition provided for R_5 is broader than the definition provided for this same variable in claim 1 whereby no substitution /optional substitution is indicated; also the definition of C_3-C_7 cycloalkyl on page 19 of the set of claims (line 4) is incomplete;

✓ the definition of the variable R_8 is again broader than the definition provided for this same variable in claim 1 whereby no optional substitution "with 1 or 2 groups" is indicated; the definition of R_{51} contains definitions not disclosed in the claim 1;
The same objections are raised for claim 8 with regard to the variables R_5, R_8 and R_{51}.

an organic liquid which is a good solvent for the processing plasticizer, a poor solvent for the organic polymer, and more volatile than the processing plasticizer. Usually, but not necessarily, both the processing plasticizer and the organic extraction liquid are substantially immiscible with water. The continuous sheet then passes to a second extraction zone where the residual organic extraction liquid is substantially removed by steam and/or water. The continuous sheet is then passed through a forced air dryer for substantial removal of residual water and retlaining residual organic extraction liquid. From the dryer the continuous sheet, which is precursor microporous material, is passed to a take-up roll.

The processing plasticizer has little solvating effect on the thermoplastic organic polymer at 60° C., only a moderate solvating effect at elevated temperatures on the order of about 100° C., and a significant solvating effect at elevated temperatures on the order of about 200° C. It is a liquid at room temperature and usually it is processing oil such as paraffinic oil, naphthenic oil, or aromatic oil. Suitable processing oils include those meeting the requirements of ASTM D 2226-82, Types 103 and 104. Preferred are those oils which have a pour point of less than 27° C. according to ASTM D 97-66 (reapproved 1978). Particularly preferred are oils having a pour point of less than 10° C. Examples of suitable oils include Shellflex®312 and Shellflex®371 oil (Shell Oil Co.) which are solvent refined and hydrotreated oils derived from naphthenic crude; ARCOprime® oil 400 (Atlantic Richfield Co.) and Kaydol® white mineral oil (Witco Corp.). ASTM D 2226-82 and ASTM D 97-66 (reapproved 1978) are, in their entireties, incorporated herein by reference. It is expected that other materials, including the phthalate ester plasticizers such as dibutyl phthalate, bis(2-ethylhexyl) phthalate, diisodecyl phthalate, dicyclohexyl phthalate, butyl benzyl phthalate, and diisooctyl phthalate will function satisfactorily as processing plasticizers.

There are many organic extraction liquids that can be used. Examples of suitable organic extraction liquids include 1,1,2-trichloroethylene, perchloroethylene, 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichlorotrifluoroethane, methylene chloride, chloroform, 1,1,2-trichlorotrifluoroethane, isopropyl alcohol, diethyl ether and acetone.

In the above described process for producing precursor microporous material, extrusion and calendering are facilitated when the substantially water-insoluble filler carries much of the processing plasticizer. The capacity of the filler particles to absorb and hold the processing plasticizer is a function of the surface area of the filler. It is therefore preferred that the filler have a high surface area. High surface area fillers are materials of very small particle size, materials having a high degree of porosity or materials exhibiting both characteristics. Usually the surface area of at least the siliceous filler is in the range of from about 20 to about 400 square meters per gram as determined by the Brunauer, Emmett, Teller (BET) method according to ASTM C 819-77 using nitrogen as the adsorbate but modified by outgassing the system and the sample for one hour at 130° C. Preferably the surface area is in the range of from about 25 to 350 square meters per gram. ASTM C 819-77 is, in its entirety, incorporated herein by reference. Preferably, but not necessarily, the surface area of any non-siliceous filler used is also in at least one of these ranges.

Inasmuch as it is desirable to essentially retain the filler in the precursor microporous material, it is preferred that the substantially water-insoluble filler be substantially insoluble in the processing plasticizer and substantially insoluble in the organic extraction liquid when precursor microporous material is produced by the above process.

The precursor microporous material comprises finely divided substantially water-insoluble filler of which at least about 30 percent by weight is siliceous, thermoplastic organic polymer which consists essentially of the UHMW polyolefin, and optional materials in essentially the same weight proportions as these discussed above in respect of the stretched sheet. The residual processing plasticizer content is usually less than 5 percent by weight of the precursor microporous sheet and this may be reduced even further by additional extractions using the same or a different organic extraction liquid.

Pores constitute from about 35 to about 80 percent by volume of the precursor microporous material. In many cases the pores constitute from about 60 to about 75 percent by volume of the precursor microporous material. The porosity of the precursor microporous material, expressed as percent by volume, is determined by the same procedure described above in respect of the stretched microporous material. In all cases, the porosity of the microporous material is, unless impregnated after stretching, greater than that of the precursor microporous material.

The volume average diameter of the pores of the precursor microporous material when made by the above-described process is usually in the range of from about 0.02 to about 0.5 micrometers. Frequently the average diameter of the pores is in the range of from about 0.04 to about 0.3 micrometers. From about 0.08 to about 0.25 micrometers is preferred.

The microporous material may be produced by stretching the precursor microporous material in at least one stretching direction above the elastic limit. Usually the stretch ratio is at least about 1.1 and often it is at least about 1.5. In many cases the stretch ratio is at least about 1.7. Preferably it is at least about 2. Frequently the stretch ratio is in the range of from about 1.2 to about 10. In many cases the stretch ratio is in the range of from about 1.5 to about 15. Often the stretch ratio is in the range of from about 1.7 to about 10. Preferably the stretch ratio is in the range of from about 2 to about 6. As used herein, and in the claims, the stretch ratio is determined by the formula:

$$S = L_2/L_1$$

where S is the stretch ratio, L_1 is the distance between two reference points located on the precursor microporous material and on a line parallel to the stretching direction, and L_2 is the distance between the same two reference points located on the stretched microporous material.

The temperatures at which stretching is accomplished may vary widely. Stretching may be accomplished at about ambient room temperature, but usually elevated temperatures are employed. The intermediate product may be heated by any of a wide variety of techniques prior to, during, and/or after stretching. Examples of these techniques include radiative heating such as that provided by electrically heated or gas fired infrared heaters, convective heating such as that provided by recirculating hot air, and conductive heating

such as that provided by contact with heated rolls. The temperatures which are measured for temperature control purposes may vary according to the apparatus used and personal preference. For example, temperature-measuring devices may be placed to ascertain the temperatures of the surfaces of infrared heaters, the interiors of infrared heaters, the air temperatures of points between the infrared heaters and the precursor microporous material, the temperatures of circulating hot air at points within the apparatus, the temperature of hot air entering or leaving the apparatus, the temperatures of the surfaces of rolls used in the stretching process, the temperature of heat transfer fluid entering or leaving such rolls, or film surface temperatures. In general, the temperature or temperatures are controlled such that the precursor microporous material is stretched about evenly so that the variations, if any, in film thickness of the stretched microporous material are within acceptable limits and so that the amount of stretched microporous material outside of these limits is acceptably low. It will be apparent that the temperatures used for control purposes may or may not be close to those of the precursor microporous material itself since they depend upon the nature of the apparatus used, the locations of the temperature-measuring devices, and the identities of the substances or objects whose temperatures are being measured.

In view of the locations of the heating devices and the line speeds usually employed during stretching, gradients of varying temperatures may or may not be present through the thickness of the precursor microporous material. Also because of such line speeds, it is impracticable to measure these temperature gradients. The presence of gradients of varying temperatures, when they occur, makes it unreasonable to refer to a singular film temperature. Accordingly, film surface temperatures, which can be measured, are best used for characterizing the thermal condition of the precursor microporous material. These are ordinarily about the same across the width of the precursor microporous material during stretching although they may be intentionally varied, as for example, to compensate for precursor microporous material having a wedge-shaped cross-section across the sheet. Film surface temperatures along the length of the sheet may be about the same or they may be different during stretching.

The film surface temperatures at which stretching is accomplished may vary widely, but in general they are such that the precursor microporous material is stretched about evenly, as explained above. In most cases, the film surface temperatures during stretching are in the range of from about 20° C. to about 220° C. Often such temperatures are in the range of from about 50° C. to about 200° C. From about 75° C. to about 180° C. is preferred.

Stretching may be accomplished in a single step or a plurality of steps as desired. For example, when the precursor microporous material is to be stretched in a single direction (uniaxial stretching), the stretching may be accomplished by a single stretching step or a sequence of stretching steps until the desired final stretch ratio is attained. Similarly, when the precursor microporous material is to be stretched in two directions (biaxial stretching), the stretching can be conducted by a single biaxial stretching step or a sequence of biaxial stretching steps until the desired final stretch ratios are attained. Biaxial stretching may also be accomplished by a sequence of one or more uniaxial stretching steps in one direction and one or more uniaxial stretching steps in another direction. Biaxial stretching steps where the precursor microporous material is stretched simultaneously in two directions and uniaxial stretching steps may be conducted in sequence in any order. Stretching in more than two directions is within contemplation. It may be seen that the various permutations of steps are quite numerous. Other steps, such as cooling, heating, sintering, annealing, reeling, shrinking, and the like, may optionally be included in the overall process as desired.

Various types of stretching apparatus are well known and may be used to accomplish stretching of the precursor microporous material. Uniaxial stretching is usually accomplished by stretching between two rollers wherein the second or downstream roller rotates at a greater peripheral speed than the first or upstream roller. Uniaxial stretching can also be accomplished on a standard tentering machine. Biaxial stretching may be accomplished by simultaneously stretching in two different directions on a tentering machine. More commonly, however, biaxial stretching is accomplished by first uniaxially stretching between two differentially rotating rollers, as described above, followed by either uniaxially stretching in a different direction using a tenter machine or by biaxially stretching using a tenter machine. The most common type of biaxial stretching is where the two stretching directions are approximately at right angles to each other. In most cases where continuous sheet is being stretched, one stretching direction is at least approximately parallel to the long axis of the sheet (machine direction) and the other stretching direction is at least approximately perpendicular to the machine direction and is in the plane of the sheet (transverse direction).

After stretching has been accomplished, the microporous material may optionally be sintered, annealed, heat set and/or otherwise heat treated. During these optional steps, the stretched microporous material is usually held under tension so that it will not markedly shrink as the elevated temperatures employed, although some relaxation amounting to a small fraction of the maximum stretch ratio is frequently permitted.

Following stretching and any heat treatments employed, tension is released from the stretched microporous material after the microporous material has been brought to a temperature at which, except for a small amount of elastic recovery encountered, at a small fraction of the stretch ratio, it is essentially dimensionally stable in the absence of tension. Elastic recovery under these conditions usually does not amount to more than about 10 percent of the stretch ratio.

The stretched microporous material may then be further processed as desired. Examples of such further processing steps include resizing, coiling, stacking, treatment to remove residual processing plasticizer or extraction solvent, and fabrication into shapes for various end uses.

Stretching is preferably accomplished after substantial removal of the processing plasticizer as described above. For purposes of this invention, however, the calendered sheet may be stretched in at least one stretching direction followed by substantial removal of the processing plasticizer by extraction and substantial removal of the residual organic extraction liquid. It will be appreciated that the stretching may be accomplished in a single step or a plurality of steps, as likewise extraction of the processing plasticizer may be accomplished

- *regarding the definition of R_8:*
    - The optional substitution of the –SO2-heteroaryl group was deleted.
- regarding the definition of R_{10}:
    - "C_3-C_7 or" was deleted;
    - the optionally substituted heterocycloalkylalkyl group was deleted.

None of the above amendments introduces subject-matter that extends beyond the scope of the application as filed.

Thus, it is respectfully submitted that the current amendments comply with Article 123(2) EPC.

Rejection under Article 123(2) EPC

Composition claim 20 was rejected under Article 123(2) EPC. The Examiner contends that the "basis for such composition in the context of each of the compounds of claim 11 is not evident in the application as originally filed".

Applicant respectfully disagrees. In fact, the compounds listed in claim 1 are all compounds falling within the scope of formulae AA, I, and X at pages 4-29 of the published PCT application. They are therefore clearly compounds that are "compounds according to the invention" as used throughout the application. In particular, it is stated at page 141, 1st paragraph, that the invention provides compositions "that contain therapeutically effective amounts of the compounds of the invention". Hence, the application as originally filed provides support for composition claim 20 referring back to claim 11.

Thus, it is respectfully submitted that claim 20 complies with the requirements of Article 123(2) EPC.

2. Clarity – Article 84 EPC

The inconsistencies between claim 1 and dependent claims 5, 7, and 8 were remedied by amending the respective dependent claims as set forth above.

Thus, it is respectfully submitted that the claims comply with the requirements of Article 84 EPC

in a single step or a plurality of steps and removal of the residual organic extraction liquid may be accomplished in a single step or a plurality of steps. The various combinations of the steps stretching, partial stretching, processing plasticizer extraction, partial plasticizer extraction, removal of organic extraction liquid, and partial removal of organic extraction liquid are very numerous, and may be accomplished in any order, provided of course, that a step of processing plasticizer extraction (partial or substantially complete) precedes the first step of residual organic extraction liquid removal (partial or substantially complete). It is expected that varying the orders and numbers of these steps will produce variations in at least some of the physical properties of the stretched microporous product.

[redacted] The coating of the coated article is an elastomeric solid at ambient temperatures. One surface of the coating may be in interlocking relationship with a surface of the microporous material, but the coating does not grossly penetrate into the interior of the microporous material. The article is therefore perceived as a multi-layered article.

As used herein and in the claims, a polymer is hydrophobic if the contact angle between a drop of water and a flat surface of the polymer upon which the drop is resting is greater than 90 degrees. Contact angle is discussed more fully in Sears and Zemansky, *University Physics*, Second Edition, Addison-Wesley Publishing Company, Inc., (1955), pages 231–235, which pages are incorporated herein by reference.

As used herein and in the claims, MVTR-B means the moisture vapor transmission rate as determined according to the procedure of ASTM E 96-80, Procedure B, with the uncoated side of the sample of the coated article facing the vapor source.

Usually the MVTR-B of the coated article of the invention is at least about 500 g/(m² day). Often the MVTR-B is at least about 700 g/(m² day). In many cases the MVTR-B is at least about 900 g/(m² day). Preferably, the MVTR-B is at least about 1000 g/(m² day).

As used herein and in the claims, MVTR-U means the moisture vapor transmission rate as determined according to the procedure of ASTM E 96-80, Procedure B, on a sample of the uncoated microporous material.

In most cases the MVTR-B of the coated article is not only high, but the moisture vapor permeability constant of the coating is also high as evidenced by only modestly lower moisture vapor transmission rates for the coated articles as compared with those of the uncoated microporous materials. Frequently the MVTR-B/MVTR-U ratio is at least about 0.5. Often the MVTR-B/MVTR-U ratio is at least about 0.6. Preferably the MVTR-B/MVTR-U ratio is at least about 0.7. [redacted] It is especially preferred that the elastomeric polysiloxane polymer be crosslinked and hence in the form of a network polymer.

There are many types of polysiloxanes and their chemistries are well known. In general, these materials are polymers in which siloxane units predominate along the polymer backbones. The polysiloxane may be thermoplastic or it may be crosslinked. Of the polysiloxanes, the polydiorganosiloxanes are preferred. In most cases the organo groups attached to silicon atoms along the backbone are lower alkyl groups such as methyl or ethyl or aromatic groups such as phenyl, tolyl, or xylyl. Many other groups, however, can be used. Examples include octadecyl, benzyl, phenylethyl, cyclopentyl, cyclohexyl, vinyl, and hydrogen. These groups are not exhaustive of the groups which can be employed. The individual organo groups in the polymer may be the same or they may be different. The preferred polydiorganosiloxane polymers are the polydimethylsiloxane polymers. These may be thermoplastic, but it is preferred that they be crosslinked.

There are many techniques for applying the coating to the microporous material. Thermoplastic polymers, for example, may be applied as a hot extruded film, as a solution, as an aqueous emulsion, or as a nonaqueous dispersion. In the case of solutions, aqueous emulsions, and nonaqueous dispersions, the solvent or continuous phase is removed after application so that the polymer will coalesce into a substantially continuous coating. Crosslinkable polymers are generally applied as a solution, aqueous emulsion, or nonaqueous dispersion, and after removal of the solvent or continuous phase, the polymer is crosslinked to form a hydrophobic network polymer. Solutions, aqueous emulsions, and nonaqueous dispersions may be applied by any technique known to the art such as, for example, drawdown using a drawdown bar or doctor blade, spraying, curtain coating, roller application, printing, and brushing. Preferred methods of application are gravure coating, reverse roll coating, and kiss over roll coating. Crosslinkable polymer which is used to form the crosslinked hydrophobic network [redacted] may be hydrophobic or hydrophilic, but usually it is [redacted]

Crosslinking may be accomplished by several mechanisms and these are themselves well known to the art. If the coating composition is substantially anhydrous, polysiloxanes containing more than two hydrolyzable terminal groups may be removed by reaction with moisture; the resulting silanol groups can then condense to form a network polymer. Polysiloxanes containing more than one alkenyl group can be crosslinked by actinic light, ionizing radiation, or free radical initiators. Catalyzed hydrosilation is another crosslinking mechanism involving alkenyl groups that can be used. Many other crosslinking mechanisms involving amino groups, epoxy groups, and the like are known.

Preferably, the coating composition is an aqueous emulsion or nonaqueous dispersion of crosslinkable polymer. The use of emulsions and nonaqueous dispersions is advantageous because the droplets of polymer in the emulsion or dispersion are larger than most of the pores in the microporous material. Consequently, when the emulsion or dispersion is applied to the microporous material, the droplets of crosslinkable polymer tend to remain mostly on the surface of the microporous material. As the water or nonaqueous dispersing liquid (i.e., the continuous phase) is removed, the droplets coalesce to form the coating which penetrates the microporous material only slightly. Crosslinking may be accomplished either after the continuous phase is removed or as the continuous phase is being removed, depending upon the kind of polymer employed.

Aqueous emulsions containing polydiorganosiloxanediol and crosslinking agent such as colloidal silica, which is preferably amorphous, are particularly useful coating compositions. After application of the coating composition to the microporous material, water is removed and the polymer droplets coalesce to form a substantially continuous coating. Upon further drying, the silanol groups condense and water is released. Some of the silanol groups of the polymer react with silanol groups of the silica. Since the surface of the silica has many silanol groups, it functions as a crosslinking agent and permits the polymer to form a network polymer. Alkali metal silicate may be used in lieu of or in addition to silica, when desired. Of the polydiorganosiloxanediols, the poly(dimethylsiloxane)diols are preferred.

Accordingly, another embodiment of the invention is a method for forming a coated article which is substantially impermeable to liquid water and permeable to moisture vapor, the method comprising: (a) applying an aqueous emulsion comprising droplets of emulsified crosslinkable polymer to one side of a sheet of microporous material having generally opposing sides, the microporous material comprising: (1) a matrix consisting essentially of essentially linear ultrahigh molecular weight polyolefin which is essentially linear ultrahigh molecular weight polyethylene having an intrinsic viscosity of at least about 18 deciliters/gram, essentially linear ultrahigh molecular weight polypropylene having an intrinsic viscosity of at least about 6 deciliters/gram, or a mixture thereof, the matrix comprising regions of stretch-induced molecularly oriented ultrahigh molecular weight polyolefin disseminated throughout the matrix, (2) finely divided particulate substantially water-insoluble filler, of which at least about 50 percent by weight is siliceous, distributed throughout the matrix, the filler constituting from about 50 percent to about 90 percent by weight of the microporous material, and (3) a network of interconnecting pores communicating throughout the microporous material, the pores in a coating-free and impregnant-free basis constituting more than 70 percent by volume of the microporous material; (b) removing water from the applied emulsion to cause the droplets to coalesce and to form a substantially continuous coating of the crosslinkable polymer on the one side of the microporous material; and (c) crosslinking the polymer of the coating to provide a substantially continuous, moisture vapor permeable coating of hydrophobic network polymer joined to the one side of the microporous material.

The microporous material may optionally be bonded on one side to at least one layer of porous material. [redacted] passageways, or channels through which matter can pass. These materials are those customarily recognized and employed for their porous properties. Examples of suitable materials include porous thermoplastic polymeric sheet or film, porous thermoset polymeric sheet or film, porous elastomeric sheet or film, and open cell foams. Other examples include fabrics, such as woven fabrics, knitted fabrics, nonwoven fabrics, and scrims. Still other examples include fiber mats, paper, synthetic paper, felt, and the like. Further examples of suitable porous materials include materials which are microporous such as the stretched microporous materials and precursor microporous materials described herein, as well as other materials which are microporous. In the porous materials which are based on fibers, the fibers may be natural, such as wood fibers, cotton fibers, wool fibers, silk fibers, and the like; or they may be any of the artificial fibers such as polyester fibers, polyamide fibers, acrylic fibers, modacrylic fibers, rayon fibers, and the like; or they may be combinations of differing kinds of fibers. The fibers may be staple and/or they may be continuous. Metal fibers, carbon fibers, and glass fibers are within contemplation.

The composite article may comprise a layer of microporous material bonded on one side to one layer or more than one layer of the porous material. The composite article may also optionally be bonded to one or more layers of porous material. For example, the microporous material may be bonded on one side to a scrim which is bonded to a nonwoven fabric. In this case, the microporous material is often also bonded through the open areas of the scrim to the nonwoven fabric. As another example, the microporous material is bonded on one side to a nonwoven fabric, the other side of which is bonded to a scrim. The combinations and permutations of possible layers are quite numerous.

Bonding may be made by conventional techniques such as, for example, fusion bonding and adhesive bonding. Examples of fusion bonding include sealing through use of heated rollers, heated bars, heated plates, heated bands, heated wires, flame bonding, radio frequency (RF) sealing, and ultrasonic sealing. Heat sealing is preferred. Solvent bonding may be used where the porous material is soluble in the applied solvent at least to the extent that the surface becomes tacky. After the microporous material has been brought into contact with the tacky surface, the solvent is removed to form a fusion bond.

Many adhesives which are well known may be used to accomplish bonding. Examples of suitable classes of adhesives include thermosetting adhesives, thermoplastic adhesive, adhesives which form the bond by solvent evaporation, adhesives which form the bond by evaporation of liquid nonsolvent, and pressure sensitive adhesives. A preferred thermosetting adhesive is a 100 percent solid polyurethane moisture curing hot melt adhesive.

Extrudable compositions may be foamed in contact with the microporous material to form a bond between the resulting porous foam and the microporous material.

Powder bonding is a technique which is particularly useful for bonding the microporous material to nonwoven webs of staple and/or continuous fibers and to woven or knitted fibers.

The microporous material may be essentially continuously bonded to the porous material, or it may be discontinuously bonded to the porous material. Examples of discontinuous bonds include bonding areas in the form of one or more spots, patches, strips, stripes, open-curved stripes, closed-curved stripes, irregular areas, and the like. When patterns of bonds are involved, they may be random, repetitive, or a combination of both.

Air disrupted extruded adhesive is another technique which is useful.

The microporous material is particularly useful for bonding to porous polyolefins such as polyethylene and polypropylene materials by heat sealing in the absence of extrinsic intervening adhesive. The bond obtained is ordinarily quite strong which is surprising inasmuch as the lamination of materials to polyolefins is usually difficult unless special adhesives are used.

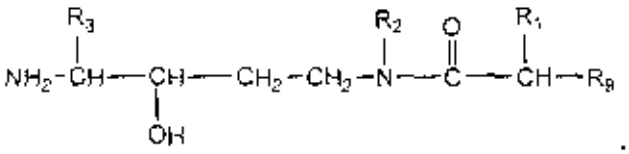
[redacted]

The coated articles of the present invention are especially useful as free hanging droplinters in garments,

3. Novelty – Article 54 EPC

The Examiner asserts that formula II at page 7 of D2 (EP 0 223 437) anticipates the presently claimed compounds. Applicant respectfully disagrees.

Formula II of D2 relates to amino carbonyl alcohol which is used as starting compound for the rennin inhibitors of the invention of D2. Formula II reads as follows:



wherein

-C(O)-CHR$_1$R$_9$ corresponds to R$_C$,

R2 corresponds to R$_N$', and

R3 corresponds to R$_1$ as named in the formula of present claim 1.

According to D2, R$_2$ (R$_C$ in the formula of claim 1) is H, lower alkyl, -(CH$_2$)$_m$-aryl, -(CH$_2$)$_m$ -cycloalkyl, and -(CH$_2$)$_n$ -heterocyclo (with m = 0, 1-5, n = 1-5); and R$_3$ (R$_C$ in the formula of claim 1) H, lower alkyl, halo substituted lower alkyl, -(CH$_2$)$_0$-aryl, -(CH$_2$)$_n$ -heterocyclo, etc (with n = 1-5).

However, D2 only discloses 5 different compounds which fall within the scope of formula II in the example section. These compounds are listed below using the definitions given for the formula in claim 1 of the subject application.

Location in Reference	R$_1$	R$_3$	R$_2$	R$_1$	R$_N$'	R$_C$
Ex. 1e; p.25	*i*-propyl	H	H	H	-C(O)CH$_3$	H
Ex. 2b; p.30	*i*-propyl	H	H	H	-C(O)CH$_2$CH$_2$Ph	H
Ex. 6b; p.36	*i*-propyl	H	H	H	-C(O)CH$_2$CH$_2$CH$_2$CH$_3$	*n*-pentyl
Ex. 7b; p.40	*i*-propyl	H	H	H	-C(O)CH$_2$CH$_2$Ph	*n*-pentyl
Ex. 8b; p.43	*i*-propyl	H	H	H	-C(O)CH$_2$CH$_2$CH$_2$CH$_3$	-CH$_2$Ph

particularly those used for outdoor or athletic wear. Alternatively, the coated article may be stitched or spot bonded to fabric of the garment. The coated articles are also useful in a variety of other applications where waterproofness and moisture vapor transmission are important, as for example in breathable diapers, adult incontinence products, sanitary napkins, medical or industrial protective garments, clean room garments, therapeutic bedding, tents, sleeping bags, and the like. In most cases it is desirable for the hydrophobic coating to face outwardly while the opposite surface of the microporous material faces inwardly, that is, toward the body.

The invention is further described in conjunction with the following examples which are to be considered illustrative rather than limiting.

EXAMPLES

Precursor Sheet Formation

The preparation of the above described materials is illustrated by the following descriptive examples. Processing oil was used as the processing plasticizer. Silica, polymer, lubricant, and antioxidant in the amounts specified in Table I were placed in a high intensity mixer and mixed at high speed for 6 minutes. The processing oil needed to formulate the batch was pumped into the mixer over a period of 12-18 minutes with high speed agitation. After completion of the processing oil addition a 6 minute high speed mix period was used to complete the distribution of the processing oil uniformly throughout the mixture.

TABLE I

Formulation		
Example No.	1	2
Ingredient		
UHMWPE (1), kg	31.91	19.09
Precipitated Silica (2), kg	59.87	59.87
Flame Retardant Concentrate (3), kg	13.95	28.33
Lubricant (4), g	600	400
Antioxidant (5), g	300	0
Antioxidant (6), g	0	100
Processing Oil (7), kg		
in Batch	86.52	93.73
in Extruder	~31.57	~30.06

(1) UHMWPE = Ultrahigh Molecular Weight Polyethylene, Hostalen 1900, Himont U.S.A., Inc.
(2) Hi-Sil ® SBG, PPG Industries, Inc.
(3) PE 1044-L, PPG Industries, Inc., Concentrate.
(4) 29 wt. % - High Density Polyethylene, UCAR 4608, Union Carbide Corp.
(5) 71.4 wt. % - Ethylene bis(tetrabromophthalimide), Saytex ® BT-93, Ethyl Corp., Bromine Chemicals Division
(6) 17.7 wt. % - Sb$_2$O$_3$, Fire Shield ® Antimony Oxide, Laurel Industries
(4) Petrac ® CZ81, Desoto Inc., Chemical Specialty Division
(5) Irganox ® B-215, Ciba-Geigy Corp.
(6) Irganox ® 1010, Ciba-Geigy Corp.
(7) Shellflex ® 371, Shell Chemical Co.

The batch was then conveyed to a ribbon blender where usually it was mixed with up to two additional batches of the same composition. Material was fed from the ribbon blender to a twin screw extruder by a variable rate screw feeder. Additional processing oil was added via a metering pump into the feed throat of the extruder. The extruder mixed and melted the formulation and extruded it through a 76.2 centimeter × 0.3175 centimeter slot die. The extruded sheet was then calendered. A description of one type of calender that may be used may be found in U.S. Pat. No. 4,734,229, the entire disclosure of which is incorporated herein by reference, including the structures of the devices and their modes of operation. Other calenders of different design may alternatively be used; such calenders and their modes of operation are well known in the art. The hot, calendered sheet was then passed around a chill roll to cool the sheet. The rough edges of the cooled calendered sheet were trimmed by rotary knives to the desired width.

The oil filled sheet was conveyed to the extractor unit where it was contacted by both liquid and vaporized 1,1,2-trichloroethylene (TCE). The sheet was transported over a series of rollers in a serpentine fashion to provide multiple, sequential vapor/liquid/vapor contacts. The extraction liquid in the sump was maintained at a temperature of 65°-88° C. Overflow from the sump of the TCE extractor was returned to a still which recovered the TCE and the processing oil for reuse in the process. The bulk of the TCE was extracted from the sheet by steam as the sheet was passed through a second extractor unit. A description of these types of extractors may be found in U.S. Pat. No. 4,648,417, the entire disclosure of which is incorporated herein by reference, including especially the structures of the devices and their modes of operation. The sheet was dried by radiant heat and convective air flow. The dried sheet was wound on cores to provide roll stock for further processing.

The two microporous sheets, as well as the hereinafter described biaxially stretched microporous sheets produced therefrom, were tested for various physical properties. Table II identifies the properties with the methods used for their determination. The various ASTM test methods and Method 502 C, referenced in Table II, are, in their entireties, incorporated herein by reference. The results of physical testing of the two precursor microporous sheets are shown in Table III.

Property values indicated by MD (machine direction) were obtained on samples whose major axis was oriented along the length of the sheet. TD (transverse direction; cross machine direction) properties were obtained from samples whose major axis was oriented across the sheet.

TABLE II

Physical Test Methods	
Property	Test Method
Processing Oil Content	Method 502 C in "Standard Methods for the Examination of Water and Wastewater", 14th Ed., APHA-AWWA-WPCF (1975).
Gurley Air Flow	ASTM D 726-58 (reapproved 1971), Method A
Mullens Hydrostatic Resistance	ASTM D 751-79, Sec. 30-34, Method A
MVTR (Moisture Vapor Transmission Rate)	ASTM E 96-80.
Strip Tensile Strength and Elongation	ASTM D 882-80

TABLE II-continued

Physical Test Methods	
Property	Test Method
Breaking Factor and Elongation	ASTM D 882-83.
Breaking Load and Apparent Elongation	ASTM D 1682-64 (Reapproved 1975), Grab Test.

TABLE III

Physical Properties of Precursor Microporous Sheets		
Example No.	1	2
Thickness, mm	0.252	0.240
Strip Tensile Strength, kN/m		
MD		3.15
TD		1.05
Elongation at break, %		
MD		354
TD		396
Processing Oil Content, wt. %	1.5	

TABLE IV

Transverse Direction Stretching				
Zone	Cumulative Distance from Beginning of Oven, meters	Approximate Transverse Stretch Ratio		Ratio
	0	1	1	1
Preheat	2.794	1.12	1.12	1.19
Stretch I	4.318	1.49	2.5	1.65
Stretch II	6.350	3	3.5	3.33
Stretch III	9.379	3.15	3	3.43
Sinter I	11.430	3.17	3	3.42
Sinter II	13.716	3.12	3	3.42

Biaxial Stretching of Precursor Microporous Sheet

Portions of the microporous materials produced in Examples 1 and 2 were unwound from cores and biaxially stretched by first uniaxially stretching in the machine direction using a single stage roll-to-roll machine direction stretching (MDS) unit and then essentially uniaxially stretching in the transverse direction using a moving clip tenter frame as a transverse direction stretching (TDS) unit. One or more preheat rolls were employed with the MDS unit to heat the sheet prior to stretching. In the TDS unit, the sheet was heated by banks of infrared radiant heaters. The Preheat and Stretch I Zones of the TDS unit each contained both upper and lower banks of such heaters. The upper banks were located about 10.16 centimeters above the precursor microporous material while the lower banks were located about 15.24 centimeters below the precursor microporous material. Electrical power to the heaters of each lower bank was controlled by an on-off controller in response to the difference between a set point and the signal provided by a thermocouple mounted in one heater of the bank. Autotransformers were used to adjust electrical power to the heaters of the upper banks. The Stretch II, Stretch III, Sinter I, and Sinter II Zones each contained upper banks of infrared radiant heaters located about 10.16 centimeters above the precursor microporous material. There were no lower banks in these zones. Electrical power to the heaters of each upper bank was controlled as described in respect of the heaters of each lower bank in the Preheat and Stretch I Zones. For a description of a typical TDS unit, see FIG. 2 and column 2, lines 43-69, of U.S. Pat. No. 2,823,421, the entire disclosure of which is incorporated herein by reference.

The MDS stretch ratio was varied by controlling the relative peripheral speeds of the feed rolls and the take-off rolls of the MDS unit. The chain track positions in the tenter frame were set to achieve the desired stretch ratio and then to essentially maintain that stretch ratio during sintering. For Examples 3, 4, and 5, the settings of the chain track positions in the tenter frame were as described in the first, second, and third columns, respectively, under the heading "Approximate Transverse Stretch Ratio" in Table IV, were employed.

The precursor sheet stock of Examples 1 and 2 were fed over the preheat roll of the MDS unit which was heated to the temperature indicated in Tables V and VI. The sheet was then stretched to the indicated stretch ratio by maintaining the relative peripheral speeds of the second and first stretch rolls at essentially the same ratio as the stretch ratio. The line speed given in Tables V and VI is the output speed of the MDS unit and the machine direction speed of the TDS unit. The linear feed rate from the roll stock of precursor microporous material to the MDS unit was set at a value given by the line speed divided by the MDS stretch ratio. Thus, with a line speed of 24 m/min and a MDS stretch ratio of 2, the linear feed rate from the roll stock of the MDS unit would be 12 m/min. The properties of several representative examples of biaxially stretched sheets are given in Tables V and VI.

TABLE V

Properties of Biaxially Stretched Microporous Sheets Produced from Precursor Sheet of Example 1	
Example No.	3
Thickness, mm	0.134
Stretch Ratio	
MD	2
TD	3.32
Line Speed, m/min	24.38
MDS Preheat Temp., °C.	96
MDS Stretch Temp., °C.	179
TDS Average Zone Set Point Temps., °C.	
Preheat (lower banks)	219
Stretch I (lower banks)	232
Stretch II	192
Stretch III	192
Sinter I	195
Sinter II	232
Weight, g/m²	31.23
Breaking Factor, kN/m	
MD	1.187
TD	0.342
Elongation at Break, %	
MD	47
TD	51
Gurley Air Flow, sec/100 cc	360
Mullens Hydrostatic, kPa	511
MVTR, g/(m² day)	
Procedure B (Upright Cup)	[illegible]

Novelty - Lack of novelty within the meaning of Article 54(1) and (2) EPC is maintained at the light of document D2 (see page 7, compound of general formula II).
If the novelty objection can be dealt with then the following should be noted:
Inventive step - The present application refers to compounds according to the general formula (AA) described starting from page 5 to page 29 (see claim 1). The application is also directed to more than thousand compounds specifically claimed in independent claim 11. The use of a compound or salt according to claim 1 for the manufacture of a medicament is claimed. A pharmaceutical composition comprising a compound according to one of claims 1-11 or 19 is also claimed.

The problem to be solved is seen in the provision of novel compound, in particular novel compounds useful in the treatment of Alzheimer's disease and related diseases (see also page 4, lines 9-19).
Documents D5, D6 and D9 describe similar 1,3-diamino-2-hydroxy compounds which are useful in treating Alzheimer's disease. The other documents cited in the Search Report , e.g. D1-D4, indicate the use in the medicinal field.
The difference between the compounds described in the art and the present compounds is the presence, in the presently claimed compounds, of a primary amino group.

The problem with regard to the inventive step for the compounds claimed is seen in the fact that not one specific biological value is provided in the application that would support that the compounds claimed in claim 1 and, as well, each of the specifically indicated compounds of claim 11, actually solve the technical problem indicated by the Applicant in the description on page 4.
In view of the extraordinary amount of subject-matter comprised by the large number of variables defined also to comprise further variables, the question is raised on the significance and the support of the claims.
The technical contribution provided by the compounds of the application needs to be demonstrated at the light of evidence which clearly satisfies the requirement that the alleged properties are exhibited by substantially all the compounds covered by the broad claim 1 and by each of the compounds specifically indicated in claim 11.
This technical contribution of the compounds claimed has to be described in precise terms in order also to allow a proper determination of whether the technical problem has indeed been solved over the entire scope of protection.
Filed submissions cannot be included in the specification but will be handled as technical

TABLE V-continued

Properties of Biaxially Stretched Microporous Sheets Produced from Precursor Sheet of Example 1	
Example No.	3
Procedure BW (Inverted Cup)	1856

TABLE VI

Properties of Biaxially Stretched Microporous Sheets Produced from Precursor Sheet of Example 1		
Example No.	4	5
Thickness, mm	0.117	0.148
Stretch Ratio		
MD	3	2.5
TD	3	3.42
Line Speed, m/min	24.4	24.4
MDO Preheat Temp., °C.	41 to 49	51
MDO Stretch Temp., °C.	121	121
TDO Average Zonal Set Point Temps., °C.		
Preheat (lower banks)	188	191
Stretch I (lower banks)	188	177
Stretch II	173	143
Stretch III	155	164
Sinter I	154	144
Sinter II	221	220
Weight, g/m²	20.09	25.2
Breaking Factor, kN/m		
MD	0.924	0.840
TD	0.347	0.411
Elongation at Break, %		
MD	33	64
TD	36	42
Gurley Air Flow, sec/100 cc	23	25.4
Mullen Hydrostatic, kPa	414	457

EXAMPLE 6

The microporous material of Example 3 and polyester non-woven fabric were laminated together using dry powder bonding equipment commonly employed for producing laminated non-woven fabrics from staple fibers. The equipment comprised a shaker box dry powder applicator, an infrared oven 12.2 meters long, a nip comprising an upper heated roll and the final support roll for the conveyor belt of the oven, and a winder. In addition, provision was made for feeding microporous material under the upper nip roll for lamination to the web exiting from the oven.

A preformed polyester non-woven, powder bonded web weighing 27.80 grams/square meter and consisting of 3.81 centimeter long, 2.0 denier polyester staple fiber (Eastman Kodel ® 425 fiber) bonded with elastomeric polyester powdered adhesive (Eastman Eastbond ® FA-252, medium grind adhesive) was unwound onto a conveyor belt which passed under the shaker box which dispensed additional elastomeric polyester powdered adhesive. The preformed web and the additional adhesive were then carried through the infrared oven which raised the web surface temperature to about 165° C. to about 177° C. A roll of microporous material produced under the conditions and during the same production run as that of Example 3 was unrolled, brought into contact with the upper nip roll located at the exit of the oven, fed under the upper nip roll, and there brought into contact with the web exiting the oven. The upper nip roll was heated to about 99° C., while the temperature of the conveyor belt exiting the infrared oven ranged from about 121° C. to about 132° C. During the preheating of the microporous material by contact with the upper nip roll, some shrinkage of the microporous material in the transverse direction was noted. The nip consolidated the microporous material, the heated web, and the heated adhesive. The laminated web from the nip was wound on cores by the winder. As a finishing operation, the laminated web was unwound, trimmed to a final width of 1.22 meters and rewound on cores. The total weight of adhesive present was 20.68 grams/square meter. The properties of the laminate are given in Table VII.

EXAMPLE 7

The flame retardant microporous material of Example 4 and flame retardant polyester non-woven fabric were laminated together using dry powder bonding equipment commonly employed for producing laminated non-woven fabrics from staple fibers. The equipment comprised an unbaler, a carding machine, a shaker box dry powder applicator, an infrared oven 12.2 meters long, a nip comprising an upper heated roll and the final support roll for the conveyor belt of the oven, and a winder. In addition, provision was made for feeding microporous material under the upper nip roll for lamination to the web exiting from the oven.

Hoechst-Celanese Trevira ® 271 flame retardant polyester staple fiber (3.5 denier; 4.8 centimeters in length) was fed to the unbaler. The unbailed fiber was forwarded to the carding machine which dispensed a staple fiber web about 2 meters wide and weighing about 33.9 grams/square meter onto a conveyor belt operating at a line speed of about 45.7 meters/minute. The conveyor belt carried the web under the shaker box which dispensed Bostik FR 5178 flame retardant, hot melt polyester powder adhesive (Emhart Corp., Bostik Division) onto the web at a net rate of from 20.3 to 21.5 grams/square meter. A second conveyor belt then carried the web through the infrared oven where the web was heated so as to have a surface temperature of from about 166° C. to about 177° C. A roll of microporous material produced under the same conditions and during the same production run as that of Example 4 and having a width of 1.52 meters was unrolled, brought into contact with the upper nip roll located at the exit of the infrared oven, fed under the upper nip roll, and there brought into contact with the web exiting the oven. The upper nip roll was heated to about 99° C. while the temperature of the conveyor belt upon exiting from the oven ranged from about 121° C. to about 132° C. During preheating of the microporous material by contact with the upper nip roll, some shrinkage of the microporous material in the transverse direction was noted. The nip consolidated the microporous material, the heated web, and the heated adhesive. The laminated web from the nip was wound on cores by the winder. As a finishing operation, the laminated web was unwound, trimmed to final widths of from 1.14 to 1.39 meters, and rewound on cores. The properties of the laminate are given in Table VII.

EXAMPLE 8

The process and equipment of Example 7 were utilized to produce a laminate with a non-woven staple fiber weight of about 50.9 grams/square meter. All other settings of Example 7 were retained. The properties of this laminate are given in Table VII.

EXAMPLE 9

The apparatus of Example 7, to which was added additional conveyor belts, a second shaker box, and a second infrared oven, was utilized to produce a three-layer laminate in which the order of the layers was microporous material-scrim-nonwoven web.

A nonwoven web of Trevira ® 271 flame retardant polyester fiber was produced as described in Example 7. At the exit of the infrared oven of Example 7 a 4×4 (4 counts per inch, viz., 1.575 counts per centimeter, in both the machine and transverse directions) polyester scrim (Bayex, Inc.) rather than the microporous material was unrolled, brought into contact with the upper nip roll located at the exit of the infrared oven, fed under the upper nip roll, and there brought into contact with the web exiting the oven. The nip consolidated the scrim, the heated web, and the heated adhesive. The scrim-nonwoven web laminate was then passed under a second shaker box dry powder applicator which dispensed additional adhesive onto the laminate. The laminate was carried through a second infrared oven operating under conditions similar to the first infrared oven. A roll of the microporous material produced during the same production run as the microporous material of Example 5 was unrolled, brought into contact with the upper nip roll located at the exit of the second infrared oven, fed under such upper nip roll, and there brought into contact with the two-layer laminate exiting the second oven. The nip consolidated the microporous material, the heated two-layer laminate, and the heated adhesive. The width of the three-layer laminate exiting the nip was 1.71 meters. The three-layer laminate was further processed as described in Example 7 to give a trimmed width of 1.52 meters.

The weight of the polyester staple fibers and the 4×4 scrim in the three-layer laminate was 27.5 grams/square meter. The total weight of adhesive present was 31.5 grams/square meter. The properties of the three-layer laminate are given in Table VII.

TABLE VII

Properties of Laminate Produced from Preformed Non-Woven Staple Fabric and Biaxially Stretched Microporous Sheet				
Example No.	6	7	8	9
Thickness, mm	0.160	0.191	0.216	0.221
Weight, g/m²	47.81	74.54	74.25	83.44
Breaking Load, kg				
MD	31.93	27.31	22.14	22.35
TD	14.47	16.19	6.62	10.60
Apparent Elongation, %				
MD	32.6	40.6	39.4	33.1
TD	48.4	71.1	40.1	27.9
Gurley Air Flow, sec/100 cc		36.6	36.1	35.1
Mullen Hydrostatic, kPa				
Microporous Material next to liquid		895.1	855.4	206.1
Non-Woven Fabric next to liquid		199.9	199.0	151.6
MVTR-B, g/(m² day)				
As prepared	1339			
After One Washing/Drying	1496			

EXAMPLES 10-16

Samples of the microporous material/non-woven web laminate of Example 6 were cut into rectangular pieces measuring 24.77 centimeters by 32.38 centimeters. A sample was affixed to an oversized absorptive sheet with a strip of double sided tape along the top and

bottom narrow edges. The non-woven fabric side of the sample faced the absorptive sheet. The absorptive sheet was typically about 38 centimeters by about 64 centimeters in size and was a blotter type of material or a sheet of precursor microporous material of about 0.40 to about 0.50 millimeter thickness. The entire assembly was placed on a level surface for coating.

Coating compositions of elastomeric silicone aqueous emulsion were prepared by diluting Dow-Corning ® 85 Additive, formerly known as X3-0525, with deionized water to various degrees as indicated in Table VIII. Approximately 20 grams of the desired coating composition were poured along one of the tape-anchored edges of the laminate and rapidly spread over the entire microporous material surface of the laminate sample by drawing a 15 millimeter diameter glass rod across the sample surface pushing the coating composition ahead of the rod. The coated samples were allowed to dry and cure in ambient air for a minimum of 24 hours. Multiple coated samples were prepared from each coating composition in order to provide sufficient materials for testing. The coating coverage obtained for each coated sample is given in Table VIII.

TABLE VIII

Elastomeric Silicone Emulsion Coating Compositions and Coating Coverage of Microporous/Non-Woven Laminates							
Example No.	10	11	12	13	14	15	16
Elastomeric Silicone Emulsion (1), wt %	100	90	80	70	60	50	40
Deionized Water, wt %	0	10	20	30	40	50	60
Dried Coating Weight, g/m²							
Sample A	44.63	16.46	14.59	11.85	7.15	6.91	4.87
Sample B	61.72	15.83	14.84	13.97	8.60	7.49	4.31
Sample C	64.83						

(1) Dow-Corning ® 85 Additive, Dow-Corning Corp.
This material is an elastomeric silicone aqueous emulsion containing [illegible] weight percent amorphous silica, 2 weight percent 2-amino-2-methyl-1-propanol, and 0.2 weight percent diethylamine. The silicone is believed to be polydimethylsiloxane[illegible].

Optical microscopic evaluation of the cross-section of a coated laminate at a magnification of 512X showed no evidence of significant penetration of the cured elastomeric silicone coating into the surface of the microporous material of the laminate.

Coated laminate samples were tested for resistance to liquid water penetration and for moisture vapor transmission rate (MVTR). Samples were tested as prepared and after machine washing and drying as described in AATCC Test Method 135-1978 using a normal wash cycle (14 minutes) with cold water and dried using the delicate (low heat) setting on the drier. The ballast load consisted of about 1.8 kilograms of cotton bath towels. Each wash load was washed with 100 grams of Tide ® detergent (Proctor and Gamble). Some samples were washed multiple times. AATCC Test Method 135-1978 is, in its entirety, incorporated herein by reference.

Mullen Hydrostatic testing was done using a restraining cloth with essentially zero hydrostatic resistance when tested separately. Coated laminate samples were tested with the coated side up, that is, away from the source of hydrostatic pressure, and with the coated side down, that is, with the coated side next to the source of hydrostatic pressure.

The MVTR testing was conducted with the coated side away from the source of moisture vapor. Testing

information submitted after the filing of the application.

An oral hearing under Article 116 EPC, as requested by the Applicant with the letter dated 07.05.08, will be appointed if no agreement will be found on the set of claims on file.
Care should be taken during revision not to add subject-matter which extends beyond the *content of the application as originally filed*, Article 123(2) EPC.
Failure to overcome the above cited objections could result in the refusal of the application under Article 97(1) EPC.

was conducted using Procedure B (upright) and using Procedure BW (inverted).

The Mullen Hydrostatic and MVTR values obtained and the washing/drying history are summarized in Table IX.

TABLE IX

Mullen Hydrostatic and MVTR Properties of Coated Laminates of Examples 10-16

Example No. Sample	Number of Washings	Mullen Hydrostatic, kPa Coating Up	Mullen Hydrostatic, kPa Coating Down	MVTR, g/(m² day) Upright	MVTR, g/(m² day) Inverted
10A	0	910	3158		
10B	1	1096	3193		
10C	0			595	
10D	1			727	
11A	5	261	1426		
11B	5			845	
12A	5	203	1356		
12B	5			883	
13A	5	154	1351		
13B	5			1095	10094
14A	5	374	1310		
14B	5			1148	11299
15A	5	296	1441		
15B	5			1166	10814
16A	5	223	1048		
16B	5			1565	12647

Preferred embodiments would be to coat the laminates of Examples 7, 8, and 9 with the coating compositions of Examples 10-16 in the manner of Examples 10-16.

The invention has been described with reference to stretched microporous material having a substantially continuous, moisture vapor permeable coating of hydrophobic polymer joined to one side of the stretched microporous material, and this is indeed the preferred embodiment of the invention. Nevertheless, it is also within contemplation to coat the precursor microporous material in the same way as has been described for coating the stretched microporous material. Therefore, another embodiment of the invention is a coated article which is substantially impermeable to liquid water and permeable to moisture vapor, the article comprising: (a) a sheet of microporous material having generally opposing sides, the microporous material comprising: (1) a matrix consisting essentially of essentially linear ultrahigh molecular weight polyolefin which is essentially linear ultrahigh molecular weight polyethylene having an intrinsic viscosity of at least about 18 deciliters/gram, essentially linear ultrahigh molecular weight polypropylene having an intrinsic viscosity of at least about 6 deciliters/gram, or a mixture thereof, (2) finely divided particulate substantially water-insoluble filler, of which at least about 50 percent by weight is siliceous, distributed throughout the matrix, the filler constituting from about 50 percent to about 90 percent by weight of the microporous material, and (3) a network of interconnecting pores communicating throughout the microporous material, the pores on a coating-free and impregnant-free basis constituting from about 35 percent to about 80 percent by volume of the microporous material; and (b) a substantially continuous, moisture vapor permeable coating of hydrophobic polymer joined to one side of the microporous material.

Although the present invention has been described with reference to specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the invention except insofar as they are included in the accompanying claims.

We claim:

1. A coated article which is substantially impermeable to liquid water and permeable to moisture vapor, said article comprising:

(a) a sheet of microporous material having generally opposing sides, said microporous material comprising:

(1) a matrix consisting essentially of essentially linear ultrahigh molecular weight polyolefin which is essentially linear ultrahigh molecular weight polyethylene having an intrinsic viscosity of at least about 18 deciliters/gram, essentially linear ultrahigh molecular weight polypropylene having an intrinsic viscosity of at least about 6 deciliters/gram, or a mixture thereof, said matrix comprising regions of stretch-induced molecularly oriented ultrahigh molecular weight polyolefin distributed throughout said matrix,

(2) finely divided particulate substantially water-insoluble filler, of which at least about 50 percent by weight is siliceous, distributed throughout said matrix, said filler constituting from about 50 percent to about 90 percent by weight of said microporous material, and

(3) a network of interconnecting pores communicating throughout said microporous material, said pores on a coating-free and impregnant-free basis constituting more than 70 percent by volume of said microporous material; and

(b) a substantially continuous, moisture vapor permeable coating of hydrophobic polymer joined to one side of said microporous material, said coating being an elastomeric solid at ambient temperatures.

2. The coated article of claim 1 wherein said essentially linear ultrahigh molecular weight polyolefin is essentially linear ultrahigh molecular weight polyethylene having an intrinsic viscosity of at least about 18 deciliters/gram.

3. The coated article of claim 2 wherein said ultrahigh molecular weight polyethylene has an intrinsic viscosity in the range of from about 18 to about 39 deciliters/gram.

4. The coated article of claim 2 wherein at least about 65 percent by weight of said filler is siliceous.

5. The coated article of claim 2 wherein said siliceous filler is precipitated silica.

6. The coated article of claim 2 wherein the volume average diameter of said pores as determined by mercury porosimetry is in the range of from about 0.6 to about 50 micrometers.

7. The coated article of claim 2 wherein said pores constitute from more than 70 percent to about 95 percent by volume of said microporous material.

8. The coated article of claim 2 wherein said microporous material has a thickness in the range of from about 0.03 to about 0.4 millimeter.

9. The coated article of claim 2 wherein other thermoplastic organic polymer is present in said matrix and wherein at least about 50 percent by weight of said matrix is said essentially linear ultrahigh molecular weight polyethylene.

10. The coated article of claim 9 wherein said other thermoplastic organic polymer is high density polyethylene.

11. The coated article of claim 2 wherein the MVTR-B of said coated article is at least about 300 g/(m² day).

12. The coated article of claim 2 wherein the MVTR-B of said coated article is at least about 500 g/(m² day).

13. The coated article of claim 2 wherein the MVTR-B/MVTR-U ratio of said coated article is at least about 0.5.

14. The coated article of claim 2 wherein the MVTR-B/MVTR-U ratio of said coated article is at least about 0.7.

15. The coated article of claim 2 wherein said hydrophobic polymer of said coating is an elastomeric polysiloxane.

16. The coated article of claim 15 wherein said elastomeric polysiloxane is in the form of a network polymer.

17. The coated article of claim 16 wherein said elastomeric polysiloxane is a polydiorganosiloxane.

18. The coated article of claim 16 wherein said elastomeric polysiloxane is polydimethylsiloxane.

19. The coated article of claim 2 wherein the other side of said microporous material is bonded to at least one layer of porous material.

20. The coated article of claim 19 wherein said layer of porous material is a nonwoven fabric.

21. The coated article of claim 19 wherein said layer of porous material is a knitted fabric.

22. The coated article of claim 19 wherein said other side of said microporous material is bonded to said layer of porous material by fused hot melt powder adhesive.

23. The coated article of claim 19 wherein said other side of said microporous material is bonded to said layer of porous material by thermoset, moisture cured, polyurethane hot melt adhesive.

24. The coated article of claim 19 wherein:

(a) said siliceous filler is precipitated silica,

(b) said pores on a coating-free and impregnant-free basis constitute more than about 80 percent by volume of said microporous material; and

(c) said hydrophobic polymer of said coating is crosslinked elastomeric poly(dimethylsiloxane).

25. The coated article of claim 24 wherein the MVTR-B of said coated article is at least about 700 g/(m² day).

26. The coated article of claim 25 wherein the MVTR-B/MVTR-U ratio of said coated article is at least about 0.6.

27. A method for forming a coated article which is substantially impermeable to liquid water and permeable to moisture vapor, said method comprising:

(a) applying an aqueous emulsion comprising droplets of emulsified crosslinkable polymer to one side of a sheet of microporous material having generally opposing sides, said microporous material comprising:

(1) a matrix consisting essentially of essentially linear ultrahigh molecular weight polyolefin which is essentially linear ultrahigh molecular weight polyethylene having an intrinsic viscosity of at least about 18 deciliters/gram, essentially linear ultrahigh molecular weight polypropylene having an intrinsic viscosity of at least about 6 deciliters/gram, or a mixture thereof, said matrix comprising regions of stretch-induced molecularly oriented ultrahigh molecular weight polyolefin distributed throughout said matrix,

(2) finely divided particulate substantially water-insoluble filler, of which at least about 50 percent by weight is siliceous, distributed throughout said matrix, said filler constituting from about 50 percent to about 90 percent by weight of said microporous material, and

(3) a network of interconnecting pores communicating throughout said microporous material, said pores on a coating-free and impregnant-free basis constituting more than 70 percent by volume of said microporous material; and

(b) removing water from said applied emulsion to cause said droplets to coalesce and to form a substantially continuous coating of said crosslinkable polymer on said one side of said microporous material, and

(c) crosslinking said polymer of said coating to provide a substantially continuous, moisture vapor permeable coating of hydrophobic network polymer joined to said one side of said microporous material, said substantially continuous, moisture vapor permeable coating being an elastomeric solid at ambient temperatures.

28. The method of claim 27 wherein said emulsified crosslinkable polymer is poly(dimethylsiloxane)diol and wherein said aqueous emulsion also comprises crosslinking agent.

29. The method of claim 28 wherein said crosslinking agent is amorphous silica.

30. A coated article which is substantially impermeable to liquid water and permeable to moisture vapor, said article comprising:

(a) a sheet of microporous material having generally opposing sides, said microporous material comprising:

(1) a matrix consisting essentially of essentially linear ultrahigh molecular weight polyolefin which is essentially linear ultrahigh molecular weight polyethylene having an intrinsic viscosity of at least about 18 deciliters/gram, essentially linear ultrahigh molecular weight polypropylene having an intrinsic viscosity of at least about 6 deciliters/gram, or a mixture thereof,

(2) finely divided particulate substantially water-insoluble filler, of which at least about 50 percent by weight is siliceous, distributed throughout said matrix, said filler constituting from about 50 percent to about 90 percent by weight of said microporous material, and

(3) a network of interconnecting pores communicating throughout said microporous material,

The examination is based on the following examination documents:
Description, Pages 1-351, as originally published
Claims, Nos. 1-20, as received on 18.12.08 with letter dated 18.12.08

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D1: Journal of Medicinal Chemistry, Vol. 38, Nr. 4 1995, pp 581-584
D2: EP-A-0.233.437
D3: WO 98/22287
D4: WO 95/06030
D5: WO 03/006423
D6: WO 02/02512
D7: Database Crossfire Beilstein - Registry Number 6790682
D8: Database Crossfire Beilstein - Registry Number 5463420
D9: WO 03/02505
D10: J. Chem. Soc., Perkin Trans. 1, 2002, pp 577-580

Oral proceedings are being convened at the Applicant's request (Art.116.1 EPC).
Discussion at the oral proceedings will be based on the following points:

Novelty - Lack of novelty within the meaning of Article 54(1) and (2) EPC is maintained at the light of document D2 (see page 7, compound of general formula II).
The fact that none of the compounds of D2 indicated by the Applicant in the letter of 18.12.08 actually falls within the scope of present claim 1 is not contradictory to the fact that the scope of the compounds according to the general formula II falls within the scope of present claim 1 and as such anticipates the present subject-matter claimed.

Inventive step - The problem to be solved is seen in the provision of novel "pharmaceutical agents" useful in the treatment of Alzheimer's disease and related diseases and thus "capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place" (see page 4, lines 9-19).
Documents D6 and D9 describe similar 1,3-diamino-2-hydroxy compounds which are useful in treating Alzheimer's disease. Other documents cited in the Search Report , e.g. D1-D4, indicate the use in the medicinal field.
The difference between the compounds described in the art and the present compounds is the presence, in the presently claimed compounds, of a primary amino group.
In the letter of 18.12.08 the Applicant has pointed out that the compounds of the claims are intended to be prodrugs of certain hydroxyethylamine (HEA) compounds. In fact, "these HEA compounds are generated by acyl group migration as explained at page 330 of the application". "Because they are prodrugs, by definition they do not need to be biologically active, but they must be capable of converting to biologically active compounds under physiological conditions". In this context it is indicated that "most of the compounds specifically listed as examples in the present application are prodrugs

of the compounds disclosed in D6". The compounds of D6 are indicated by the Applicant to be "biologically active" and are said to "generally have IC_{50} values of less than 50µM in both an enzyme inhibition assay and a cell-free inhibition assay (see page 341, lines 19-23 and page 342, lines 19-21). Therefore, in the view of the Applicant "one of art would recognize that the claimed prodrugs will convert to biologically active compounds under physiological conditions".

In the view of the Examining Division, based on the fact that the compounds specifically listed as examples in the present application are prodrugs of the compounds in fact disclosed in D6 and based also on the fact that the acyl group migration is a known reaction and described for similar compound in D10 (see D10, Scheme 2, 15->16) an inventive step connected with an unexpected and surprising effect remains not evident. Moreover it is not demonstrated that, within the broad scope covered by the claims, that exposing a compound according to claim 1 to an aqueous media, the claimed prodrug compounds convert to a compound of formula Y which is an active compound and can be used in the treatment of Alzheimer's disease, and it has not been demonstrated that, within the broad scope covered by the claims, the prodrug compounds are *per se* active compounds and can be used in the treatment of Alzheimer's disease (see page 341, lines 26-29). Thus the technical effect needs to be demonstrated and rendered credible within the whole of the claimed area.

With regard to the claims 12-16 directed to a method of converting the prodrug compound to an "active" drug by exposing the prodrug "to an aqueous media", the principles of this reaction are known and in fact it is within the definition of prodrug, as precursor or forerunner of an active compound, that this prodrug must undergo a chemical conversion by metabolic processes, that is in aqueous media, before becoming an active pharmacological agent. An inventive step for the method described in claims 12 to 16 is not evident.

Defects - Claim 11 includes all the features of claim 1. Hence, claim 11 should be reformulated as a claim dependent on claim 1 (cf. Rule 43(4) EPC and Guidelines C-III, 3.4). In this context the attention of the Applicant is also drawn to the fact that under Article 84 in combination with Rule 43(2) EPC, an application may contain more than one independent claim in a particular category only if the subject-matter claimed falls within one or more of the exceptional situations set out in paragraph (a), (b) or (c) of Rule 43(2) EPC which is not the case in the present application.

Failure to overcome the above cited objections could result in the refusal of the application under Article 97(1) EPC.

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United States Patent [19]

Michaels

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[54] **MEMBRANE LAMINATES AND METHODS FOR THEIR PREPARATION**

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[58] **Field of Search** 427/244, 245, 427/246, 296, 140, 352, 378, 379; 428/421, 507, 508, 509, 510, 704; 210/460, 500.21, 500.23, 500.24, 500.27, 500.41, 500.42, 506; 202/267.1

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[57] **ABSTRACT**

This invention presents novel membrane laminate structures useful for osmotic distillation, and methods for their preparation.

55 Claims, No Drawings

(c) rapidly evaporating volatile components from the coating;

(d) optionally washing the membrane; and

(e) drying the polymer to remove residual moisture to produce the laminate.

In some preferred embodiments, the methyl, hydroxypropyl- or hydroxypropylmethyl celluloses have a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane.

In some particularly preferred embodiments the prepolymer is a hydroxypropylmethyl cellulose.

Also provided in accordance with the present invention are methods comprising the steps of:

(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer;

(b) feeding the coating solution to the feed-side flow channel of a sheet- or hollow-fiber-microporous hydrophobic membrane module at sufficient quantity and at a sufficient rate to form a polymer coating on the membrane surface of the desired thickness, while simultaneously passing an inert gas to the strip-side of the module to evaporate volatile components;

(c) evaporating residual volatile components from the coated membrane by flowing a gas through both the feed and strip channels of the coated module;

(d) optionally crosslinking the prepolymer by contacting the coated surface of the membrane with a solution of a crosslinking agent capable of crosslinking the polymeric coating and rendering it water-insoluble; and

(e) drying the coating to remove residual moisture.

Some preferred embodiments of the methods of the invention further comprise repeating steps (b)–(d).

In some preferred embodiments, the prepolymer has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

In further preferred embodiments, the prepolymer in the first step (b) has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

In some preferred embodiments, the prepolymer is a cellulose ether or ester, polyvinyl alcohol, polyvinyl alcohol copolymer with vinyl acetate, N-alkyl polyacrylamide, N-alkyl polyacrylamide copolymer with acrylamide, an isocyanate capped, polyethylene glycol-based polyurethane, an esterified or etherated polysaccharide, a hydroxyalkylated polyacrylate, a polymethacrylate, or a hydroxylated polymethacrylate.

In further preferred embodiments, the prepolymer is a linear isocyanate capped polyethylene glycol based polyurethane, cellulose, methylcellulose, hydroxypropylmethyl cellulose, or copolymers of vinyl acetate and vinyl alcohol.

In some preferred embodiments, the volatile low surface tension organic liquid is a water-soluble lower aliphatic alcohol, a water-soluble lower aliphatic ketone, a water-soluble lower aliphatic ether, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, mixtures thereof, or aqueous solutions thereof.

In more preferred embodiments, the volatile low surface tension organic solvent is methyl alcohol, ethyl alcohol,

n-propyl alcohol, isopropyl alcohol, acetone, methyl ethyl ketone, tetrahydrofuran, dioxane, dimethylformamide, N-methyl pyrrolidinone, mixtures thereof, or aqueous solutions thereof, with acetone, isopropyl alcohol, or an aqueous mixture thereof being especially preferred.

Preferably, the microporous membrane is a PVDF, polytetrafluoroethylene, polysulfone, polyethylene, or polypropylene membrane.

Also provided by the present invention are novel methods for producing a laminate, the laminate comprising a hydrogel layer bound to a microporous hydrophobic membrane, comprising the steps of:

(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer;

(b) applying the coating solution to one surface of a sheet or hollow fiber microporous hydrophobic membrane, or to the surface of a woven fabric containing microporous, hydrophobic hollow fiber membranes;

(c) rapidly evaporating the volatile low surface tension organic liquid from the coating;

(d) optionally crosslinking the polymer by contacting the coated surface with a solution of a crosslinking agent capable of crosslinking the polymeric coating and rendering it water insoluble; and

(e) drying polymer to remove residual moisture.

Some preferred embodiments of the methods of the invention further comprise repeating steps (a)–(d).

In some preferred embodiments, the prepolymer has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

In further preferred embodiments, the prepolymer in the first step (b) has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

In some preferred embodiments, the prepolymer is a cellulose ether or ester, polyvinyl alcohol, polyvinyl alcohol copolymer with vinyl acetate, N-alkyl polyacrylamide, N-alkyl polyacrylamide copolymer with acrylamide, an isocyanate-capped, polyethylene-glycol based polyurethane, an esterified or etherated polysaccharide, a hydroxyalkylated polyacrylate, a polymethacrylate, or a hydroxylated polymethacrylate.

In further preferred embodiments, the prepolymer is a linear isocyanate-capped, polyethylene-glycol-based polyurethane, cellulose, methylcellulose, hydroxypropylmethyl cellulose, or copolymers of vinyl acetate and vinyl alcohol.

In some preferred embodiments, the volatile low surface tension organic liquid is a water-soluble lower aliphatic alcohol, a water-soluble lower aliphatic ketone, a water-soluble lower aliphatic ether, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, mixtures thereof, or aqueous solutions thereof.

In more preferred embodiments, the volatile low surface tension organic solvent is methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, acetone, methyl ethyl ketone, tetrahydrofuran, dioxane, dimethylformamide, N-methyl pyrrolidinone, mixtures thereof, or aqueous solutions thereof, with acetone, isopropyl alcohol, or an aqueous mixture thereof being especially preferred.

Preferably, the microporous membrane is a PVDF, polytetrafluoroethylene, polysulfone, polyethylene, or polypropylene membrane.

In some particularly preferred embodiments of the foregoing methods, the sheet microporous membrane or membrane laminate module is provided by cleaning a sheet microporous membrane or a membrane laminate module, which has a damaged hydrogel layer.

Also provided are membrane laminates produced by the methods of the invention.

DETAILED DESCRIPTION

The present invention provides novel materials and methods for producing membrane laminates suitable for use in the concentration or dealcoholization of liquid foodstuffs, beverages, ferments, and aqueous solutions of heating-sensitive products. The laminates comprise one or more thin layers of non-porous, defect-free polymeric hydrogels bonded to the surface of a microporous, non water-wettable (i.e., hydrophobic) membrane.

In some preferred embodiments, the methods for producing a laminate are provided, said laminate comprising a thin hydrogel layer firmly bonded to a microporous hydrophobic membrane, comprising:

(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer;

(b) applying the coating solution to one surface of a microporous hydrophobic membrane sheet, or to the external surface of a microporous hydrophobic hollow fiber membrane;

(c) rapidly evaporating the volatile components from the coating;

(d) crosslinking the prepolymer by contacting the coated surface with a solution of a crosslinking agent capable of rendering the coating water-insoluble;

(e) optionally water-washing the crosslinked polymer to remove water soluble components therefrom; and

(f) drying the coating to remove residual moisture, thereby producing the desired laminate.

The laminates of the present invention can be in sheet or hollow-fiber configuration. The methods of the present invention will permit fabrication of laminates by simpler and more economic procedures than those currently in use. In some preferred embodiments of the invention, methods are provided for the preparation of laminates by treatment of finished, pre-assembled membrane modules.

In further preferred embodiments, methods are provided for the in-situ recoating of deteriorated or damaged laminate modules, comprising the steps of:

(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer;

(b) feeding the coating solution to the feed side flow channel of a sheet- or hollow-fiber-microporous hydrophobic membrane module in sufficient quantity and at a sufficient rate to form a polymer coating on the membrane surface of the desired thickness, while simultaneously passing an inert gas to the strip-side of the module to evaporate volatile components;

(c) evaporating residual volatile components from the coated membrane by flowing a gas through both the feed and strip channels of the coated module;

(d) optionally crosslinking the polymer by contacting the coated surface of the membrane with a solution of a crosslinking agent capable of crosslinking the polymeric coating and rendering it water-insoluble; and

(e) drying the coating to remove residual moisture.

The methods of the invention can be used for producing a suitable thin hydrogel-film/hydrophobic microporous membrane laminate for osmotic distillation applications in situ in assembled sheet-membrane and hollow-fiber membrane modules or contactors.

In a further aspect, the present invention presents novel methods for producing a laminate, the laminate comprising a hydrogel layer bound to a microporous hydrophobic membrane, comprising the steps of:

(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer;

(b) applying the coating solution to one surface of a sheet or hollow fiber microporous hydrophobic membrane, or to the surface of a woven fabric containing microporous, hydrophobic hollow fiber membranes;

(c) rapidly evaporating the volatile low surface tension organic liquid from the coating;

(d) optionally crosslinking the polymer by contacting the coated surface with a solution of a crosslinking agent capable of crosslinking the polymeric coating and rendering it water insoluble; and

(e) drying polymer to remove residual moisture.

As used herein, the term "inert gas" denotes any gas, or mixture of gases, that will not detrimentally react with components of the coating solution. Preferred inert gases include argon, dry air, and nitrogen.

The preferred hydrophobic, microporous membranes for use in this invention are those familiar to the skilled practitioner in the art of osmotic distillation. [redacted] (for example, those manufactured by Hoechst Celanese Separation Products under the trade name of [redacted], and by AKZO NV under the trade name of Accurel®), microporous polyvinylidene fluoride (PVDF) membranes (for example, those manufactured by Millipore Corporation), microporous polytetrafluoroethylene membranes by W. L. Gore under the trade name of Gore-Tex®, and microporous polyester and polyether sulfone membranes.

In accordance with preferred embodiments of the invention, each of the foregoing hydrophobic, microporous membranes are non-water wettable, and all but the PTFE membranes are wettable by liquids of surface tension of ca. 35 dynes/cm or less.

The methods of the invention are useful for the preparation of membrane laminates from new membrane modules, as well as for the repair of membrane laminate modules which have undergone deterioration with age, or have otherwise suffered damage to the hydrogel layer of the laminate.

Most hydrophilic polymers used as hydrogel layers for membrane laminates are amenable to depolymerization and/or resolubilization by treatment with aqueous solutions of reagents (e.g., acids or bases) under conditions which will not adversely affect the underlying microporous membrane or other module components. Thus, in accordance with preferred embodiments of the invention, such a solution is passed through the feed channel of a module, and the

damaged or deteriorated hydrogel layer is solubilized and removed. After washing of the treated module with water to remove residual reagents and soluble impurities, and then drying the module with, for example, warm, dry air, the module is then recoated according to the procedure described above.

In order to provide a membrane laminate with sufficient permeability to water and other water soluble volatile solutes to be useful for osmotic distillation, it is greatly preferred that the hydrogel layer of the laminate be as thin as possible consistent with mechanical strength and freedom from liquid-permeable defects, and of adequately high water content to provide minimal obstruction to permeation by water and microsolutes. Thus, in preferred embodiments of the invention the hydrogels have water contents at use temperature in excess of about 40% by weight.

The mechanical strength and durability of a hydrogel decreases quite rapidly with increasing water content. Thus, in preferred embodiments, hydrogels of the invention contain from about 40% to about 90% water by weight, more preferably from about 50% to about 80% by weight. Hydrogels having greater than about 90% water by weight are less preferred, as they may be too fragile.

It will be recognized by those skilled in the membrane art that it is very difficult to produce, whether by coating or other techniques, reliably defect free membranes of a thickness less than about 5 micrometers. Hence, in preferred embodiments hydrogel coatings on laminate membranes of the invention are preferably no less than 5 micrometers in their hydrated state. More preferably, the hydrogel layers should be deposited in a thickness of from about 10 to about 20 micrometers (in the hydrated state).

In accordance with the present invention, the thickness of the hydrogel layer of the final laminate can be controlled either by adjusting the concentration of polymer in the coating solution, or by adjusting the volume of solution applied to the substrate membrane, or by adjusting both.

In general, hydrophilic polymers suitable for producing hydrogel films of the desired properties for this purpose are water-soluble synthetic or natural polymers with good film-forming properties, and which are capable of covalent crosslinkage under mild conditions to render them water-insoluble, yet water absorptive. Such polymers are widely used in the papermaking, packaging, photographic film manufacturing, and textile finishing industries as paper coating binders, textile sizing and stiffening agents, grease-resistant coatings, adhesives, dyeing assistants, and the like. Further information on the properties, characteristics, methods of making and using, and manufacturers of such polymers can be found in "Industrial Gums, Polysaccharides and Their Derivatives," Whistler, R. L. and BeMiller, J. N. Eds. Academic Press, San Diego, 1993, the disclosure of which is hereby incorporated by reference in its entirety.

Preferred polymers useful in the present invention include naturally occurring polysaccharides obtained from marine or terrestrial vegetable sources, such as agar, carrageenan, algin, starch, cellulose, guar, gum arabic, and the like, and their chemically-modified derivatives thereof. Useful derivatives of such hydroxylated polymers, which render them more readily soluble in water or organic solvents, impart improved mechanical and film-forming properties, and/or facilitate crosslinkage, include alkyl and hydroxyalkyl ether, carboxyalkyl, alkyl ether, hydroxyalkyl ether, amino, aminoalkyl, and sulfoalkyl substituents.

Further preferred polymers include synthetic linear polymers such as polyacrylamide and its N-alkyl or N-hydroxyalkyl derivatives, polyacrylic and polymethacrylic acids and salts and esters thereof, polyvinyl alcohol and its copolymers with vinyl acetate, copolymers of maleic acid and vinyl methyl ether or vinyl acetate and salts and esters thereof, and polyoxyalkylene polymers such as polyethylene glycol and its copolymers with propylene glycol.

Particularly preferred polymers for use in the present invention are the alkyl and hydroxyalkyl ethers of cellulose, especially those containing both methyl and hydroxypropyl ether substituents. These polymers are amphiphilic, displaying solubility in both water and water-miscible, volatile, polar organic solvents such as, for example, the lower aliphatic alcohols, lower aliphatic ketones, lower aliphatic ethers, methyl cellosolve, acetone, acetonitrile, tetrahydrofuran, dioxane, N-methyl pyrrolidinone, and mixtures thereof. [redacted] Significantly, these solvents and solvent mixtures are of low enough surface tensions to readily wet the surface of microporous polyolefin, PVDF, and polysulfone membranes in accordance with the methods of the invention.

Other suitable amphiphilic polymers include the hydroxyalkyl acrylates and methacrylates, vinyl alcohol/vinyl acetate copolymers, polyethylene glycol, and block copolymers of ethylene and propylene glycols.

Particularly preferred polymers for use in the present invention include polyethylene glycols and/or polyethylene glycol/polypropylene glycol block copolymers which have been contacted with di- and tri-isocyanates in excess to produce linear or branched isocyanate-capped, urethane-linked polyglycols, such as, for example, those marketed under the trade name of Hypol® by Hampshire Chemical Company of Lexington, Mass. These prepolymers are viscous liquids which are freely soluble in water and polar organic solvents, and mixtures thereof. Upon dissolution in liquid water or exposure to water vapor, however, slow hydrolysis reaction with the terminal isocyanate groups occurs to yield first a carbamic acid, which decomposes into carbon dioxide and a primary amine. These terminal amine groups then react rapidly with the residual isocyanate termini to form a stable interchain urea linkage, thereby yielding a stable hydrogel. In accordance with the present invention, the water uptake of such gel is readily controlled by proper choice of the molecular weight of the starting polyglycol. See, for example the Hampshire product literature, and James A. Braatz, *Biocompatible Polyurethane-Based Hydrogel*," J. Biomaterials Applications, 9, 71 (1994). In addition, in solution in aprotic organic solvents such as acetone, tetrahydrofuran, ethyl acetate, methylene chloride, and other aprotic solvents having adequately low surface tension to be useful in the present invention, the prepolymers are shelf-stable for long periods, provided they are kept out of contact with water or other protic compounds, such as alcohols or acids.

Hence, in accordance with preferred methods of the invention, a microporous, hydrophobic membrane is coated with such a polymer applied from solution in a volatile, aprotic organic liquid, the organic liquid is rapidly removed by evaporation; and the coating is then exposed to steam or moist air to cause crosslinkage of the coating and its conversion into a stable hydrogel film. Thus, the present invention provides a considerably simpler methods for the production of the membrane laminates, by avoiding the necessity of a separate chemical treatment step to effect crosslinkage of the polymer.

In some preferred embodiments, the polymer solution is applied by standard coating techniques, preferably by dip coating, roll coating, or spraying.

In further preferred embodiments of the present invention, a multi-step coating operation is performed in which one hydrophilic polymer is applied to the microporous membrane substrate as above described, and after drying, one or more additional layers of hydrophilic polymer are similarly applied and allowed to dry. The resulting double-layer coating is then optionally subjected to post treatment by chemical or thermal means to crosslink the polymers.

In preferred embodiments, such a two-step process is employed if a polymer has a sufficiently high molecular weight to prevent its penetration into the substrate membrane pores, but yields a solution of such high specific viscosity that the coating solution suitable for application is too dilute to yield a coating of adequate thickness. In this event, the polymers selected for the second and any subsequent coating steps can, if desired, be of lower molecular weight than that required for the first layer, to allow the use of more concentrated solutions, and thus fewer coating steps to achieve the desired final coating thickness.

In accordance with the present invention, it has been discovered that where the soluble polymer employed for the coating is of adequately high molecular weight, a dilute solution or colloidal dispersion prepared by dissolving or dispersing the prepolymer in a volatile organic liquid or liquid mixture of low surface tension, when applied to the surface of the microporous membrane, will spread on and wet out the membrane surface to yield a uniform liquid film. However, the pores in the substrate membrane are too small to permit entry of the polymer molecules or particles in the solution, although the solvent will be imbibed by capillarity into the pores. As a result of this spontaneous imbibition and sieving effect, the polymer is constrained to remain on the membrane surface. If evaporation of solvent from either side (or both sides) of the coated membrane is allowed to take place, all the polymer present in the applied solution will be deposited as a uniform, adherent layer on the surface to which it was applied.

Thus, it is greatly preferred that the prepolymer in the coating solution, or the final crosslinked polymer, not penetrate into the pores of the substrate microporous membrane at any point in the methods of the invention. Such penetration would lead to defects in the membrane, and/or obstructions to vapor flow. Thus, in preferred embodiments of the invention, the prepolymer is of sufficiently high molecular weight that its hydrodynamic diameter in solution is sufficiently greater than the diameter of the pores in the substrate membrane for it to be excluded from the membrane pores, and be retained as a homogeneous thin film on the membrane surface.

In some preferred embodiments of the invention this requirement can also be met by selecting as the solvent component of the coating solution a low surface tension organic liquid or liquid mixture in which the polymer is not in true molecular solution, but is present as a dispersion of submicroscopic particles whose dimensions exceed those of the pores of the substrate membrane. Subsequent coalescence of these particles during the drying process into a homogeneous, defect free layer will yield the desired laminate of this invention.

As used herein, the term "low surface tension" means a liquid of surface tension at room temperature (i.e., about 20–25° C.) not higher than about 40 dynes/cm.

In accordance with some preferred embodiments of the invention, one or more prepolymers is first dissolved in a volatile, low surface tension organic liquid (i.e., a solvent) to produce a coating solution. The coating solution is then applied to a sheet or hollow fiber microporous hydrophobic membrane under conditions where the volatile components of the coating solution can be rapidly removed by evaporation.

In some preferred embodiments of the present invention laminates are produced with amphiphilic, reactive prepolymers which form stable hydrogels on exposure to water. Typically, a prepolymer solution is applied to a sheet or hollow fiber microporous hydrophobic membrane by conventional dip-coating, roll-coating, or spray-coating applications, under conditions where the volatile liquid can be rapidly removed by evaporation. Because this solution will wet out the membrane surface, a highly uniform and adherent coating will be produced. Under conditions of rapid solvent evaporation, however, the viscosity of the remaining prepolymer will be too high to permit wicking of the prepolymer into the pores of the substrate. Thus, in some preferred embodiments of the invention, the thickness of the final coating can be controlled by varying the prepolymer concentration in the prepolymer coating solution.

A wide variety of prepolymers can be used as the hydrophilic coating on a hydrophobic microporous membrane in accordance with the present invention. It is desirable that the prepolymer is intrinsically water-soluble and capable of covalent crosslinkage to yield a stable hydrogel. In preferred embodiments, the polymer is also soluble in polar, water-miscible, volatile organic liquids having low surface tension such as the lower aliphatic alcohols, lower aliphatic ketones, lower aliphatic ethers, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, acetone, tetrahydrofuran, dioxane, dimethylformamide, and ethylene glycol dimethyl ether (Cellosolve), or aqueous mixtures thereof. Preferably, the prepolymer is of sufficiently high molecular weight to be excluded from the pores of the substrate microporous membrane.

Preferred polymers for use in the present invention include the cellulose ethers and esters, polyvinyl alcohol and its copolymers with vinyl acetate, polyethylene oxide and its copolymers with polypropylene oxide, N-alkyl polyacrylamides and their copolymers with acrylamide, isocyanate capped polyethylene-glycol-based polyurethanes, starch esters, starch ethers, other esterified or etherated polysaccharides, and hydroxyalkylated polyacrylates and polymethacrylates.

Some preferred prepolymers especially useful in the present invention are linear or branched isocyanate capped polyethylene glycol (PEG) urethanes formed from intermediate molecular weight (e.g., from 200 to 10000 Daltons) PEGs by reaction in stoichiometric excess with diisocyanates. These PEG-urethane prepolymers are reacted with additional diisocyanate to yield isocyanate terminated, linear PEG urethane prepolymers. These prepolymers are amphiphilic, soluble in both water and a variety of polar organic liquids, and react with water to form urea crosslinked, stable hydrogels. They also possess the advantage of being highly reactive, yet shelf-stable viscous liquids possessing the solubility characteristics of the component polyethers.

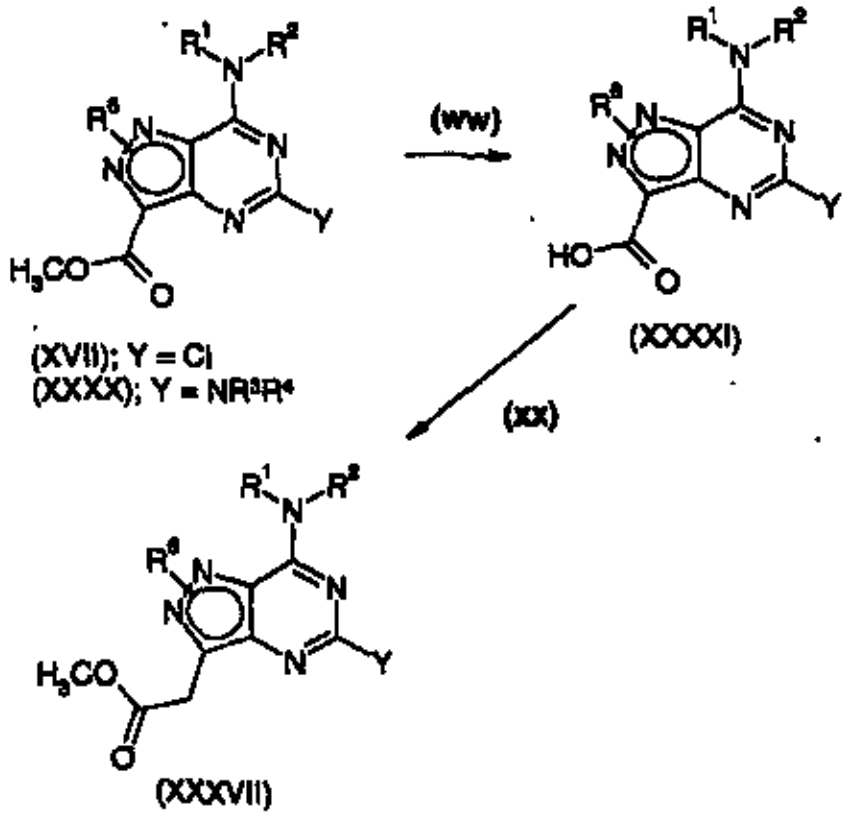
In some preferred embodiments of the present invention, the prepolymer is a linear or branched polyethylene-glycol based isocyanate capped polyurethane, cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, or copolymers of vinyl acetate and vinyl alcohol.

In some especially preferred embodiments of the present invention, hydroxypropyl methyl cellulose, a water-soluble

ring system, or with a sulphonium ylid or a carbene equivalent to give a 2-(pyrazolopyrimidinyl)-cyclopropane-1-carboxylate derivative.

10. The homologated esters of formula (XXXVII) can also be prepared by the method illustrated in Scheme 10.

Scheme 10



Step (ww)

The methyl esters of formulae (XVII) and (XXXX) may be hydrolysed to provide the acids of formula (XXXXI) following the methods of part 2, step (n), above. *(The esters of formula (XXXX) may be obtained from the esters of formula (XVII)* following the methods of part 1, step (g) above.)

Step (xx)

The acids of formula (XXXXI) may be homologated following the methods of the *Arndt-Eistert reaction. The carboxylic acid is converted to a reactive* intermediate such as the acid chloride (by reaction with oxalyl chloride) or a

film-forming cellulosic polymer, is employed as the prepolymer in the polymer solution. Hydroxypropylmethyl cellulose is produced commercially in a variety of methoxyl contents, and ratios of methyl to hydroxypropyl substitution. One particularly preferred hydroxypropylmethyl cellulose suitable for use in the present invention is Methocel® 175M-SN, which has a molecular weight of ca 200,000, and is commercially available from Dow Chemical Company, Midland, Mich.

Other particularly preferred prepolymers include hydroxypropylcelluloses having higher methoxyl content, and/or higher ratios of methyl to hydroxypropyl substitution than Methocel 175. These polymers are less soluble in water at ambient temperature than is Methocel 175, and can be applied from low surface tension organic liquid mixtures such as acetone/water solutions, deposited as uniform films by simple drying, and require no post treatment (i.e., no crosslinking step) to render them water-insoluble. Thus, in some preferred embodiments, the present invention provides methods for producing laminate membranes comprising the steps of:

(a) dissolving one or more cellulose polymers selected from methyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose in a volatile, low surface tension organic liquid, or an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution, the cellulose polymer having high methoxyl content, and/or high ratios of methyl to hydroxypropyl substitution;

(b) applying the coating solution to one surface of a sheet or hollow fiber microporous hydrophobic membrane;

(c) rapidly evaporating volatile components from the coating;

(d) optionally washing the membrane; and

(e) drying the polymer to remove residual moisture to produce the laminate.

As used herein, the term "high methoxyl content, and/or high ratios of methyl to hydroxypropyl substitution" is intended to indicate either a methoxyl content or ratio of methyl to hydroxypropyl substitution approximately as high as that of Methocel® 175M-SN; i.e., a methoxy content of about 1.3 substitutions per glucopyranose, and ratio of methyl to hydroxypropyl substitution of about 1.50.

The present invention also includes use of prepolymer solutions containing more than one type of prepolymer dissolved in the volatile, low surface tension organic liquid.

Thus, in some preferred embodiments of the invention, a hydrophobic microporous membrane is first coated with a prepolymer solution as described above. The coated membrane then is optionally crosslinked to produce a first hydrogel layer, and coated again with one or more successive prepolymer solutions. It will be appreciated that only the first prepolymer coating of the membrane need be of high molecular weight, or be in a low surface tension organic liquid, as successive prepolymers will contact the first hydrogel layer, and will not contact the hydrophobic membrane surface.

The prepolymer (or prepolymers) is dissolved in an organic liquid of high volatility and low surface tension (or aqueous solution thereof) to produce a prepolymer solution, which is then used to coat the microporous membrane. The prepolymer can be dissolved in the organic liquid or aqueous mixture thereof by any conventional method. The term "high volatility" is intended to mean a liquid whose normal boiling point is lower than or not notably higher than that of water, and/or whose partial pressure over its aqueous solutions is greater than that of water.

Organic liquids (or organic solvent components of the coating solution) for use in the polymer solution, besides functioning as good solvents or cosolvents for the polymers, preferably should be miscible with, or have high solubility in water. Thus, preferred organic liquids (or solvents) include the lower aliphatic alcohols (i.e., methyl, ethyl, or propyl), lower aliphatic ketones, lower aliphatic ethers, acetone, tetrahydrofuran, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, methylene chloride, and mixtures thereof. Other suitable organic solvents will be apparent to those of skill in the art, once armed with the present disclosure.

In preferred embodiments of the invention, the thickness of prepolymer coating typically ranges from about 0.5 microns to about 20 microns, more preferably from about 2 microns to about 10 microns. However, it will be appreciated by those of skill in the art that the optimum prepolymer thickness will vary for different prepolymer solutions and for different microporous membranes, especially where the hydrogel layer contains more than one individual coating of prepolymer solution.

The ability of a microporous membrane to retain a prepolymer in solution is dependent on the pore size of the membrane, and the molecular weight of the polymer. Substantially complete retention will be achieved if the pore size of the membrane is substantially smaller than the hydraulic diameter of the dissolved prepolymer. If this condition is satisfied, then the thickness of the resulting coating will be determined solely by the concentration of polymer in solution, and the quantity of solution contacting the membrane surface (per unit area) prior to solvent evaporation. Thus, in some preferred embodiments of the invention, prepolymers are soluble in volatile polar organic solvents, and/or in mixtures of these solvents with water, and have sufficiently high molecular weight (i.e., sufficiently large hydrodynamic diameters) to be retained on the surface of conventional microporous hydrophobic membranes. The thickness of the coating of such prepolymers is then controlled, in preferred embodiments, by varying the prepolymer concentration in the coating solution.

While there is, in principle, no upper limit to the polymer molecular weight which will meet these requirements, there is a practical limit imposed by the increase in solution viscosity which is a consequence of increasing polymer molecular weight. If the polymer solution is too viscous, deposition of the solution uniformly over the membrane surface, and controlling the thickness of the liquid film, becomes difficult to achieve. Although the viscosity of such a solution can be reduced by dilution with additional solvent, the resulting decrease in polymer concentration can result (after solvent evaporation) in the deposition of a layer of hydrogel on the laminate which is too thin.

Thus, in accordance with preferred embodiments of the invention, the coating solution should preferably have a viscosity of from about 100 to about 1000 centipoises, preferably 100 to about 500 centipoises, and more preferably from about 100 to about 200 centipoises.

For membrane laminates produced by a single coating of polymer solution, the coating solution preferably contains a polymer of molecular weight of from about ca. 200,000 to about one million Daltons, and preferably from about 200,000 to about 500,000 Daltons. In preferred embodiments, the coating solution contains the polymer at a concentration of from about 0.05% to about 10% by weight, more preferably from about 0.5% to about 5%, and more preferably from about 1.0% to about 2.0%, with a concentration of about 1.0% by weight being most preferred.

Coating solutions having polymer concentrations lower than about 0.05% will be acceptable where successive applications of coating solutions are desired, such as in the formation of laminates having multiple hydrogel layers. Preferably, a solvent evaporation step is employed between successive coatings.

In some preferred embodiments of the present invention, the polymer solution is prepared by adding prepolymer (e.g., Methocel® 175M-SN) in powder form to an organic solvent of low surface tension (for example isopropyl alcohol), to produce a suspension (the gum being insoluble in the alcohol), and then slowly adding a more polar solvent (e.g. water) to the suspension until the resulting viscous and nearly transparent solution appears to be a true solution of the polymer. It has been discovered in accordance with the present invention that the slow addition to this solution of an additional small amount of organic solvent will cause the viscosity of the solution to rapidly drop, and the solution to become somewhat opalescent. When used as the coating solution in the methods of the invention, this solution produces coatings which are equal to or superior to those obtained with the clear viscous solution. Additionally, this less viscous solution is advantageous in that it is easier to apply, and seems to dry more rapidly.

While not wishing to be bound by any specific theory, it is believed that in a mixture of a "good" and "poor" solvent for a polymer (like water and isopropyl alcohol, respectively) the polymer may not be in true solution if the concentration of the good solvent is too low. In such a solvent mixture, the polymer can be present as a microgel dispersion, consisting of submicronic particles of polymer swollen with water, suspended in the alcohol rich medium. Such a dispersion, when applied to the membrane, will spread and wet out the surface, while the liquid phase wicks into the pores, leaving the microgel particles behind as a layer on the surface. As the film is allowed to dry by evaporation, the more volatile (poor) solvent leaves first, thereby enriching the remaining liquid in good solvent (water). The microgel particles on the surface then go into solution, forming a continuous film much too viscous to enter the pores, prior the final complete drying.

Thus, in some especially preferred embodiments of the present invention, the prepolymers (1) are water soluble or, more preferably, insoluble but swollen in water, (2) also insoluble in a water-miscible organic solvent, but (3) soluble in a limited range of mixtures of these two solvents. It is additionally preferred that the water-miscible organic solvent be more volatile than water.

In preferred embodiments, the prepolymer solution is applied to a sheet or hollow fiber microporous membrane. Suitable sheet or hollow fiber microporous hydrophobic membranes include those known to be suitable for membrane distillation processes, such as, for example, Celgard (Hoechst Celanese Separation Products Division); Accurel® microporous polypropylene (AKZO NV); and Gore-Tex® (Gore Corporation), and PVDF membrane (Millipore Corporation). Additional hydrophobic microporous membranes suitable for use in the present invention will be readily apparent to those of skill in the art.

Application of the prepolymer solution to the microporous hydrophobic membrane can be accomplished by any of the conventional methods known in the art, such as for example, dip-coating, roll-coating, or spray-coating.

After application of the prepolymer solution to the hydrophobic microporous membrane, the organic solvent is removed from the coated membrane surface by rapid evaporation. It will be understood that complete removal of the solvent is not necessary; some trace may remain. It is only necessary that sufficient solvent be removed to cause deposition of the prepolymer on the membrane surface.

It is greatly desirable to evaporate the solvent at a rate that is sufficient to ensure that the viscosity of the remaining prepolymer will be too high to permit wicking of the prepolymer into the pores of the substrate. The possibility of such wicking is overcome to a great extent by selecting, in accordance with preferred embodiment of the invention, a prepolymer having a hydrodynamic diameter larger than the pores of the hydrophobic membrane, or a solvent system in which the polymer is present as submicron sized colloidal particles.

In some preferred embodiments, the laminates of the invention contain more than one hydrogel layer. Accordingly, in some preferred embodiments the solvent is evaporated from the coated membrane prior to application of a further prepolymer solution.

In some preferred embodiments of the invention, no crosslinking step is required to stabilize the hydrogel layer. However, for applications where high flow rates across the membrane surface are expected, or where the hydrogel layer is expected to encounter stress, it is preferred that the hydrogel layer be crosslinked to ensure the mechanical stability of the hydrogel.

Thus, in some preferred embodiments of the present invention, after removal of the solvent by evaporation, the dried prepolymer is crosslinked and insolubilized (i.e., "cured"). In accordance with preferred embodiments of the invention utilizing Hypol prepolymer films, crosslinking can be accomplished by contacting the polymer with warm aqueous solution, for example by spraying the prepolymer with warm water (containing, if desired, a low concentration of alkali such as sodium hydroxide to accelerate the crosslinking process) or by exposure to steam or moist air. It is preferred that crosslinking be performed immediately after the drying of the prepolymer.

After crosslinking, the resulting laminate is dried, for example in warm air, to remove residual moisture prior to storage. In accordance with preferred embodiments of the invention utilizing Hypol-based laminates, where the prepolymer contains a polyglycol, the dry coating retains considerable flexibility and resiliency due to the inherent thermoplasticity of the prepolymer. Thus, there is little danger of damage to the coating during subsequent manipulations. The final laminate, in either sheet or hollow fiber form, is therefore suitable for further processing, such as incorporation into membrane modules by customary fabrication procedures.

In accordance with preferred embodiments of the invention having laminates whose hydrogel layers are formed from cellulosic polymers which embrittle on drying, it is desirable to rinse the hydrogel-containing membrane surface with a dilute solution of glycerin or other nonvolatile, nontoxic humectant prior to drying. This will render the coating plasticized by the humectant and flexible so that it will not crack during the drying process. Such humectant will be rapidly and completely removed during rehydration of the membrane prior to use.

When the (dry) module is installed for use, for example, in an osmotic distillation process, and water or an aqueous feed stream is introduced into the feed compartment, water will rapidly be absorbed by the coating to yield the desired, stable hydrogel layer. Since hydrogels formed from Hypol prepolymers absorb and release their water of hydration reversibly, modules containing laminates with these coatings are capable of being cleaned in a conventional manner, dried

The term "extended release coating" as used herein means a coating designed to effect the delivery of a hydrophilic therapeutic agent, an enzyme inhibitor, or the carrier, over an extended period of time. Preferably, the extended release coating is a pH-independent coating formed of, for example, ethyl cellulose, hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, acrylic esters, or sodium carboxymethyl cellulose. Various extended release dosage forms can be readily designed by one skilled in art to achieve delivery of a hydrophilic therapeutic agent, an absorption enhancing carrier or an enzyme inhibitor to both the small and large intestines, to only the small intestine, or to only the large intestine, depending upon the choice of coating materials and/or coating thickness.

Dosage forms of the compositions of the present invention can also be formulated as enteric coated delayed release oral dosage forms, *i.e.*, as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to effect release of a hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier in the lower gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, pellets, beads or particles of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier, which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or granules of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier which are themselves coated or uncoated.

The term "enteric coating" as used herein relates to a mixture of pharmaceutically acceptable excipients which is applied to, combined with, mixed with or otherwise added to the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier. The coating may be applied to a compressed or molded or extruded tablet, a gelatin capsule, and/or pellets, beads, granules or particles of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier. The coating may be applied through an aqueous dispersion or after dissolving in appropriate solvent. Additional additives and their levels, and selection of a primary coating material or materials will depend on the following properties:

1. resistance to dissolution and disintegration in the stomach;

if desired, and then restored to the wet condition without danger of delamination or structural change of the hydrogel layer. For those prepared from cellulosic and most other hydrophilic polymers, however, treatment prior to final drying is highly desirable.

Hydrogels formed from the preferred prepolymers of the invention are dimensionally and chemically stable, display low adsorptive affinity for proteins and other amphiphilic biopolymers as are present in liquid foodstuffs and biological fluids, and are nontoxic to humans and animals. This renders them eminently suitable candidates for osmotic distillation of liquid solutions of any ingestible solutes such as foodstuffs, vitamins, drugs, and other biologically important compositions.

In further preferred embodiments of the invention laminates are produced by adsorption from aqueous solution of ultrathin layers of amphiphilic, high molecular-weight, linear polymers followed by crosslinkage in the adsorbed state with water-soluble reagents.

It is well known in the art that certain water-soluble, high-molecular weight, linear polymers exhibiting amphiphilic character are capable of selective, virtually irreversible adsorption onto hydrophobic surfaces from aqueous solution to yield extremely thin water-wettable films. This property has been utilized to produce stable oil-in-water emulsions and polymer lattices, and to treat hydrophobic ultrafiltration membranes to render them nonadsorptive for many proteins and other lipophiles which foul these membranes, without reducing their water permeability and changing their permselectivity. Among the most useful polymers for this purpose are water-soluble amphiphilic derivatives of cellulose (most particularly methylcellulose, and hydroxypropylmethyl cellulose, produced by Dow Chemical Company, Midland, Mich., under the trade name Methocel®), and copolymers of vinyl acetate and vinyl alcohol of relatively low acetyl content.

Aqueous solutions of these polymers containing as little as 1.0 g/liter of polymer are suitable for surface treatment of such substrates. The adsorption process is rapid, and will deposit in a layer of the order of 1000–2000 Angstroms (0.1–0.2 micrometer) in thickness. Adsorption is nearly irreversible for polymers of molecular weight of ca. 200,000 or greater. Accordingly, the highest molecular weight polymers available are preferred for the application of the present invention.

Once the adsorption of a complete monolayer has taken place, further adsorption ceases. The adsorbed layer thus protects the pores of the substrate membrane from penetration of polymer. While the adsorbed layer may itself be inadequate to protect the underlying membrane from contamination by food-components, it provides a polymer-impermeable barrier for application of a polymer coating of suitable thickness. This provides assurance that polymer deposited in this manner will not penetrate the membrane pores.

Thus, when a microporous hydrophobic membrane of the type used in osmotic distillation is exposed to a solution of such a polymer, adsorption will occur substantially uniformly over the entire exposed surface, forming a hydrogel of the order of 1000–2000 Angstroms thick. However, the pores of such membrane are typically in the range of 0.05–0.05 micrometer (500–500 Angstroms) in diameter, which is too small to allow entrance of these macromolecules. Hence, adsorption will be confined to the exposed membrane surface, and thus will not alter the wettability of the pore surfaces.

It is preferred that the adsorbed polymer layer be further stabilized against detachment, or changes in degree of

hydration with time, to assure consistent performance of the laminate for long periods in service. In some preferred embodiments, cellulose ethers useful in the present invention (as well as the polyvinyl alcohol-acetate copolymers useful in the present invention) contain accessible alcoholic hydroxyl groups which are capable of reacting with certain classes of water-soluble, polyfunctional reagents to generate stable cross-linkages between adjacent polymer chains. Typical reagents of this type include (1) diepoxides such as 1,4-butane diepoxide or diglycidyl glycerine; (2) diisocyanates such as ethylene or tolylene diisocyanate; (3) polyfunctional aldehydes or formaldehyde adducts such as glyoxal, glutaraldehyde, dimethylol urea or other water-soluble urea/aldehyde adducts, tris (hydroxymethyl) melamine (or other water-soluble melamine/formaldehyde adducts), or (4) dicarboxylic acids such as oxalic acid, succinic acid, or phthalic acid. More preferred are the urea/aldehyde and melamine formaldehyde adducts, because of their higher reactivity, reduced toxicity, and higher chemical stability.

Only relatively low levels of crosslinkage (and thus small amounts of these crosslinking reagents) are required to provide suitable stabilization of the adsorbed films in accordance with the invention. In some preferred embodiments, crosslinkage is accomplished by contacting a dilute aqueous solution of the reagent (the pH of which has been adjusted to provide maximum rate of reaction with the hydroxyl groups of the adsorbed polymer) with the (wet) membrane after the adsorption step, and allowing sufficient time of contact for adequate reagent uptake and reaction. Because of the thinness of the layer, the reaction time should be rapid, typically from a few seconds to a few minutes after contact. When the reaction is complete, the remaining reagent solution is flushed from the membrane, for example with pure water, in sufficient quantity to insure removal of residual unreacted reagent and soluble byproducts. The washed membrane is then ready for service.

A further preferred class of crosslinking agents for hydroxylated polymers such as cellulose and other polysaccharides and their derivatives is aqueous solutions of zirconium salts of weak acids such as acetic and carbonic. Such products are marketed under the trade name of Bacote® (Magnesium Elektron Ltd., Manchester, England). These compounds react with vicinal hydroxyl groups in such polymers to form zirconium chelate complexes that serve as stable crosslinkages between polymer chains. Dilute solutions of these compounds, when contacted with such polymers in the hydrated state at room temperature, react to form crosslinkages in seconds or minutes, converting the polymer to an insoluble but hydratable gel.

The present invention provides several important advantages over current methods for the production of coated membranes. For example, the methods of the invention can be performed on commercially available modules containing microporous hydrophobic membranes. This eliminates all the costly and tedious steps required to produce membrane laminates by multistep treatment of sheet- or hollow-fiber membranes prior to their incorporation into modules. Moreover, the methods of the invention can readily be carried out on "virgin" (i.e., uncoated) modules as received from the supplier, within the facilities of, for example, an osmotic distillation plant, thus advantageously minimizing the likelihood of errors in treatment, or damage to the laminate by mishandling in storage or shipment.

A further significant advantage of the methods of the present invention is that they can be employed to repair (i.e., recoat) microporous membranes which have been rendered unserviceable by failure of the ultrathin hydrogel layer of

the laminate (and not because of failure of the underlying microporous membrane or other module components). Thus, such a laminate can be cleaned (i.e., stripped of residual hydrogel coating) by, for example, flushing of the feed-side of the membrane or compartment of the membrane module with relatively concentrated (e.g., 1%) warm caustic. Such solution will completely depolymerize and solubilize the hydrogel layer, allowing rapid removal of all layer components. Such treatment will have no detrimental effects on the base microporous membrane, nor on other module components. After thorough water rinsing and drying, the module will be restored to its "virgin" (i.e., uncoated) condition. The module is then recoated with a fresh hydrogel layer in accordance with the methods of the invention. Thus, the methods of the invention are useful for substantially increasing the ultimate service-lifetime of membrane modules, and thus significantly reduce the costs associated with osmotic distillation.

In preferred embodiments, sheet membranes, hollow fiber membranes, or woven fabrics containing hollow fiber membranes are coated with the polymer solution by conventional dipping, spraying, roll coating, or immersion methods, followed by rapid drying by a gas. In some preferred embodiments, the gas is warm, dry air.

Thus, the present invention also provides methods comprising the steps of:

(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface-tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer;

(b) filling the feed-side flow path of a microporous hydrophobic, sheet membrane or hollow fiber membrane module with the coating solution;

(c) flowing warm, dry air or other inert gas through the strip-side of the membrane module to evaporate volatile components while continuing to feed coating solution to the feed side flow path of the module for a time period sufficient to coat the membrane with the desired thickness of prepolymer;

(d) displacing the majority of the coating solution from the feed-side flow path;

(e) evaporating remaining volatile components from the coated membrane by flowing a gas through both the feed and strip channels of the module;

(f) optionally crosslinking the polymer by contacting the coated surface of the membrane with a solution of a crosslinking agent capable of crosslinking the polymeric coating and rendering it water-insoluble; and

(g) drying the coating to remove residual moisture.

In another preferred embodiment, the methods of the invention comprise the procedure above described, modified to allow repetition of steps (b), (c), (d), (e), and (f) with one or more additional polymer solutions or dispersions containing the same or different hydrophilic polymers, in order to form a multilayer coating of the desired composition and thickness.

In these modes of application, the coating thickness can be varied and controlled by, for example, varying the concentration of polymer in the coating solution, and/or the volume of coating solution supplied to the module during the coating and drying process.

After displacement of the majority of the polymer solution in the foregoing methods, the resulting coated membrane or membrane module consists of a dry thin hydrophilic polymer bonded to a non-water wettable microporous substrate.

The resulting membrane coating may, if desired, then be crosslinked as described above. The crosslinking can be accomplished by a variety of means, depending on the chemical reactivity of the polymer and crosslinking reagent, and the optimal conditions for reaction.

In some preferred embodiments crosslinking is accomplished by exposing the coated surface of the laminate to a dilute solution of the crosslinking agent at a temperature suitable for rapid crosslinking of the polymer. Preferably, the dilute solution of the curing agent is aqueous. Under these conditions, water and dissolved crosslinking agent will diffuse into and swell the coating, with simultaneous crosslinking and insolubilization of the polymer. It is important that the rate of crosslinkage be relatively rapid compared with the rate of dissolution of the uncrosslinked polymer. Typically, rates of chemical reaction increase exponentially with temperature, whereas rates of dissolution of polymers in solvents are much less temperature-dependent. Hence, for each polymer and crosslinking agent, there will be an optimum treatment temperature which will insure adequate crosslinkage without loss of coating by dissolution. It will be appreciated that the determination of such optimum treatment temperature is well within the skill of those in the art, once armed with the present disclosure.

In other preferred embodiments, certain reactive polymer/crosslinker combinations can be commingled in solution without significant chemical reaction occurring for rather long periods of time at low temperatures (or low concentrations), but will rapidly interact when concentrated and/or exposed to elevated temperature. Such combinations may be incorporated into the coating solution, allowing uniform coating and drying as observed with the polymer component alone. However, during the terminal drying step, elevation of the temperature will permit rapid interaction and crosslinkage, thereby yielding a water-swellable but water-insoluble hydrogel layer.

In further preferred embodiments, the polymer-crosslinking agent components of the coating solution are selected such that initiation of the reaction can be induced by the presence of a soluble catalyst, typically an acid or a base. In the absence of such catalyst, the combination can be considered to be nonreactive, permitting coating as described above. After the prepolymer coating has been deposited and dried, a solution of the catalyst, which preferably is aqueous, can be passed over the coated surface by flow through the feed channel, to allow the catalyst to diffuse into the (water-swollen) film and promote the crosslinking reaction. In some preferred embodiments, volatile acids or bases (e.g., HCl or NH_3) are employed as catalysts. With these reagents, the crosslinking reaction is initiated by passage of the vapors of the volatile acid or base through the flow channels of the module.

In further preferred embodiments, prepolymers are employed that do not require addition of separate crosslinking agents.

Additional advantages and novel features of this invention will become apparent to those skilled in the art upon examination of the examples thereof provided below, which should not be construed as limiting the appended claims.

EXAMPLE 1

Hydroxypropylmethyl cellulose (Methocel® J75MSN, Dow Chemical Company, Midland, Mich.) was dissolved at a concentration of 1% by weight in a solvent mixture of isopropyl alcohol and water in equivolume proportions to form a clear, viscous coating solution. The coating solution was spread on the surface of a Celgard® 2500 membrane

6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la que *se reivindica prioridad es 24-11-2003, se buscaron documentos del estado de la* técnica relacionados, con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	CO05-110249	5,7-diaminopirazol[4,3-d]piridinas útiles en el tratamiento de la hypertension.	22-04-2004 (fecha presentación internacional)
D2	WO0213798	Treatment of the insulin resistance syndrome	21-02-2002

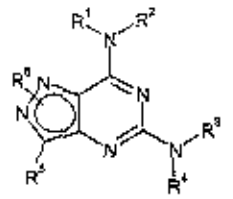
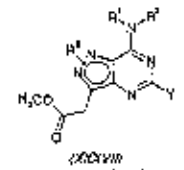
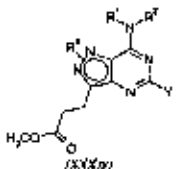
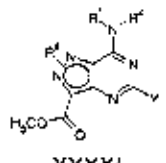
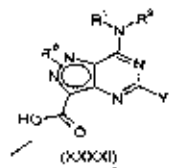
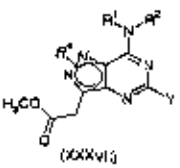
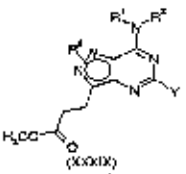
Anterioridad **D1** en folios 744-759 y **D2** en folios 760-764.

7. Análisis de patentabilidad (artículo 14 D486)

7.1 Novedad *(artículo 16 D486)*

- Se solicita en las reivindicaciones 1-55, 57-59 y 73-78un compuesto de fórmula (I), un tautómero o una sal o un solvato farmacéuticamente aceptable de dicho tautómero, en las 56 y 79-84 una composición farmacéuticamente que lo contiene en un vehiculo farmacéuticamente aceptable.

Comparando elemento por elemento la materia solicitada con el estado de la técnica, esta Oficina encuentra que:

SOLICITUD	D1
Un compuesto de formula (I)  (I) Con sustituyentes R^1-R^6 capitulo reivindicatorio.	Compuestos de formula:  (xxxvii) Y: NR^3R^4 (folio (749; pág. 76)  (xxxix) Y: NR^3R^4 (folio (749; pág. 76)  XXXXI Y: NR^3R^4 (folio (750; pág. 78)  (xxxxii) Y: NR^3R^4 *(folio (750; pág. 78)*  (xxxxiii) Y: NR^3R^4 *(folio 750; pág. 78)*  (xxxix) Y: NR^3R^4 *(folio 751; pág. 80)* R^1: igual a R` de solicitud (folios 752-756; pág. 329-333) R^2: igual a R^2 de solicitud (folios 352; pág. 329) R^3 y R^4: igual a R^3 y R^4de solicitud (folios 752-756; pág. 329-333) R^6: igual a R^6 de solicitud (folios 753-756; pág. 329-333)

D1 ya divulga compuestos reclamados bajo la formula (I) tal como se enseña en el cuadro comparativo, en consecuencia éstos compuestos no son nuevos, así como

with a nominal pore size of about 50 nanometers (i.e., 500 Angstroms). Immediately on application of the coating solution, the white, translucent membrane became semitransparent, indicating liquid penetration into the membrane pores. The membrane was then allowed to dry by solvent evaporation in air at about 40° C., whereupon it recovers its original translucent appearance, indicating the removal of liquid from the membrane pores.

When the uncoated membrane was moistened with vegetable oil (a low surface tension liquid), it nearly instantaneously became transparent due to penetration of the oil into the pore spaces. However, when the coated side of the laminate was moistened with the same oil, there was no change in the translucence of the membrane, indicating that the oil had not penetrated into the substrate pores. However, when the reverse side of the laminate was moistened with the same oil, immediate transparency was observed, confirming that the pore space of the membrane had not been obstructed by the coating polymer.

EXAMPLE 2

A Celgard membrane was coated with Methocel® F50LV-SN according to the of Example 1 above. The prepolymer film was crosslinked using Freerez 900 Reactant (sold by Freedom Textile Chemicals Co. located in Charlotte, N.C.), an aqueous solution of a glyoxal-urea adduct which crosslinks hydroxylated polymers like cellulose by forming acetal linkages with vicinal hydroxyls on the polymer. The reaction was accelerated under acidic conditions by Freecat 9® Accelerator (also sold by Freedom Textile Chemicals Co.), which is an aqueous solution of a mixture of magnesium and aluminum chlorides (about 25% solids, pH 3.0).

A dilute solution of the reactant concentrate was prepared by mixing 1 part by volume of concentrate with 3 parts (v/v) distilled water (this solution is shelf stable). Immediately prior to use, approximately 3 ml of the Freecat concentrate was added to 100 ml of the diluted Freerez solution at room temperature, and the resultant solution was mixed well.

A section of dry, Methocel-coated membrane (coating side up) prepared according to the procedure of Example 1) was taped to a glass plate, using waterproof pressure sensitive tape around all edges. Care was exercised to ensure that no liquid could leak under the membrane.

The plate was placed in a shallow glass pan, and sufficient catalyst solution was poured into the pan to cover the coated surface to a depth of about 1/4th of an inch. The pan was covered with either plastic wrap or a plate to prevent evaporation, and placed either on a hot plate set at 50° C., or in a laboratory oven set at the same temperature. After about 1-2 hours the plate was removed from the heat, and allowed to cool and stand (covered) at room temperature overnight.

The plate carrying the membrane was removed from the pan, and washed thoroughly but gently in running tap water for 5-10 minutes. The plate and membrane were then stored vertically and allowed to dry in air at room temperature.

When the membrane was dried, the plate was placed membrane up on a flat surface. Using a small glass rod, 3 or 4 small drops of olive oil (light mineral or vegetable are also suitable) were placed on the coated surface to check the coating. The coating under the oil drops remained translucent like the adjacent area for 30 min at least, indicating that the coating was intact and void free. (Had it rapidly become transparent, it would have indicated that the coating was defective.)

To confirm that the cross-linking procedure had not damaged the coating, the same oil-test was performed with a sample of the uncrosslinked Methocel coated membrane. Had the membrane absorbed the oil, this would have indicated that the initial coating process was inadequate. Had it showed no oil uptake, while the crosslinked coating had done so, it would have indicated that the crosslinking treatment had damaged the coating.

The plate and membrane was submerged in a pan filled with deionized water, and allowed to soak for 12-24 hours at room temperature. The same procedure was performed with an uncrosslinked Methocel-coated membrane.

The plate and membrane were removed from the water, allowed to drain free of liquid, and then allowed to dry in the vertical position at room temperature for 15-20 minutes.

The oil-drop test was repeated as described above. A lack of oil uptake indicated that the coating was adequately crosslinked. Had oil been imbibed (but not prior to the long water-soaking), it would have indicated that the coating was inadequately crosslinked.

EXAMPLE 3

A Celgard membrane was coated with Methocel according to the of Example 1 above. The prepolymer film was crosslinked using Bacote 20 (sold by Magnesium Elektron Ltd. located in Manchester, England), an aqueous solution of ammonium zirconyl carbonate (pH about 9). This compound reacts with the hydroxyl groups of cellulose and other hydroxylated polymers to form a hydroxylated zirconium coordination complex which functions as a stable crosslink. The ammonia and carbon dioxide are eliminated as gases on drying.

A 5% solution of the Bacote reagent was prepared by diluting 1 part of the concentrate with 9 parts chilled, distilled or deionized water. This working solution can be stored in the refrigerator (1-10° C.) for several weeks without deterioration.

A plate-mounted, Methocel-coated membrane sample was prepared as described in Example 2 above. The same pan immersion procedure described above was used for contacting the coated surface with the reagent solution.

The pan and contents were warmed to 40° C. on a hot plate or in an oven, held for about 30 minutes at that temperature, then allowed to cool to room temperature and stand in contact with the solution for 3-4 hours (or overnight). The remaining procedure was identical to that described in Example 2.

The coatings prepared and crosslinked by the procedures of Examples 2 and 3 both remained water-insoluble and intact. Surprisingly, the uncrosslinked Methocel membranes also appeared to be water insoluble and intact. Accordingly, in some preferred embodiments, membranes of the present invention can be prepared by the methods described herein, but without need for a crosslinking step.

EXAMPLE 4

A polymer solution is prepared as described in the previous examples, by adding the Methocel powder to isopropyl alcohol to produce a suspension (the gum being insoluble in the alcohol), and then slowly adding water to the suspension until the solution becomes quite viscous and nearly transparent. The resulting solution appears to be a true solution of the polymer.

When a small amount of additional isopropyl alcohol is added slowly to this solution, the viscosity rapidly drops, and the solution becomes opalescent. This indicates that the dissolved polymer solution has been converted to a colloidal dispersion because of partial polymer-solvent incompatibility. This solution is then used to coat membranes as described in Examples 1-3. The coatings obtained with this solution are at least as good as those obtained with the clear, viscous solution, and possibly even somewhat better. Additionally, this less viscous solution is advantageous in that it is easier to apply, and seems to dry more rapidly.

EXAMPLE 5

The procedures of Examples 1-4 are repeated using acetone as the organic liquid, or an aqueous mixture thereof.

It is intended that each of the patents, applications, and printed publications mentioned or referred to in this specification be herein incorporated by reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

What is claimed is:

1. A method for producing a laminate, the laminate comprising a hydrogel layer bound to a microporous hydrophobic membrane, comprising:
(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer, the coating solution having a viscosity of from about 100 to about 1000 centipoise;
(b) applying the coating solution to one surface of a microporous hydrophobic membrane sheet, or to the external surface of a microporous, hydrophobic hollow fiber membrane to form a coating on the surface;
(c) evaporating the volatile components from the coating;
(d) contacting the coated surface with a solution of a cross-linking agent to crosslink the coated surface and thereby render the coating water-insoluble;
(e) optionally water-washing the crosslinked polymer to remove water soluble components therefrom; and
(f) drying the coating to remove residual moisture, to produce the laminate.

2. The method of claim 1 further comprising repeating steps (a)-(c).

3. The method of claim 1 wherein the prepolymer has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

4. The method of claim 2 wherein the prepolymer in the first step (b) has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane or is dispersed in aggregates that are larger than the pores of the membrane.

5. The method of claim 1 wherein the prepolymer is a cellulose ether or ester, polyvinyl alcohol, polyvinyl alcohol copolymer with vinyl acetate, N-alkyl polyacrylamide, N-alkyl polyacrylamide copolymer with acrylamide, a polyethylene-glycol-based, isocyanate-capped polyurethane, an esterified or etherated polysaccharide, a hydroxyalkylated polyacrylate, a polymethacrylate, or a hydroxyalkylated polymethacrylate.

6. The method of claim 5 wherein the prepolymer is a linear or branched, polyethylene-glycol-based isocyanate capped polyurethane, methylcellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, or a copolymer of vinyl acetate and vinyl alcohol.

7. The method of claim 1 wherein the volatile low surface tension organic liquid is a water soluble lower aliphatic alcohol, a water soluble lower aliphatic ketone, a water soluble lower aliphatic ether, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, mixtures thereof, or aqueous solutions thereof.

8. The method of claim 1 wherein the volatile low surface organic volatile liquid is methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, acetone, methyl ethyl ketone, tetrahydrofuran, dioxane, dimethylformamide, N-methyl pyrrolidinone, mixtures thereof, or aqueous solutions thereof.

9. The method of claim 8 wherein the volatile low surface tension organic liquid is acetone, isopropyl alcohol, or an aqueous mixture thereof.

10. The method of claim 1 wherein said microporous membrane is a polyvinylidene fluoride, polytetrafluoroethylene, polysulfone, polyethylene, or polypropylene membrane.

11. A method comprising the steps of:
(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer, said coating solution having a viscosity of from about 100 to about 1000 centipoise;
(b) providing a microporous hydrophobic sheet membrane or hollow fiber membrane module having a feed-side flow path and a strip-side flow path, and filling the feed-side flow path of the microporous hydrophobic sheet membrane or hollow fiber membrane module with the coating solution;
(c) flowing warm, dry air or other inert gas through the strip-side flow path of the membrane module to evaporate volatile components while continuing to feed coating solution to the feed-side flow path of the module for a time period sufficient to coat the membrane with a preselected thickness of prepolymer to form a coated membrane;
(d) displacing the coating solution from the feed-side flow path;
(e) evaporating remaining volatile components from the coated membrane by flowing a gas through both the feed and strip flow paths of the module;
(f) optionally contacting the polymeric coating with a solution of a crosslinking agent to crosslink the coating of the membrane and thereby render the coating water-insoluble; and
(g) drying the coating to remove residual moisture.

12. The method of claim 11 further comprising repeating steps (a)-(f).

13. The method of claim 11 wherein the prepolymer has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

14. The method of claim 11 wherein the prepolymer in the first step (b) has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

15. The method of claim 11, wherein the prepolymer is a cellulose ether or ester, polyvinyl alcohol, polyvinyl alcohol copolymer with vinyl acetate, N-alkyl polyacrylamide, N-alkyl polyacrylamide copolymer with acrylamide, an isocyanate capped, polyethylene-glycol-based

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
J. IAN RAISBECK

ASUNTO	Radicación	06-47841
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	
	Folios	026

Patente de Invención	X	Patente de Modelo de Utilidad			
Vía Nacional					
Vía PCT (fase nacional)	X	Cap.I		Cap. II	X

No. Sol. Internacional PCT/IB2004/003747
Fecha de Presentación Internal. 12/11/2004

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción:	Folios 293-634 como se radicó inicialmente
Reivindicaciones:	Folios 635-664como se radicó inicialmente
	Folios 698-737 como se radicó el 25-09-2006
Prioridad:	Folio 1 GB, 327319.0, 24-11-2003

2. Objeto de la invención

Título de la solicitud: 5,7-DIAMINOPIRAZOLO[4,3-d]PIRIMIDINAS CON ACTIVIDAD INHIBIDORA DE PDE-5 (folio 1)

El problema técnico planteado en esta solicitud esta relacionado con la necesidad de obtener otros compuestos derivados 5,7-diaminopirazolo[4,3-d]pirimidinas con actividad inhibidora de PDE5, útiles en el trastorno de hipertensión (folio 293; pág. 1).

Para solucionar este problema técnico la solicitud en estudio proporciona en: Reivindicaciones 1-55, 57-59 y 73-78: un compuesto de fórmula (I), un tautómero o una sal o un solvato farmacéuticamente aceptable de dicho tautómero.

polyurethane, an esterified or etherated polysaccharide, a hydroxyalkylated polyacrylate, a polymethacrylate, or a hydroxyalkylated polymethacrylate.

16. The method of claim 15 wherein the prepolymer is a linear or branched polyethylene glycol-based isocyanate capped polyurethane, cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, or copolymers of vinyl acetate and vinyl alcohol.

17. The method of claim 12 wherein the volatile low surface tension organic liquid is a water-soluble lower aliphatic alcohol, a water-soluble lower aliphatic ketone, a water-soluble lower aliphatic ether, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, mixtures thereof, or aqueous solutions thereof.

18. The method of claim 17 wherein the volatile low surface tension organic liquid is methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, acetone, methyl ethylketone, tetrahydrofuran, dioxane, dimethyl formamide, N-methyl pyrrolidinone, mixtures thereof, or aqueous solutions thereof.

19. The method of claim 18 wherein the volatile low surface tension organic liquid is acetone, isopropyl alcohol, or an aqueous mixture thereof.

20. The method of claim 11 wherein the microporous membrane is a polyvinylidene fluoride, polytetrafluoroethylene, polysulfone, polyethylene, or polypropylene membrane.

21. The method of claim 11 wherein the microporous hydrophobic sheet membrane or hollow fiber membrane module is provided by cleaning a sheet-microporous membrane or a membrane laminate module which has a damaged hydrogel layer.

22. A method for producing a laminate, the laminate comprising a hydrogel layer bound to a microporous hydrophobic membrane, comprising:

(a) dissolving one or more cellulose polymers selected from the group consisting of methyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose in a volatile, low surface tension organic liquid, or an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution, the cellulose polymer having high methoxyl content, and/or high ratio of methyl to hydroxypropyl substitution;

(b) applying the coating solution to the surface of a sheet or hollow fiber microporous hydrophobic membrane;

(c) evaporating volatile components from the coating;

(d) optionally washing the membrane; and

(e) drying the polymer to remove residual moisture to produce the laminate.

23. The method of claim 22 wherein the prepolymer has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane.

24. The method of claim 23 wherein the prepolymer is a hydroxypropylmethyl cellulose.

25. The method of claim 22 wherein the volatile low surface tension organic liquid is a water-soluble lower aliphatic alcohol, a water-soluble lower aliphatic ketone, a water-soluble lower aliphatic ether, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, mixtures thereof, or aqueous solutions thereof.

26. The method of claim 25 wherein the volatile low surface tension organic liquid is methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, acetone, methyl ethylketone, tetrahydrofuran, dioxane, dimethyl formamide, N-methyl pyrrolidinone, mixtures thereof, or aqueous solutions thereof.

27. The method of claim 26 wherein the volatile low surface tension organic liquid is acetone, isopropyl alcohol, or an aqueous mixture thereof.

28. The method of claim 22 wherein the microporous membrane is a polyvinylidene fluoride, polytetrafluoroethylene, polysulfone, polyethylene, or polypropylene membrane.

29. A method comprising the steps of:

(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer, said coating solution having a viscosity of from about 100 to about 1000 centipoise;

(b) feeding the coating solution to the feed-side flow channel of a sheet- or hollow-fiber microporous hydrophobic membrane module in sufficient quantity and at a sufficient rate to form a polymer coating on the membrane surface of a preselected thickness, while simultaneously passing an inert gas to the strip-side of the module to evaporate volatile components;

(c) evaporating residual volatile components from the polymer coating on the membrane surface by flowing a gas through both the feed and strip channels of the coated module;

(d) optionally contacting the polymer coating on the surface of the membrane with a solution of a crosslinking agent capable of crosslinking the polymeric coating to crosslink the polymeric coating and thereby render the polymeric coating water insoluble; and

(e) drying the coating to remove residual moisture.

30. The method of claim 29 further comprising repeating steps (a)–(d).

31. The method of claim 29 wherein the prepolymer has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

32. The method of claim 29 wherein the prepolymer in the first step (b) has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

33. The method of claim 29 wherein the prepolymer is a cellulose ether or ester, polyvinyl alcohol, polyvinyl alcohol copolymer with vinyl acetate, N-alkyl polyacrylamide, N-alkyl polyacrylamide copolymer with acrylamide, an isocyanate-capped, polyethylene glycol based polyurethane, an esterified or etherated polysaccharide, a hydroxyalkylated polyacrylate, a polymethacrylate or a hydroxyalkylated polymethacrylate.

34. The method of claim 33 wherein the prepolymer is a linear or branched polyethylene glycol based isocyanate capped polyurethane, methylcellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, or copolymers of vinyl acetate and vinyl alcohol.

35. The method of claim 29 wherein the volatile low surface tension organic liquid is a water-soluble lower aliphatic alcohol, a water-soluble lower aliphatic ketone, a water-soluble lower aliphatic ether, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, mixtures thereof, or aqueous solutions thereof.

36. The method of claim 35 wherein the volatile low surface tension organic liquid is methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, acetone, methyl ethylketone, tetrahydrofuran, dioxane, dimethyl formamide, N-methyl pyrrolidinone, mixtures thereof, or aqueous solutions thereof.

37. The method of claim 36 wherein the volatile low surface tension organic liquid is acetone, isopropyl alcohol, or an aqueous mixture thereof.

38. The method of claim 29 wherein said microporous membrane is a polyvinylidene fluoride, polytetrafluoroethylene, polysulfone, polyethylene, or polypropylene membrane.

39. The method of claim 29 wherein the sheet-microporous membrane or a membrane laminate module is provided by cleaning a sheet-microporous membrane laminate or a membrane laminate module that has a damaged hydrogel layer.

40. A method for producing a laminate, the laminate comprising a hydrogel layer bound to a microporous hydrophobic membrane, comprising the steps of:

(a) dissolving or dispersing one or more hydrophilic prepolymers in a volatile, low surface tension organic liquid, or in an aqueous mixture of a volatile, low surface tension organic liquid, to produce a coating solution of the prepolymer, said coating solution having a viscosity of from about 100 to about 1000 centipoise;

(b) applying the coating solution to one surface of a sheet- or hollow fiber microporous hydrophobic membrane, or to the surface of a woven fabric containing microporous hydrophobic hollow fiber membranes to form a polymeric coating thereon;

(c) evaporating the volatile low surface tension organic liquid from the coating;

(d) optionally contacting the polymer coating on the surface of the membrane with a solution of a crosslinking agent capable of crosslinking the polymeric coating to crosslink the polymeric coating and thereby render the polymeric coating water insoluble; and

(e) drying the polymer to remove residual moisture.

41. The method of claim 40 further comprising repeating steps (a)–(d).

42. The method of claim 40 wherein the prepolymer has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

43. The method of claim 40 wherein the prepolymer in the first step (b) has a molecular weight sufficiently high to prevent entry of the prepolymer into the pores of the microporous membrane, or is dispersed in aggregates that are larger than the pores of the membrane.

44. The method of claim 40 wherein the prepolymer is a cellulose ether or ester, polyvinyl alcohol, polyvinyl alcohol copolymer with vinyl acetate, N-alkyl polyacrylamide, N-alkyl polyacrylamide copolymer with acrylamide, an isocyanate-capped, polyethylene-glycol-based polyurethane, an esterified or etherated polysaccharide, a hydroxyalkylated polyacrylate, a polymethacrylate or a hydroxyalkylated polymethacrylate.

45. The method of claim 44 wherein the prepolymer is a linear or branched polyethylene-glycol-based isocyanate capped polyurethane, cellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, or copolymers of vinyl acetate and vinyl alcohol.

46. The method of claim 40 wherein the volatile low surface tension organic liquid is a water-soluble lower aliphatic alcohol, a water-soluble lower aliphatic ketone, a water-soluble lower aliphatic ether, acetonitrile, N-methyl pyrrolidinone, methyl cellosolve, mixtures thereof, or aqueous solutions thereof.

47. The method of claim 46 wherein the volatile low surface tension organic liquid is methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, acetone, methyl ethylketone, tetrahydrofuran, dioxane, dimethyl formamide, N-methyl pyrrolidinone, mixtures thereof, or aqueous solutions thereof.

48. The method of claim 47 wherein the volatile low surface tension organic liquid is acetone, isopropyl alcohol, or an aqueous mixture thereof.

49. The method of claim 40 wherein said microporous membrane is a polyvinylidene fluoride, polytetrafluoroethylene, polysulfone, polyethylene, or polypropylene membrane.

50. The method of claim 40 wherein the sheet-microporous membrane or a membrane laminate module is obtained by cleaning a sheet microporous membrane laminate or a membrane laminate module that has a damaged hydrogel layer.

51. The laminate produced by the method of claim 1.

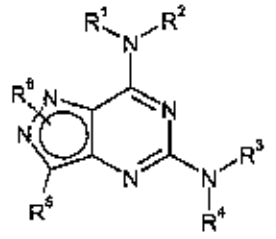
52. The laminate produced by the method of claim 4.

53. The laminate produced by the method of claim 11.

54. The laminate produced by the method of claim 29.

55. The laminate produced by the method of claim 40.

* * * * *



(I)

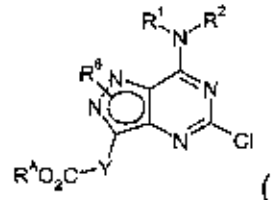
Reivindicación 56 y 79-84: una composición farmacéutica que comprende un compuesto de formula (I) y un diluyente o vehículo farmacéuticamente aceptable.

Reivindicación 66: una composición farmacéutica que comprende un compuesto de formula (I) y un segundo agente activo seleccionado de un listado dado de varios grupos farmacológicos.

Reivindicación 60: relacionado con un método de tratamiento.

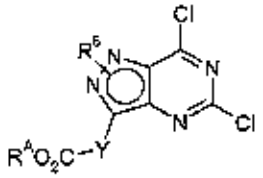
Reivindicaciones 61-65 y 67-68: uso de un compuesto de formula (I).

Reivindicaciones 69-70: un compuesto de formula (III) (intermediario)



(III)

Reivindicación 71-72: compuestos de formula (V) (intermediario)



(V)

Clasificación Internacional de Patentes (IPC): C07D487/04, A61K31/505, A61P9//08.

3. De la solicitud de Patente

3.1. Reivindicaciones *(artículo 30 D 486)*

- Se solicita en las reivindicaciones 1-55, 57-59 y 73-78un compuesto de fórmula (I), un tautómero o una sal o un solvato farmacéuticamente aceptable de dicho tautómero, con radicales R^1- R^6. No obstante, se encuentra que existe falta de claridad, concisión y sustento de la materia solicitada, al examinar los sustituyentes, los compuestos ejemplificados con actividad como inhibidores de PDE5.

- No existe sustento de ningún solvato de un compuesto de formula (I) en la descripción.

United States Patent [19]

Gore et al.

[11] 4,194,041

[45] Mar. 18, 1980

[54] WATERPROOF LAMINATE

[75] Inventors: Robert W. Gore, Hockessin; Samuel B. Allen, Jr., Newark, both of Del.

[73] Assignee: W. L. Gore & Associates, Inc., Newark, Del.

[21] Appl. No.: 920,275

[22] Filed: Jun. 29, 1978

[51] Int. Cl.[2] A41B 17/00; A41D 3/04; B32B 27/40; B32B 27/28

[52] U.S. Cl. 428/315; 2/82; 2/87; 2/135; 2/DIG. 1; 2/DIG. 5; 264/127; 428/321; 428/422; 428/513; 428/516; 428/523; 428/423.1

[58] Field of Search ..... 428/424, 425, 422, 310, 428/315, 321, 322, 421, 513, 516, 523; 2/DIG. 1, DIG. 5, 82, 87, 89, 135; 264/127

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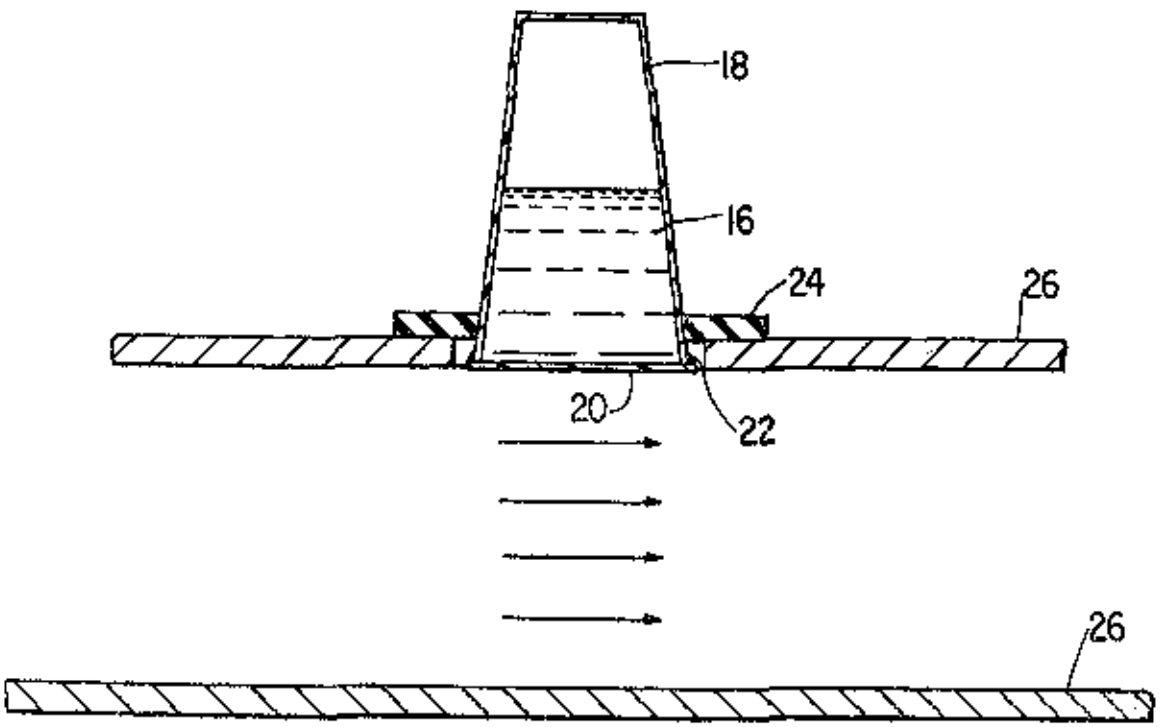
Attorney, Agent, or Firm—John S. Campbell

[57] ABSTRACT

A waterproof article for use in, for example, protective clothing. The article prevents liquid water from penetrating through to undergarments while at the same time permitting moisture vapor such as perspiration to pass out through the article. The article is thus both breathable and waterproof. The article is layered: a microporous hydrophobic outer layer which permits the passage of moisture vapor but resists penetration by liquid water at pressures up to about 345 Kn/m^2; a hyrophilic inner layer permitting the transfer of moisture vapor but preventing surface tension lowering agents such as those contained in perspiration and/or body oils from reaching the hydrophobic layer.

28 Claims, 4 Drawing Figures



WATERPROOF LAMINATE

FIELD OF THE INVENTION

This invention relates to [redacted]os [redacted]. The article is suitable for use in rainwear garments and tents.

BACKGROUND OF THE INVENTION

Protective garments for wear in rain and other wet conditions should keep the wearer dry by preventing the leakage of water into the garment and by allowing perspiration to evaporate from the wearer to the atmosphere. In the past, and through a long history of rainwear development, truly waterproof materials have not allowed the evaporation of perspiration, so that a wearer who is physically active, becomes sweat soaked. "Breathable" materials that do permit evaporation of perspiration, have tended to wet through from the rain, and they are not truly waterproof. Oilskins, polyurethane coated fabrics, polyvinyl chloride films and other materials are waterproof but do not allow satisfactory evaporation of perspiration.

Fabrics treated with silicone, fluorocarbon, and other water repellants usually allow evaporation of perspiration but are only marginally waterproof; they allow water to leak through them under very low pressures, and usually leak spontaneously when rubbed or mechanically flexed. Rain garments must withstand the impingement pressure of falling and wind blown rain and the pressures that are generated in folds and creases in the garment.

It is widely recognized that garments must be "breathable" to be comfortable. However, it is not necessary that air pass through the garment for it to be comfortable, only that water vapor from perspiration be transmitted from inside to outside so that undergarments do not become wet and so that the natural evaporative cooling effect can be achieved. Breathability and ability to transport interior moisture vapor to the external environment are used interchangeably in this discussion.

The transport of water through a layer can be achieved in a number of ways. Wicking is the most common when large quantities of moisture are to be transferred. Wicking materials are hydrophilic in that a drop of water placed on the surface of these materials forms an advancing water contact angle of less than 90 degrees so that they wet spontaneously. They are also porous with pores that interconnect to make complete pathways through the wicking material. Liquid water moves by capillary action from interior surface to exterior surface where it evaporates. Although some wicking materials may resist pressure induced flow of liquid water through them due to the tortuosity and length of flow path, they readily transport water by capillary action from the exterior surface to the interior surface and so are unsuitable for rain material. The comfort attributed to cotton garments in warm climates results from its ability to transport water to the exterior surface where it can readily evaporate and provide cooling. Another natural wicking material is leather which owes its great comfort to breathability via wicking.

A recent invention (U.S. Pat. No. 3,953,566) has provided porous membranes that satisfy the two comfort requirements of being waterproof while also being permeable to the flow of water vapor. For rainwear, these membranes are usually laminated to fabrics for mechanical protection and style. The membranes are inherently hydrophobic and contain very small pores that resist the entry of liquid water even at substantial pressures or when rubbed or flexed, but readily allow the flow of gases, including water vapor. Unlike wicking materials, breathability is achieved by evaporation of liquid water inside the garment or on the inner surface of the membrane followed by gaseous flow or diffusion of water vapor through the membrane to the outside.

However, when these new garments are worn for strenuous activities causing the wearer to perspire copiously, surface active agents in the perspiration gradually penetrate the hydrophobic membrane, coat its interior surfaces and cause it to lose its waterproof characteristics and become a wicking material. In order to restore waterproofness, the garment must be cleaned to remove the surface active contaminates. In practice this is a drawback to widespread commercial acceptance of such garments.

BRIEF DESCRIPTION OF THE INVENTION

This invention provides a layered article, for use in waterproof garments or tents, that is waterproof, resistant to surface active agents in perspiration, but still permits the evaporation of the perspiration and the transfer of moisture vapor through the layered article.

The invention comprises a combination of at least two layers: (1) [redacted] that readily allows water to diffuse through, prevents the transport of surface active agents and contaminating substances such as those found in perspiration, and is substantially resistant to pressure induced flow of liquid water, and (2) [redacted] that permits the transmission of water vapor and provides thermal insulating properties even when exposed to rain.

Garments made of these materials are permanently waterproof from exterior water sources yet allow the evaporation of perspiration whenever the partial pressure of water vapor inside the garment exceeds that outside. In practice this encompasses nearly all climatic conditions.

The hydrophilic film has a moisture vapor transmission rate exceeding 1000 gms./m^2 day, and preferably above about 2000 gms./m^2. day, permits no detectable transmission of surface active agents and preferably permits no detectable flow of liquid water at hydrostatic pressures up to 172 kN/M^2.

The hydrophobic layer has a moisture vapor transmission rate exceeding 1000 gms./m^2. day and preferably exceeding 2000 gms./m^2. day, and an advancing water contact angle exceeding 90 degrees, and is preferably formed of a porous hydrophobic polymer.

DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the apparatus for determining Moisture Vapor Transmission Rate (MVTR) as described in ASTM-E96-66B.

FIG. 2 shows the modified test configuration used to bring water 16 directly in contact with the surface of the test material 20.

FIG. 3 shows the test apparatus for the 25 cm water head waterproofness test.

FIG. 4 shows the Mullin's Burst Test apparatus used in the 172 kN/M^2 and 345 kN/M^2 waterproofness tests.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

Breathability is achieved in this invention by transport of water by diffusion. The driving force for this mechanism of transfer is the water vapor partial pressure difference across the layered article.

An interior layer of the layered article of this invention is a continuous hydrophilic layer. The term "hydrophilic" has been used by others in reference to several different characteristics of materials, which include the following:

(1) Materials that absorb substantial amounts of water when immersed in it.

(2) Materials that absorb moisture from the atmosphere.

(3) Porous materials that wet through easily when brought in contact with water.

(4) Porous materials that absorb water into their structure when brought in contact with it.

(5) Materials that have surfaces easily wet with water.

(6) Materials that are permeable to water vapor.

The term "Hydrophilic film" used in this invention is restricted to continuous films, including closed cell, foamed film. These films do not allow the flow of gases or liquids through open pore channels in the materials but do transfer substantial amounts of water through the film by absorbing water on one side of the film where the water vapor concentration is high, and desorbing or evaporating it on the opposite side of the film where the water vapor concentration is low.

If a continuous film of hydrophilic material is exposed to air containing substantial water vapor on one side of the film, and to air containing less water vapor on the other side, the side of the film exposed to the higher water vapor concentration will absorb water molecules which diffuse through the film and are desorbed or evaporated on the side exposed to the lower water vapor concentration. [redacted]cale by [redacted]. The hydrophilic materials of this invention do not necessarily have hydrophilic surface characteristics as indicated by advancing water contact angle. In fact, the two specific examples cited here as suitable hydrophilic materials have advancing water contact angles exceeding 90 degrees and may be considered hydrophobic from that point of view.

The hydrophilic materials of this invention are selective in absorbing and transporting water and not surface active agents and organic materials generally, nor do they allow gases such as oxygen and nitrogen to flow through them readily under hydrostatic pressure. They are also resistant to hydraulic flow of liquids, including water. These continuous, hydrophilic films are unique in transporting water solely by the absorption evaporation mechanism. They do not transfer water by capillary action or by wicking. Water molecules are not believed to be transferred in association with other water molecules as with normal hydraulic and capillary flows. [redacted]ission [redacted] supported hydrophilic films tend to be weak and easily torn, especially when swollen with water. Therefore, they need to be supported and protected by physically strong, flexible, abrasion resistant coverings that are permeable to the passage of water vapor. If the outer covering of a garment is not hydrophobic, it will become wet through by rain, and thus allow the hydrophilic film to chill.

The hydrophilic layer cannot be porous in the sense that there are passageways larger than molecular size. Still it can be a foam so long as the foam is not open celled. Somewhere there must be a continuous barrier layer to the passage of surface active molecules. One of the preferred hydrophilic materials is a foam.

Two commercially available hydrophilic materials have been found that embody the requisite properties of this invention. One is an organic polymer with a hydrophilic backbone sold under the trademark Hypol ® by W. R. Grace & Co. Hypol ® is a reactive prepolymer that can be crosslinked by water and/or multifunctional amines, including blocked carbamate amines. Hypol has a backbone of polyoxyethylene units which end with toluene diisocyanate groups. The structure is essentially a branched polyether with a maximum of three reactive isocyanate (NCO) groups per molecule. [redacted] by E. I. duPont de Nemours & Co. Nafion ® is a perfluorosulfonic acid product. It is described as a copolymer of tetrafluoroethylene and a monomer such as perfluoro 3, 6-dioxa-4methyl-7-octenesulfonic acid.

Because of the great chemical difference of these hydrophilic polymers, it is believed there are additional suitable hydrophilic materials that could be useful.

[redacted]t of [redacted]o [redacted]. Hydrophobic, as used here, means that water will not spread on the material and wick into its porous structure. A drop of water placed on the surface of a highly hydrophobic layer will remain in the form of a nearly spherical bead with an advancing water contact angle greater than 90 degrees. Water vapor which evaporates or desorbs from the inner hydrophilic layer is free to flow or diffuse as a gas through the pores of the hydrophobic layer to the exterior environment.

Where the external relative humidity is 100% as it may be in raining conditions, a favorable vapor pressure differential can only be achieved when the inside temperature is higher than outside. For this reason, it is desirable to have an insulating layer outside the hydrophilic layer. This steepens the thermal gradient produced by body heat, increases the vapor pressure difference (presuming 100% relative humidity inside), and thus increases the moisture vapor transmission rate. If the inside surface of the garment is too cool, perspiration vapor will condense on the cool surface and wet the clothing and person within.

It is undesirable for the outer layer to lose most of its thermal insulating properties when it becomes wet with rain. [redacted]. It is preferred that this layer be waterproof at water pressures exceeding 172kN/M^2 so as to retain its thermal insulating properties and not become wet even when it is subjected to high velocity wind blown rain, and/or mechanical flexing and rubbing. A film of porous, expanded polytetrafluoroethylene, which has been heated above its crystalline melt point after expansion, has been found to be an ideal hydrophobic layer for rainwear applications. These films are highly porous, a property which gives them good thermal insulating qualities, yet the pores are very small in size which leads to high water entry pressures. This

4. Inventive Step – Article 56 EPC

Documents D1 to D6 and D9 were opposed to inventive step of the claimed invention. Applicant respectfully submits that D5 is not prior art for the assessment of inventive step since it is an PCT application designating EP which was filed before but published after the priority date of the invention. D5 is therefore not considered here.

That requirement is met here. The application provides ample information showing that the claimed prodrugs rearrange into active compounds. In particular, the prodrugs convert readily to HEA drugs under physiological conditions, as can be

porous material allows water vapor to diffuse from a zone of relatively high water vapor pressure inside a warm rainwear garment to a zone of lower water vapor pressure at the colder outside. U.S. Pat. No. 3,953,566 describes the preparation of the desirable microporous, expanded, polytetrafluoroethylene hydrophobic films.

Other hydrophobic materials for use in the outer layer include highly crystalline films of expanded PTFE, which have not been heated above their crystalline melt point, and films of other microporous hydrophobic polymers such as polypropylene, which possess the necessary moisture vapor transmission and waterproofness characteristics. Celanese Plastics Co. sells such a microporous polypropylene film under the trademark Celgard®. Other hydrophobic layers, which are less useful for their insulating properties because water wets through them at lower pressures, are still useful. [illegible] woven fabrics of fine hydrophobic fibers including polyolefin fibers such as polyethylene and polypropylene, polytetrafluoroethylene fibers, and other fibers treated with hydrophobic agents. Also, tightly spaced nonwoven webs of the above described fibers may be useful.

Hydrophilic and hydrophobic layers [illegible]ched [illegible] procedures. Edges of the layers can be attached, for example, by sewing or by an adhesive. Alternately, an adhesive can be applied to join other portions of the surface area of the two layers. This technique may reduce somewhat the area available for transmission of water vapor, but most of the area remains.

Another technique which can be used is to cast a hydrophilic layer directly on a microporous hydrophobic layer with the application of sufficient hydraulic pressure to force the hydrophilic polymer to penetrate into the surface void spaces of the hydrophobic layer and thereby bond the hydrophilic layer to the hydrophobic layer.

The novel layered article of this invention can be usefully incorporated into a variety of laminar combinations. Textile layers can be added for strength and aesthetic characteristics to both the hydrophilic layer and the hydrophobic layer, so that these two necessary layers are sandwiched in the middle and there is a total of four layers. For example, in applications such as rainwear and mountaineering equipment, it is desirable to provide an outer layer of a textile fabric, such as nylon or polyester, adjacent to the hydrophobic layer, and an inner layer of another textile fabric, such as a nylon tricot knit, adjacent to the hydrophilic layer for wear resistance and to provide the composite with a typical textile feel and hand. For down jackets and sleeping bag shells, a textile layer positioned adjacent the interior of the hydrophilic layer is not needed.

The moisture vapor transmission rate through the layered article of the invention should be above 1000 and is preferably above 2000 gms./m². day to provide for escape of moisture from the interior of an enclosure formed by the article. These extremely high levels of moisture vapor transmission can be achieved, even when the hydrophobic layer and hydrophilic layer are adhesively bonded together over dotted portions of the area of the sheets.

The individual layers and the assembled layered article should be flexible, and preferably soft and pliable, if the article is to be used in garments such as rain suits, or in tents, sleeping bag covers and the like. One significant advantage of the present invention is that water-

proofness and moisture vapor transmission can be achieved with a lightweight construction, and thus the sheet material is desirable for use in outer garments, tents and other uses by backpackers, mountain climbers and others who desire lightweight equipment.

Finally, this invention provides material suitable for truly all-weather garments, not just rain garments. Because these layered articles are impermeable to air, they make excellent windbreakers. They also provide sufficiently high moisture vapor transmission rates to allow men to survive desert conditions whereas garments which are impervious to moisture vapor transport allow no cooling effect and quickly lead to heat exhaustion by the wearer.

The following examples illustrate embodiments of the invention. All parts and percentages are by weight, unless otherwise noted.

A. The tests used in the examples are:

1. Tests For Waterproofness

The only true test for waterproofness is actual use where there is mechanical stress, flexing, rubbing, temperature cycling and the possibility of contamination by a myriad of substances. In order to provide a means of comparison in the laboratory, the following two tests were used. The first used a modified Suter's test apparatus. FIG. 3 is a schematic diagram of this apparatus. Water 40, under a hydrostatic head of 25 cm water is forced against a sample 42 sealed by two silicone rubber gaskets 44 between a container 46 with a clear plexiglass top 48. The top 48 and container 46 being forced together by clamps. The top 48 has a 1/32" air vent 50. The 25 cm water head corresponds to a test pressure on the sample of about 2 KN/M². The upper surface 52 of the sample 42 is visually observed for the appearance of any water which may be forced through the sample. It should be noted that a reasonably long time period is required at the test for leakage to be detected, especially for microporous materials where the water flow is slowed by the small, often tortuous flow channels. If no water is detected after 20 minutes, the material has passed this test for waterproofness. Passing this test is considered to be a very minimum criteria for a material to be considered waterproof.

The second laboratory test method utilizes apparatus employed in the Mullin's Burst Test (Fed. Std. 191, Method 5512) and is shown schematically in FIG. 4. The test procedure consists of raising the pressure of water 60 to the test level over a period of approximately 10 seconds, holding the pressure at that level for 30 seconds, and visually determining leakage as in the previous test. The water pressure is raised by forcing water 60 from a cylinder 62 by means of a piston 64 into a cylindrical container 66. The sample 68 is held above container 66 by clamping on a top of annular ring 70. The pressure is shown on gauge 74.

A metal screen 72 is placed on top of the test sample to prevent it from bursting at elevated test pressures. A test pressure level of 172 kN/M² level has been used by the U.S. Army as an acceptance level of waterproofness for their waterproof garments. Their test method, however, differs in that the pressure is continually increased until leakage is observed. This procedure can yield misleading and overly favorable results when used on microporous materials. The better procedure of maintaining the pressure at a pre-determined level for a fixed time is used to obtain the values reported herein. 2. Test For Air Permeability

The permeability to air of the samples was measured by a Gurley densometer (ASTM D72658) manufactured by W. & L. E. Gurley & Sons. Results are reported in terms of Gurley number which is the time in seconds for 100 cm of air to pass through one square inch of the sample under a pressure of 4.88" of water head pressure. This measurement can be converted into metric permeability units (cm³cm/sec. cm²cm Hg) by the following formula: thickness of sample×0.0432/Gurley number.

3. Test Method For MVTR

The test apparatus for determining moisture vapor transmission rates (MVTR), as described in ASTM-E96-B 66B, is shown in FIG. 1. This method is not suitable for determining the very high MVTR of materials described in this invention because the air gap between the surface 10 of the water 12 and the material 14 to be tested is itself a significant resistance to the passage of water vapor. This stagnant air gap has an estimated MVTR of about 900 gms./m². day which establishes the upper limit of MVTR that can be detected with this test configuration.

For the high MVTR materials of this invention which are also waterproof, a modified test configuration has been used in which the air gap is eliminated by inverting the cup to bring the water directly in contact with the surface of the test material (FIG. 2).

The procedure is as follows. Approximately 80 cc of water 16 is placed in a tapered polypropylene cup 18 which is 4.5 inches high with a 2.5" diameter mouth. The material 20 to be tested is sealed to the lip of the cup with a silicone adhesive 22. The cup assembly is weighed to the nearest 1/100 gram and an elastic rubber collar 24 is placed on the cup under tension. In an environmental chamber 26, the assembly is suspended upside down through a circular opening in a support plate, its position being adjusted by means of the rubber collar so that the mouth of the cup is aligned with the lower surface of the plate. Between this surface and the bottom of the chamber there is an approximately 4" air space across which air is caused to flow at about 650 ft./min. The chamber is held at a temperature of 73 degrees F.±2 degrees F. and a relative humidity of 50%±2%. The sample remains in the chamber for three hours and is then removed and weighed again to within 1/100 of a gram. The moisture vapor rate is then expressed in grams of water lost per square meter of sample surface area per 24 hours.

EXAMPLE I

Human perspiration was collected by wringing a sweat soaked garment. 25 ml was placed in a cup for the moisture vapor transmission rate test. A GORE-TEX® microporous PTFE membrane, which had been tested to determine that it was waterproof when subjected to tests at 25 cm water head, and at 172 kN/M² and 345 kN/M² water pressure, was sealed onto the lip of the test cup.

The cup was inverted and left inverted under ambient conditions until all the perspiration had evaporated through the Gore-tex® membrane, a period of about two days.

The naturally white membrane now appeared brown and visibly contaminated on both sides. The dry, contaminated membrane showed a weight gain of 0.265 gm. due to residual contamination in and on it.

The contaminated membrane was pressure tested at a 25 cm head of water and found to leak almost immediately in one spot and was visibly leaking over its entire surface in three to four minutes.

When the membrane was subjected to the 172 kN/M² test, water flowed through it profusely.

EXAMPLE II

Hypol FHP3000® foamable hydrophilic polyurethane polymer was cast about 0.0025 inch thick onto a Gore-tex® PTFE membrane, which was used in this case only as a release sheet. The sample was also covered with a Gore-tex® membrane release sheet. Care was taken not to rub the Hypol polymer such that adhesion occurred. The Hypol® polymer and release sheets were placed in a humidity chamber at 96% relative humidity and cured for one hour. After curing a Hypol® film was removed from the release sheet.

Water reacts to crosslink the Hypol® polymer. If water is introduced quickly or at an elevated temperature, foaming occurs. In a high humidity chamber at ambient temperature, water is introduced slowly enough that a nonporous cured film is obtained.

A sample of Hypol® film prepared above was tested for moisture transmission rate in the inverted cup test and found to have a value of 11,575 gms./m². day. Another sample of film was tested for air permeability in a Gurleyometer and found to have no permeability within the testing capability. A further sample of the film was tested for waterproofness at 25 cm head water pressure for 20 minutes and at 172 kN/M² for 30 seconds and no leaks were detected.

25 ml of human perspiration from the same source as was used in Example I was placed in a moisture vapor test cup and covered first with the Hypol® membrane and then with the Gore-tex® membrane similar to that used in Example I. The edges were sealed and the cup was inverted. The perspiration was allowed to evaporate as in Example I. After the perspiration had evaporated, the Gore-tex® membrane did not appear to be contaminated, and it did not have a measurable weight increase. However, the Hypol® membrane was stained and covered with residue from the perspiration on the side that had been in contact with perspiration.

When the Gore-tex® membrane was tested for waterproofness in the standard ways at 25 cm head of water and at 172 kN/M² for 30 seconds, it did not leak, indicating that it had not been contaminated. When the Hypol® film was tested for waterproofness, it also did not leak at either test condition. The Gore-tex® membrane was then tested at 172 kN/M² for 20 minutes and did not leak. When the Hypol® membrane was tested at this condition, there was no gross leakage, but there was detectable moisture having penetrated through the membrane.

EXAMPLE III

A 0.0025" film of Hypol FHP3000® prepolymer was cast on a Gore-tex® microporous PTFE sheet similar to that used in Example I. The Hypol® prepolymer was then uniformly sprayed with water. The reacting liquid was massaged by hand over the surface of the Gore-tex® sheet until the curing reaction had proceeded far enough for the Hypol polymer to be viscous and tacky. The sample was placed in a humidity chamber at 96% relative humidity for 30 minutes to effect a complete cure. The composite sheet had a thickness of 0.008" and an MVTR of 7,300 gms./m². day. The sample was waterproof under both standard tests,

porous material allows water vapor to diffuse from a zone of relatively high water vapor pressure inside a water-rainwear garment to a zone of lower water vapor pressure at the colder outside. U.S. Pat. No. 3,953,566 describes the preparation of the desirable microporous expanded, polytetrafluoroethylene hydrophobic films.

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Hydrophilic and hydrophobic layers can be attached using a variety of presently known methods. Edges of the layers can be attached, for example, by sewing or by an adhesive. Alternately, an adhesive can be applied to join other portions of the surface area of the two layers. This technique may reduce somewhat the area available for transmission of water vapor, but most of the area remains.

Another technique which can be used is to cast a hydrophilic layer directly on a microporous hydrophobic layer with the application of sufficient hydraulic pressure to force the hydrophilic polymer to penetrate into the surface void spaces of the hydrophobic layer and thereby bond the hydrophilic layer to the hydrophobic layer.

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The moisture vapor transmission rate through the layered article of the invention should be above 1000 and is preferably above 2000 gms./m², day to provide for escape of moisture from the interior of enclosures formed by the article. These extremely high levels of moisture vapor transmission can be achieved, even when the hydrophobic layer and hydrophilic layer are adhesively bonded together over dotted portions of the area of the sheets.

The individual layers and the assembled layered article should be flexible, and preferably soft and pliable, if the article is to be used in garments such as rain suits, or in tents, sleeping bag covers and the like. One significant advantage of the present invention is that waterproofness and moisture vapor transmission can be achieved with a lightweight construction, and thus the sheet material is desirable for use in outer garments, tents and other uses by backpackers, mountain climbers and others who desire lightweight equipment.

Finally, this invention provides materials suitable for truly all-weather garments, or rain garments. Because these layered articles are moisture vapor permeable to air, they make excellent windbreakers. They also provide sufficiently high moisture vapor transmission rates to allow men, in sunbelt desert conditions wherein garments which are impervious to moisture vapor transport allow no cooling effect and quickly lead to heat exhaustion by the wearer. [0]

The following examples illustrate embodiments of the invention. All parts and percentages are by weight, unless otherwise noted.

A) The tests used in the examples are:

1. Test For Waterproofness

The only true test for waterproofness is actual use where there is mechanical stress & flexing, rubbing, temperature cycling and the possibility of contamination by a myriad of substances. In order to provide a means of comparison in the laboratory, the following two tests were used. The first uses a modified Suter test apparatus (FIG. 3) in a schematic diagram of the apparatus. Water 48, under a hydrostatic head of 25 cm water is forced against a sample 42 sealed with gaskets of silicone rubber gaskets 44 between a container 46 with a clear plexiglass top 45. The top 45 has a 1/32" air escape 49. The 25 cm water head corresponds to a test pressure on the sample of about 2 KN/M². The upper surface 47 of the sample 42 is visually observed for the appearance of any water which may be forced through the sample. It should be noted that a reasonably long time period, required at the test for leakage to be detected, especially for microporous materials which the water flow is caused by the small, often tortuous flow channels. If no water is detected after 20 minutes, the material has passed this test for waterproofness. Passing this test is considered to be a very minimal criteria for a material to be considered waterproof.

The second laboratory test method utilizes apparatus employed in the Mullins Burst-Test (Fed. Std. 191, Method 5512) and is known schematically in FIG. 4. The test procedure consists of raising the pressure of water 60 to the test level over a period of approximately 10 seconds, holding the pressure at that level for 50 seconds, and visually determining leakage as in the previous test. The water pressure is raised by forcing water 60 from a cylinder 62 by means of a piston 64 into a cylindrical container 66. The sample 68 is held above container 66 by clamping on a top of annular ring 70. The pressure is shown on gauge 68.

A metal screen 72 is placed on top of the test sample to prevent it from bursting at elevated test pressures. A test pressure level of 172 kN/M² level has been used by the U.S. Army as an acceptance level of waterproofness for their waterproof garments. Their test method, however, differs in that the pressure is continually increased until leakage is observed. This procedure can yield misleading and overly favorable results when used on microporous materials. The better procedure of maintaining the pressure at a pre-determined level for a fixed time is used to obtain the values reported herein. 2. Test For Air Permeability

The permeability to air of the samples was measured by a Gurley densometer (ASTM D726-58) manufactured by W. & L. E. Gurley & Sons. Results are reported in terms of Gurley number which is the time in seconds for 100 cm³ of air to pass through one square inch of the sample under a pressure of 4.88" of water-head pressure. This measurement can be converted into metric permeability units [cm³/cm²/sec. cm/cm.Hg] by the following formula: thickness of sample × 0.0432 / (Gurley number).

3. Test Method For MVTR

The test apparatus for determining moisture vapor transmission rate (MVTR) is described in ASTM-E96-B 66D, is shown in FIG. 1. This method is not suitable for determining the very high MVTR of materials described by this invention because the air gap between the surface 10 of the water 12 and the material 14 to be tested is itself a significant resistance to the passage of water vapor. This method has an estimated MVTR of about 5,000 gms./m². day which establishes the upper limit of MVTR that can be detected with this test configuration.

For the high MVTR materials of this invention which are also waterproof, a modified test configuration has been used in which the air gap is eliminated by inverting the cup to bring the water directly in contact with the surface of the test material (FIG. 2).

The procedure is as follows. Approximately 30 cc of water 18 is placed in a tapered polypropylene cup 20 which is 4.5 inches high with a 2.5"-diameter mouth. The material 26 to be tested is sealed to the lip of the cup with a silicone adhesive 22. The cup assembly is weighed to the nearest 1/100 gram and an elastic rubber collar 24 is placed on the cup under tension to an annular projection 28 on the cup. The cup is inverted and suspended upside down through a circular opening in a support plate, its position being adjusted by means of the rubber collar so that the mouth of the cup is aligned with the lower surface of the plate. Between this surface and the bottom of the chamber there is an approximately 4" air space across which air is caused to flow at about 650 ft./min. The chamber is held at a temperature of 73 degrees F. ±2 degrees F. and a relative humidity of 50% ± 5%. The sample remains in the chamber for three hours and is then removed and reweighed again to within 1/100 of a gram. The moisture vapor rate is then expressed in grams of water lost per square meter of sample surface area per 24 hours.

EXAMPLE I

Human perspiration was collected by wringing a sweat soaked garment. 25 ml was placed in a cup for the moisture vapor transmission rate test. A GORE-TEX® microporous PTFE membrane, which had been tested to determine that it was waterproof when (a) subjected to tests at 25 cm water head, and at 172 kN/M² and 345 kN/M² water pressure was sealed onto the lip of the test cup.

The cup was inverted and left inverted under ambient conditions until all the perspiration had evaporated through the Gore-tex® membrane, a period of about two days.

The naturally white membrane now appeared brown and visibly contaminated on both sides. The dry, contaminated membrane showed a weight gain of 0.265 gms. due to residual contamination in and on it.

The contaminated membrane was pressure tested at a 25 cm head of water and found to leak almost immediately in one spot and was visibly leaking over its entire surface in three to four minutes.

When the membrane was subjected to the 172 kN/M² test, water flowed through it productively.

EXAMPLE II

Hypol FHP3600® foamable hydrophilic polyurethane polymer was cast about 0.002" inch thick onto a Gore-tex® PTFE membrane, which was used in this case only as a release sheet. The sample was also covered with a Gore-tex® membrane release sheet. Care was taken not to wet the Hypol polymer such that adhesion occurred. The Hypol polymer and release sheets were placed in a humidity chamber at 96% relative humidity and cured for one hour. After curing, a Hypol polymer film was removed from the release sheets.

Water reacts to crosslink the Hypol® polymer. If water is introduced quickly be at an elevated temperature, foaming occurs. In a high humidity chamber at ambient temperature, water is introduced slowly enough that a nonporous cured film is obtained.

A sample of Hypol® fiber prepared above was tested for moisture transmission rate in the inverted cup test and found to have a value of 1,575 gms./m². day. Another sample of film was tested for air permeability in a Gurley densometer and found to have no permeability within the testing capability. A further sample of the film was tested for waterproofness at 25 cm head water pressure for 20 minutes and at 172 kN/M² for 30 seconds and no leaks were detected.

25 ml of human perspiration from the same source as was used in Example I was placed in a moisture vapor test cup and covered first with the Hypol® membrane and then with the Gore-tex® membrane similar to that used in Example I. The cups were sealed and the cup was inverted. The perspiration was allowed to evaporate as in Example I. After the perspiration had evaporated, the Gore-tex® membrane did not appear to be contaminated, and it did not have a measurable weight increase. However, the Hypol® membrane was stained and contained some residue from the perspiration on the side that had been in contact with perspiration.

When the Gore-tex® membrane was tested for waterproofness in the standard ways at 25 cm. head of water and at 172 kN/M² for 90 seconds, it did not leak, indicating that it had not been contaminated. When the Hypol® film was tested for waterproofness, it also did not leak at either test condition. The Gore-tex® membrane was then tested at 172 kN/M² for 30 minutes and did not leak. When the Hypol® membrane was tested for this condition, there was no gross leakage, but there was detectable moisture having penetrated through the membrane.

EXAMPLE III

A 0.025" film of Hypol FHP3000® prepolymer was cast on a Gore-tex® microporous PTFE sheet (similar to that used in Example I. The Hypol® prepolymer was then uniformly sprayed with water. The reacting liquid was massaged by hand over the surface of the Gore-tex® sheet until the curing reaction had proceeded far enough for the Hypol polymer to be viscous and tacky. The sample was placed in a humidity chamber at 96% relative humidity for 30 minutes to effect a complete cure. The composite sheet had a thickness of 0.008" and an MVTR of 7,300 gms./m². day. The sample was waterproof under both standard tests.

before and after 25 ml of perspiration had been evaporated through the sample.

EXAMPLE IV

Celgard® microporous polypropylene is a product of Celanese Plastics Co. A sheet of Celgard 2500®-was tested and found to have a thickness of 0.001 inch, an air permeability of zero on the Gurley densometer. It was tested for waterproofness and found to be waterproof by the standard tests at 25 cm water head and at 172 kN/M² water pressure. When 25 ml of perspiration were evaporated through this film as in Example I, it subsequently failed the waterproofness test at 25 cm water head and therefore was not tested at 172 kN/M².

By a procedure similar to Example III, a layer of Hypol® 3000 polymer was cast onto one side of an uncontaminated Celgard® sheet to form a firmly adhered composite sheet. The composite sheet was tested for MVTR and found to have a value of 7,700 gms./m². day. The thickness of the composite sheet was 0.005 inch. No permeability to air was detected on the Gurley-meter.

In a procedure similar to Example I, 25 ml of perspiration was evaporated through the sample. The sample was then tested for waterproofness and found to be waterproof at both standard test conditions of 25 cm water head and 172 kN/M² water pressure.

EXAMPLE V

A sheet of Nafion 120® perfluorosulphonic ion exchange membrane was measured to have an MVTR of 12,000 gms./m². day, an immeasurable air permeability, and a thickness of 0.005 inch. When combined with a PTFE sheet, similar to that used in Example I, by adhering them together with dots of silicone adhesive, the composite two layered sample had a MVTR of 4,900 gms./m². day. In a procedure similar to that of Example I, 25 ml of perspiration was evaporated through the sample, the Nafion 120® membrane being in contact with the perspiration. After the perspiration had been evaporated, the Gore-tex® PTFE sheet did not appear to be contaminated. The Gore-tex® sheet was then delaminated from the Nafion sheet and tested for waterproofness. It was found to be waterproof at both 25 cm water head and 172 kN/M² water pressure.

EXAMPLE VI

A laminate was made consisting of the following four layers:

Layer	Material	Wt oz/sq yd
1	Water repellent nylon taffeta	1.9
2	Gore-tex® microporous PTFE membrane	0.44
3	Hypol 3000® hydrophilic polyurethane	0.5
4	Nylon tricot knit	3.5

The laminate was made in two steps.

First the nylon taffeta was affixed to the Gore-tex® membrane by gravure printing a dot pattern of adhesive onto the Gore-tex® PTFE membrane and passing the nylon taffeta to it through a nip roll and then over a heated roll to further melt and bond the adhesive. This resulted in a well bonded laminate of the first two layers. The Gore-tex® membrane of this laminate was then gravure printed with Hypol 2000® prepolymer and passed through a nip roll to spread the Hypol 2000® prepolymer and press it into the Gore-tex® membrane. Nylon tricot knit was run through a water dip and then brought into contact with the layer of Hypol 2000® prepolymer. The purpose of the water contained in the tricot knit was to initiate curing of the Hypol 2000® prepolymer. The entire four-layer laminate was fed over a tenter frame and through an oven at 170 degrees C. to accelerate the cure. The resulting laminate was well adhered with the Hypol 2000® layer acting as an adhesive to bond the knit to the Gore-tex® membrane.

Microscopic examination of the Hypol® layer revealed that considerable foaming had occurred. However, the properties of the laminate proved that there was a continuous layer of Hypol® hydrophilic polymer present.

The properties of the laminate were as follows:

MVTR	3500
Air permeability*	0
Waterproofness	
25 cm water pressure - passed - no leak after 24 hrs.	
25 psig water pressure - passed - no leak after 30 sec.	
345 kN/m² psig water pressure - passed - no leak after 30 sec.	

* Air permeability was measured on a Gurley densometer.

A jacket was then made up from the laminate and given to a person who had participated in field testing outdoor garments, and who had previously experienced loss of waterproofness due to contamination by perspiration of a garment containing a layer of microporous polytetrafluoroethylene.

After wearing the jacket under conditions that he would have expected to contaminate it—camping, skiing, and mountain climbing—he reported that the garment remained waterproof. Further he found the garment continued to be breathable and served as an excellent windbreaker.

What is claimed is:

1. A flexible layered article suitable for use in waterproof garments or tents, which permits transfer of water vapor to prevent the build-up of moisture, the layered article resisting its resistance to transmission of liquid water even when the interior face of the article is exposed to a surface tension lowering agent, such as perspiration and body oils, comprising:

(a) a flexible, first layer of hydrophobic material having a moisture vapor transmission rate exceeding 1000 gms./m². day and an advancing water contact angle exceeding 90 degrees; and

(b) a continuous hydrophilic layer attached to the inner face of said first layer, said hydrophilic layer having a moisture vapor transmission rate exceeding 1000 gms./m². day and forming a barrier to passage of a surface tension lowering agent that would if present in said first layer tend to reduce the waterproofness of said first layer.

2. The layered article of claim 1 in which said hydrophilic layer does not permit detectable passage of liquid water therethrough at a pressure of at least about 25 cm water head for 20 minutes.

3. The layered article of claim 1 in which said hydrophilic layer does not permit detectable passage of liquid water therethrough at pressures of between about 25 cm water head and about 172 kN/M² for 30 seconds.

4. The layered article of claim 1 in which said hydrophilic layer does not permit detectable passage of liquid water therethrough at a pressure of about 172 kN/M² for 30 seconds.

5. The layered article of claim 1 in which said hydrophobic layer is in laminar contact with said hydrophilic layer.

6. The layered article of claim 1 in which said hydrophobic layer is microporous.

7. The layered article of claim 1 in which said hydrophobic layer is porous polytetrafluoroethylene.

8. The layered article of claim 1 in which said hydrophilic layer is impermeable to air.

9. The layered article of claim 1 in which said hydrophilic layer is impermeable to air.

10. The layered article of claim 1 in which said hydrophilic layer is a polyether-polyurethane.

11. The layered article of claim 1 in which said hydrophilic layer is a perfluorosulphonic acid membrane.

12. The layered article of claim 1 in which said hydrophilic layer has a moisture vapor transmission rate above 2000 gms./m². day and no detectable transmission rate for liquid water at hydrostatic pressures of between about 25 cm water head and about 172 kN/M² for 30 seconds.

13. The layered article of claim 1 in which said hydrophilic layer has a moisture vapor transmission rate above 3000 gms./m². day and no detectable transmission rate for liquid water at hydrostatic pressures of between about 25 cm water head and about 172 kN/M² for 30 seconds.

14. The layered article of claim 1 in which said hydrophilic layer has a moisture vapor transmission rate above 2000 gms./m². day and no detectable transmission rate for liquid water at hydrostatic pressures of about 172 kN/M² for 30 seconds.

15. The layered article of claim 1 in which a wear-resistant textile layer is attached to the outer face of said hydrophobic layer and aligned in laminar relationship therewith.

16. The layered article of claim 15 in which a textile layer is attached to the inner face of said hydrophilic layer and aligned in laminar relationship therewith.

17. The layered article of claim 15 in which said hydrophobic layer is in laminar contact with both said hydrophilic layer and said wear-resistant textile layer.

18. The layered article of claim 17 in which a textile layer is in laminar contact with said hydrophilic layer.

19. The layered article of claim 1 in which said hydrophilic layer has a moisture vapor transmission rate above 2000 gms./m². day.

20. The layered article of claim 19 in which said hydrophobic layer is in laminar contact with said hydrophilic layer.

21. The layered article of claim 19 in which a textile layer is attached to the inner face of said hydrophilic layer and aligned in laminar relationship therewith.

22. The layered article of claim 19 in which said hydrophobic layer is a polyether-polyurethane.

23. The layered article of claim 19 in which said hydrophilic layer is a perfluorosulphonic acid membrane.

24. The layered article of claim 19 in which said hydrophobic layer is microporous.

25. The layered article of claim 19 in which said hydrophobic layer is porous polytetrafluoroethylene.

26. The layered article of claim 19 in which a wear-resistant textile layer is attached to the outer face of said hydrophobic layer and aligned in laminar relationship therewith.

27. The layered article of claim 26 in which said hydrophobic layer is in laminar contact with said hydrophilic layer and said wear-resistant textile layer.

28. The layered article of claim 27 in which a textile layer is in laminar contact with said hydrophilic layer.

* * * * *

Table 3. [illegible] Profile of [illegible] (BIBR 953 [illegible])

human enzymes	K_i (nM)	human enzymes	K_i (nM)
thrombin	4.5 ± 0.2	[illegible]	[illegible]
[illegible]	[illegible] ± 20	[illegible]	[illegible]
trypsin	50.3 ± 0.3	[illegible] protein Ca	[illegible]

[illegible] EC [illegible] 0.08 [illegible]

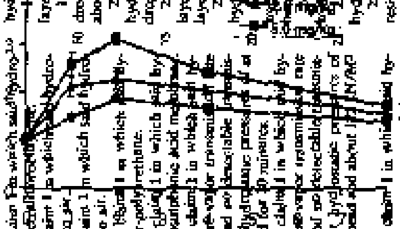

Figure 3. [illegible] oral administration of compound 31 (BIBR 1048) [illegible] monkeys. Data represent [illegible] SEM.

bulk solvent. [illegible] teristics of this inhibitor that [illegible] the canonical hydrogen-bonding pattern with the enzyme, which is a common feature of almost all high affinity thrombin inhibitors reported so far. Apart from the salt bridge with Asp189, the binding energy of **24** solely results from hydrophobic interactions, which underscores the general importance of this binding force in drug receptor interactions.[16]

Because of its strong in vivo activity and its favorable selectivity profile vs related serine proteases (Table 3), **24** was investigated biologically in depth and turned out to be a very potent anticoagulant in vivo. Among all of the inhibitors of this structural class, it exhibited the strongest activity and the longest duration of action in anesthetized rats after i.v. administration. Unlike compound [illegible] was well-tolerated in these animals up to the [illegible] dose of 10 mg/kg. It was, however, not orally active, which is not surprising considering that it is a very polar, permanently charged molecule with a log P [illegible] (n-octanol/buffer, pH 7.4).

[illegible] compounds with physicochemical [illegible] acteristics such as this can be converted into orally active prodrugs by [illegible] the carboxylate [illegible] group and by masking the amidinium moiety as a carbamate [illegible], provided [illegible] the [illegible] and the amidinium will be restored in vivo by hydrolytic cleavage of the prodrug. Accordingly, we synthesized a series of double prodrugs of this type [illegible] exemplified by **31** (Scheme [illegible]), which is a rather lipophilic compound with a log P [illegible] (n-octanol/buffer, pH 7.4). After oral [illegible], this prodrug **31** exhibited strong and long-lasting anticoagulant [illegible] measured by the [illegible] thrombin [illegible] (aPTT) [illegible] (Figure 3). [illegible] of the biological [illegible] of BIBR 953 and its prodrug **31** (BIBR 1048) [illegible]

Conclusion

On the basis of the X-ray [illegible] of NAPAP complexed with bovine thrombin, we designed a [illegible] structural class of nonpeptidic inhibitors employing a benzimidazole as the central scaffold. Supported by a series of X-ray structure analyses, we optimized the inhibitory activity of these compounds in a number of iterative steps. During this process, enzyme inhibition in the lower nanomolar range could be achieved although, apart from the salt bridge of the amidinium group with Asp189 of thrombin, the binding energy solely results from hydrophobic interactions. To reduce plasma protein binding, we increased the hydrophilicity of the inhibitors by introducing a carboxylate group at a position of the molecules, where it does not interfere with the thrombin binding site interaction. From this series of inhibitors, **24** (BIBR 953) exhibited the most favorable in vivo activity profile following i.v. administration to rats. Because of its highly polar, zwitterionic nature, oral absorption of **24** was insufficient. Therefore, a number of prodrugs were synthesized, from which **31** (BIBR 1048) exhibited strong and long-lasting anticoagulant effects after oral administration in different animal species. On the basis of these encouraging results, **31** was chosen for development and is currently undergoing phase II clinical trials in patients with thromboembolic disorders.

Experimental Section

Chemistry. Procedures for the preparation of all final products are presented below along with representative procedures for all methods used in the preparation of intermediates. All solvents and reagents were used without purification as acquired from commercial sources.

^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 200 MHz on a Bruker AC200 spectrophotometer in the solvent indicated. Chemical shifts are reported in parts per million relative to tetramethylsilane. Melting points were recorded on a HWS SG 2000 melting point apparatus and are uncorrected. Elemental analyses were performed on a Heraeus CHN Rapid elemental analyzer and are within 0.4% of the calculated values. Mass spectra were recorded on the following instruments, using the stated ionization methods: Finnigan MAT [illegible] mass spectrometer, electron impact ionization (EI); Finnigan TSQ 700 mass spectrometer, electrospray ionization (ESI) [illegible].

[illegible]-2-ylmethyl)benzonitrile [illegible]. A solution of [illegible] acetic acid ([illegible]) [illegible] mL of tetrahydrofuran [illegible] for [illegible]. Then, [illegible] mmol) in [illegible] was added and the resulting solution was [illegible] solvent [illegible], water [illegible] was added, and the precipitate was collected [illegible] subsequently [illegible] 2-(4-cyano-phenyl)-N-[illegible]-amino-5-nitro-phenyl)acetamide (14.8 g, 79%). This intermediate was dissolved in glacial acid (150 mL) and refluxed for 1 h. The [illegible] was then concentrated to dryness and the residue was [illegible] stirred in ammonia solution [illegible] mL), [illegible] after it was filtered. [illegible]-1H-benzimidazol-2-ylmethyl)benzonitrile [illegible]. The nitro [illegible] then reduced by hydrogenation [illegible] charcoal, [illegible] mixture of methanol and [illegible] 200 mL [illegible] the desired **25** (11.[illegible]). Low-resolution mass spectrometry (LRMS) (EI): M^+ [illegible] NMR (DMSO-d_6) [illegible] 4.31 [illegible], 4.[illegible] (d, 1H), [illegible] (d, 1H), [illegible]

N-[illegible]-cyanobenzyl)-1-methyl-1H-benzimidazol-5-yl]benzenesulfonamide [illegible]. A solution of [illegible] (6.1 [illegible]) benzenesulfonyl chloride [illegible] mmol) in 30 mL of pyridine was kept at room temperature [illegible] h. The solvent was then evaporated, and the residue was vigorously

~~131~~ 132

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
EMILIO FERRERO
Abogado

ASUNTO		
	Radicación	06-73857
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	[illegible]
	Folios	06

Patente de Invención [X] Patente de Modelo de Utilidad

Vía PCT (fase nacional) [X] Cap.I [x] Cap. II [ ]

No. Sol. Internacional PCT/EP2004/014718
Fecha de Presentación Internal. 27 de diciembre de 2004

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción:	Folios: 96 a 102	modificada
Reivindicaciones:	Folios: 103 a 106	modificadas
Dibujos:	Folios: 46	como se radicó inicialmente
Prioridad:	IT 30 de diciembre de 2003, PD2003A000314	

2. Objeto de la invención

Titulo de la invención:

Articulo multicapa impermeable y permeable al vapor.

El problema planteado en esta solicitud es la condensación de la traspiración en las prendas de vestir o en el calzado la cual no puede ser expulsada produciendo un efecto "húmedo" desagradable.

Para solucionar este problema técnico la solicitud en estudio proporciona un artículo multicapa impermeable y permeable al vapor o al aire, que es estructuralmente resistente y soportado por sí mismo.

Clasificación internacional (IPC) en A43B13/12, B32B7/02

3. De la solicitud de Patente (según el caso)

Reivindicaciones (artículo 30 D 486)

- Las reivindicaciones 21 a 33 están definiendo un artículo multicapa en términos de las condiciones del proceso de obtención (deposición por plasma) de una de las capas que lo conforman, lo cual es inaceptable, ya que las reivindicaciones de producto son las que definen substancias y composiciones, entidades físicas tales como artículos, maquinas, mecanismos, aparatos, etc. lo cual no observa en las citadas reivindicaciones. Es así como las reivindicaciones de producto deben definir las características del producto, tales como por la forma o constitución del mismo y las partes que lo componen. No se aceptan reivindicaciones que caractericen resultados, usos, ventajas o efectos. Por lo anterior, las reivindicaciones 21 a 33 debe eliminarse del capítulo en cuestión.

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de claridad y concisión de acuerdo al art. 30 de la Decisión 486.

4. Determinación del Estado de la Técnica

La fecha para determinar el estado de la técnica es 30 de Diciembre de 2003, de acuerdo al la fecha de prioridad invocada.
Tendiendo en cuenta la anterior fecha indicada, se realiza la búsqueda de las anterioridades de la presente solicitud, encontrándose los siguientes documentos relevantes:

Nº	Documento	Título	Fecha de publicación
D1	US5032450	MICROPOROUS MATERIAL HAVING A COATING OF HYDROPHOBIC POLYMER	1991-07-16
D3	US4686135	COMPOSITE SHEET MATERIAL	1987-08-11
D4	ES 2219922* Equiv. WO99/27156	POLIMERIZACIÓN POR PLASMA SOBRE UNA SUPERFICIE DE MATERIAL	1999-06-03
D5	US6112908	MEMBRANE LAMINATES AND METHODS FOR THEIR PREPARATION	2000-09-05
D6	US4194041	WATERPROOF LAMINATE	1980-03-18

Equiv*: Documento que pertenece a la misma familia de patentes.
D3: folios 74 a 75, D4 folios: 76 a 78.

5. Análisis de patentabilidad (según requisito) (artículo 14 D486)

Novedad (artículo16 D486)

Respecto a la reivindicación 18

La reivindicación 18 describe un "Procedimiento para fabricar un artículo multicapa según una de las reivindicaciones anteriores".

Respecto al estado de la técnica:

D4 describe un método para producir laminas, las cual comprende una lámina hidrogel unida a un membrana microporosa hidrofóbica, el cual comprende:
a) Disolver o dispersar uno o más pre-polímeros en un líquido orgánico volátil con

una tensión superficial baja, para producir una solución de recubrimiento del pre-polímero.
b) Aplicar la solución de recubrimiento en una de la superficie de la capa microporosa, hidrofóbica.
c) Evaporar los componentes volátiles del recubrimiento.
d) Reticulación del pre-polímero por contacto por contacto con un agente reticulante.
e) Secado par remover la humedad residual (Col 2 líneas 51-67, Col 3 lineas 12).

Comparación con el estado de la técnica:

El documento D4 muestra las características de la reivindicación 18 así:
a) Preparar un solución o dispersión de la mezcla polimérica (Col 2 líneas 61-64).
b) Aplicar dicha solución extendiéndola sobre la superficie (Col 20 líneas 66- 67).
c) Evaporar los componentes volátiles de la solución de extensión (Col 3 líneas 3-4).
d) Secar el revestimiento (Col 3 líneas 11-12).

Como conclusión de acuerdo a lo reportado en D4 todas las características técnicas de la reivindicación 18 y sus dependientes, ya eran conocidas en el estado de la técnica, por lo tanto no puede considerarse nueva.

Respecto a la reivindicación 19 y 20

La reivindicación *19* describe un *"Procedimiento para fabricar un artículo multicapa* según una de las reivindicaciones 1 a 16, que consiste en acoplar dicha primera capa y dicha segunda capa laminando una encima de otra".

Respecto al estado de la técnica:

El artículo compuesto puede comprender una lámina de material microporoso con unido sobre un lado de la lámina. La unión puede hacerse de una forma convencional, por unión por fusión o fusión de adhesivo, por ejemplo, unión por fusión, radio frecuencia, entre otras. (Col 16 líneas 3-22).

Comparación con el estado de la técnica:

De acuerdo a la información reportada en D1, la forma de fabricar el artículo multicapa por laminación de dos capas y unidas por adhesivo o ultrasonido, encontraban divulgadas en el estado de la técnica antes de la fecha de prioridad de la solicitud, por lo tanto las citadas reivindicaciones no pueden considerarse nuevas.

Nivel inventivo (artículo18 D486)

Respecto a la reivindicación 1:

La reivindicación 1 dice: "Artículo multicapa impermeable y permeable al vapor, caracterizado porque comprende por lo menos una primera capa (11, 111, 211, 311) realizada en un material permeable al vapor, microporoso e higroscópico que puede adoptar características higroscópicas con el tiempo, y por lo menos una segunda capa (12, 112, 212, 312) impermeable y permeable al vapor e hidrofobica."

Respecto al estado de la técnica:

D1 describe un artículo substancialmente impermeable al agua y permeable al vapor del agua compuesto por:
(a) una hoja de material microporoso: (1) Matriz de una poliolefina de peso molecular ultra alto (UHMW), (2) Relleno de partículas finamente divididas insolubles en agua,

135

donde el 50% de toda la matriz corresponde a silicio. (3) Red de intercomunicación entre los poros.
(b) Un recubrimiento substancialmente continuo permeable al vapor, a base de un polímero hidrofóbico unido por un lado al material microporoso (Col 25, línea 39-62).

D5 describe un artículo laminado impermeable en forma de hoja que tiene una alta transmisión de vapor de agua (Col 1 líneas 5-7). La invención comprende al menos dos laminas: (1) una lámina interior continua hidrofílica (Col 2 líneas 30-36), (2) una lamina exterior hidrofobica, porosa, permeable a los gases e impermeable al agua (Col 4 líneas 31-33 y 56-57).

Análisis de las diferencias con respecto al estado de la técnica:

Características Esenciales	D1 US5032450	D5 US 4194041
una primera capa realizada en un material permeable al vapor	SI (Col 15 líneas 46-47)	SI (Col 2 líneas 45-51)
microporoso	SI (Col 2 lineas 2-3)	NO
e higroscópico	SI (Col 1 líneas 50-51)	NO
una segunda capa impermeable	NO	SI (Col 4 líneas 56-57).
y permeable al vapor	SI (Col 2 línea 23)	SI (Col 4 líneas 32)
e hidrofobica	SI (Col 2 líneas 24)	SI (Col 4 líneas 31-33 y 56-57)

Respecto a la reivindicación independiente 1, el documento del estado de la técnica más cercano es D1 porque describe un artículo multicapa permeable al vapor e impermeable al agua.

La reivindicación 1 de la solicitud colombiana se diferencia en D1, porque la segunda capa no es impermeable.

El problema técnico objetivo de esta solicitud es lograr que articulo sea impenetrable por el agua.

El anterior problema técnico objetivo es solucionado en la anterioridad D3, ya que describe un articulo respirable e impermeable conformado por una lamina donde la lamina externa es impermeable al agua.

Es así como un técnico medio en la materia que tuviera acceso a los documentos D1y D3, podría verse motivado a desarrollar un articulo multicpa impermeable y permeable al vapor, tal como lo propone la solicitud en estudio.

Dado lo anterior, las características técnicas del articulo multicapa de esta solicitud, no representa un avance tecnológico sobre el estado de la técnica.

En conclusión, esta reivindicación y sus dependientes se encuentran afectadas en su nivel inventivo ya que se derivan de manera evidente del estado de la técnica y pueden ser obvias para un técnico medio en la materia.

Respecto a la reivindicación 34

La reivindicación 34 dice: "Procedimiento para fabricar un articulo multicapa según una de las reivindicaciones anteriores 21 a 32".

a) Cargar dicha primera capa
b) Ajustar presión de la cámara
c) Generar plasma
d) Inyectar el monómero precursor
e) Esperar un tiempo de deposición

Respecto al estado de la técnica:

D3 relaciona una hoja de material compuesto resistente a la decoloración y a la llama. En el ejemplo 9, se describe el tratamiento por plasma frío a una hoja precursora. Esta hoja precursora es colocada en el aparato de plasma frio. La presión en el aparato es reducida a 10^{-5} Torr. El gas argón fue introducido para reducir la presión en el aparato y se ajusto a 0.2 Torr. El tratamiento por plasma frio a la hoja precursora se realizo a una frecuencia de 13.6 MHz con un consumo de potencia de 100W por 30 min (Col 15 líneas 5-10).

D4 se refiere a una polimerización por plasma para producir un polímero con carácter hidrófobo o hidrofilico sobre un superficie de un material mediante el uso de una descarga CC o descarga RF, y al polímero formado durante la polimerización por plasma. En la reivindicación 11 de este documento, se describe un procedimiento para el tratamiento de una superficie:

- Proporcionar un electrodo de ánodo y un electrodo de cátodo que es sustancialmente un metal.
- Mantener el nivel de vacio en la cámara.
- Inyectar un gas hidrocarburo monomérico alifático o un gas monomérico que contiene flúor a una presión determinada y un gas no polimerizable a una presión determinada a la cámara, y
- Aplicar una tensión a los electrodos con el fin de obtener una descarga de RF, en la que para obtener un plasma constituido por iones positivos y negativos y radicales generados a partir de un gas hidrocarburo monomérico alifático o un gas monomérico que contiene flúor y el gas no polimerizable, y después formando un polímero hidrófilo o hidrófobo sobre un sustrato a recubrir mediante la deposición por plasma caracterizado porque el sustrato a recubrir se posiciona en el ánodo

Análisis de las diferencias con respecto al estado de la técnica:

Características Esenciales	D3 US4686135	D4 ES 2219922
Cargar dicha primera capa a(211, 311) a revestir en la cámara de reacción.	Esta hoja precursora es colocada en el aparato de plasma frío (col 15 líneas 8-9)	NO
Llevar dicha cámara de reacción a una presión de vacio predeterminada	La presión en el aparato es reducida a 10^{-5} Torr (col 15 líneas 9-10)	Mantener el nivel de vacio en la cámara (Reiv. 1)
Iniciar dicha descarga eléctrica que genera el plasma	El tratamiento por plasma frio a la hoja precursora se realizo a una frecuencia de 13.6 MHz con un consumo de potencia de 100W (col 15 líneas 13-14)	Aplicar una tensión a los electrodos con el fin de obtener una descarga de RF (Reiv. 1)
Inyectar el monómero precursor vaporizado en dicha cámara de reacción	NO	Inyectar un gas hidrocarburo monomérico alifático o un gas monomérico que contiene flúor a una presión determinada y un gas no polimerizable a una presión determinada a la cámara (Reiv. 1)
Esperar un tiempo de deposición determinado	30 min (col 15 línea 15)	1-60 min (Reiv. 15)

137

De acuerdo a la reivindicación 37, el documento del estado de la técnica más cercano es D4, porque describe los pasos característicos en la deposición por plasma frio de un polímero sobre una superficie.

La reivindicación 37 de la solicitud colombiana se diferencia en D4, por el paso de cargar dicha primera capa (211, 311) a revestir en la cámara de reacción.

Esta diferencia no parece darle un efecto técnico sorprendente porque este es un paso obvio dentro del proceso de deposición por plasma, ya que siempre se debe disponer de una superficie en la cual ocurrirá la deposición o sino el proceso no se lleva a cabo. Es así como en la anterioridad D3 se describe una hoja precursora (superficie a depositar) que es colocada en el aparato de plasma frio (Col 15 líneas 8-9) para iniciar el proceso de deposición.

Esta reivindicación es afectada por nivel inventivo porque no va más allá del progreso normal del estado de la técnica y que simplemente se puede deducir de este al combinar los documentos D3 y D4.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	US5032450	19,20 1-17	Novedad Nivel Inventivo
D3	US4686135	21-35	Nivel Inventivo
D4	ES 2219922	21-35	Nivel Inventivo
D5	US6112908	18	Novedad
D6	US4194041	1-17,19,20	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.
Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 28 [illegible].

CONCEPTO TÉCNICO Nº 2628	EXAMINADOR TÉCNICO Código Nº 202090