

Clarke, M
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-107315- -00004-0000

Fecha: 2009-04-27 15:04:00 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **05.107.315**
Solicitud de patente a nombre de **NEXMED HOLDINGS, INC.**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como obrando como apoderada sustituta de la sociedad **NEXMED HOLDINGS, INC.**, de acuerdo con el documento de sustitución de poder adjunto, domiciliada en New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, en respuesta al oficio No. 1125 notificado por fijación en lista el 30 de enero de 2009, relacionado con el concepto técnico de fondo No. 246 me permito manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio, el cual consta de 7 reivindicaciones y reemplaza completamente el capítulo presentado anteriormente.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones de patentabilidad, planteadas por el examinador en su concepto técnico.

De acuerdo con la respuesta del señor Superintendente Delegado, Dr. Giancarlo Marcenaro Jiménez, al derecho de petición radicado por la Dra. Ana María Castro Wey bajo el número 09-012566 del 4 de marzo de 2009, no anexamos recibo de pago por esta modificación dado que el número de reivindicaciones del nuevo capítulo reivindicatorio es inferior a 15.

2. Claridad de la Solicitud

El examinador objeta la claridad del capítulo reivindicatorio, por lo cual el solicitante quisiera hacer los siguientes comentarios:

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- Se ha corregido la reivindicación 1 para corregir los errores de traducción, eliminando las oraciones objetadas.

- Puesto que se esta presentando un nuevo capítulo reivindicatorio que sustituye el que se encontraba originalmente en la solicitud, se han subsanado todos los problemas de claridad ocasionados por la reiteración de la composición en diferentes reivindicaciones.

- El nuevo capítulo reivindicatorio anexo presenta la materia objeto de la invención como una sola composición que comprende varios ingredientes, en lugar de dos composiciones separadas.

- Se han eliminado las reivindicaciones relacionadas con el empaque y el kit del producto.

- Se han eliminado las reivindicaciones 84 y 85.

- Se han eliminado las reivindicaciones 22 y 65, por lo tanto el capítulo reivindicatorio adjunto se encuentra plenamente sustentado.

3. Unidad de Invención

El examinador objeta la unidad de invención de la solicitud, argumentando que las reivindicaciones 44, 46, 81 y 83 se relacionan con kits. Con el fin de superar esta objeción, el solicitante elimina las reivindicaciones mencionadas.

4. Excepciones a la Patentabilidad

El examinador argumenta que las reivindicaciones 23-24, 38-42 y 77-79 no son patentables por tratarse de un método de tratamiento. El solicitante acepta la objeción y retira dichas reivindicaciones.

5. Novedad

El examinador objeta la novedad de la solicitud a la luz de lo establecido por la anterioridad EP 0.515.312 (en adelante D1) argumentando que la misma ya enseñaba composiciones solubles en agua de un revestimiento antifúngico para uñas, el cual comparado elemento por elemento contiene la misma materia de la presente solicitud.

En cuanto al estudio de la novedad, cabe recordar que el la novedad solo se ve afectada si todas y cada una de las características de la invención se encuentran contenidas en el estado de la técnica. No basta con que algunas de las

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características se compartan entre las dos solicitudes, sino que debe ser posible identificar absolutamente todos los elementos reivindicados para poder afirmar que una invención carece de novedad.

En este sentido, me permito manifestar que el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que la invención se considera como nueva cuando no está comprendida en el estado de la técnica.

Si de acuerdo con el espíritu de la norma legal indicada anteriormente, la invención no se considera como nueva si está "*comprendida*" en el estado de la técnica, dicha norma se está refiriendo, naturalmente, a la **totalidad del invento y no a alguno o a algunos de los componentes**. Para que la invención pierda su calidad de novedosa, es claro que **TODA ELLA**, ha de estar contenida en el "*conjunto de conocimientos existentes que son aplicables al proceso industrial*" como define el estado de la técnica el Tribunal de justicia del Acuerdo de Cartagena (Proceso No. 6-IP-89, sentencia de 31 de octubre de 1989, publicada en Jurisprudencia del Tribunal de Justicia del Acuerdo de Cartagena, Tomo 11, BID-INTAL, Buenos Aires, 1994, página 60).

Esto se conoce como **NOVEDAD ABSOLUTA**, de conformidad con lo cual para desvirtuar el requisito de novedad de una invención será necesario que lo reivindicado por la invención bajo estudio corresponda de **forma total** con lo revelado en un documento o anterioridad señalada, conclusión a la que se llega después de un análisis íntegro mediante una comparación entre el capítulo reivindicatorio de la invención en estudio y la divulgación D1.

Es necesario resaltar que el examinador esta considerando los aspectos generales de la invención, sin tener en cuenta que son las particularidades las que conceden la novedad. } *4º u. d. b. v. 2*

Ahora bien, si un determinado elemento, condición o circunstancia de la nueva creación ya hace parte del estado de la técnica, no quiere ello decir, desde luego, que la invención deba ser rechazada por carecer del requisito de novedad. No sin razón ha dicho el mencionado Tribunal: "*hay que advertir que toda creación es en cierta forma, producto del estado de la técnica existente, en el sentido de que el inventor ha de tener en cuenta un conjunto de conocimientos técnicos que le permitan crear nuevos procedimientos aplicables a la industria*" (Ibidem, páginas 53 y 54) (el subrayado es mío).

Por lo tanto, como mínimo la novedad debe contemplar los siguientes aspectos:

-Que la invención en estudio esté contenida de forma **TOTAL y ABSOLUTA** en el documento que se menciona como anterioridad o de forma independiente en los documentos que se mencionan, si son varios; y

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-Que la invención en estudio puede partir de conocimientos conocidos, caso en el cual habrá que hacer la comparación no de lo conocido sino de lo inédito y novedoso, teniendo que analizarse el valor agregado que aporta la invención con sus nuevas características al campo técnico al cual pertenece la invención en estudio.

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Aplicando lo anterior al caso concreto, para que las razones que aduce ese despacho para desvirtuar la novedad fuesen ciertas, sería forzoso que se demostrara que la invención de mi mandante esté comprendida en el estado de la técnica de forma **TOTAL**, lo cual no sucede como se demuestra a continuación.

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El técnico con habilidad ordinaria en la materia puede observar con facilidad que las composiciones de la anterioridad D1 no comprenden anti-hongos de **Azole o clorhidrato de dodecil-2-(N,N-dimetilamino) isopropionato** como las divulgadas en la presente solicitud. Por lo tanto, en vista que existe una diferencia entre la anterioridad y la invención en estudio, a la luz de la normativa vigente es claro que la solicitud cumple con el requisito de novedad exigido.

6. Nivel Inventivo

El examinador objeta la altura inventiva de la solicitud, a la luz de lo divulgado por las anterioridades EP 0.515.312 (en adelante D1), US 6.019.988 (en adelante D2) y WO 01/60325 (en adelante D3). De acuerdo con el examinador la anterioridad D1 no enseña el uso de clorhidrato de dodecil-2-(N,N-dimetilamino) isopropionato, pero la anterioridad D2 si lo hace. Por lo tanto el técnico con habilidad ordinaria en la materia podría combinar las formulaciones de D1 y D2 para llegar a la invención solicitada. Prosigue el examinador argumentando que dicho técnico podría también combinar las enseñanzas de D1 y D3 para llegar a una combinación que comprende un agente anti-infeccioso auxiliar.

Al respecto, el solicitante quisiera anotar que ninguna de las anterioridades citadas por el examinador enseña o sugiere de manera clara la presente solicitud. El técnico con habilidad ordinaria en la materia no podría determinar a partir de la lectura de D2 cual mejorador de la permeabilidad es el más apropiado para la composición de la invención de entre todos los allí enumerados. El técnico solo podría encontrar obvia la selección hecha por el solicitante si se estudia el arte previo en retrospectiva. El examinador no proporciona argumentos sólidos que demuestren que la selección del clorhidrato de dodecil-2-(N,N-dimetilamino) isopropionato es mejor que cualquiera de los otros mejoradores mencionados, considerando que todos proporcionan una composición soluble en agua que podría tener las características de la presente invención.

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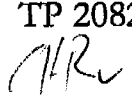
De igual manera, un técnico con habilidad ordinaria en la materia no podría llegar a la composición de la solicitud en estudio a partir de la combinación de D1 y D3 ya que D3 no menciona la inclusión de clorhidrato de dodecil-2-(N,N-dimetilamino) isopropionato.

Se le recuerda al examinador que el estudio del nivel inventivo debe partir del arte previo para llegar a la solicitud y no al revés. Es claro que se hizo un estudio retrospectivo puesto que en ninguno de los documentos citados se proporcionan información determinante que permita concluir que la terbinafina deba combinarse con clorhidrato de dodecil-2-(N,N-dimetilamino) isopropionato y no con otro mejorador, de los muchos que se enumeran en D2 y de los muchos que pueden existir en el estado de la técnica. { NITM
NO NO

En resumen, me permito decir que gracias a las modificaciones expuestas en el punto 1 de este memorial y los argumentos anteriormente mencionados, la presente solicitud cumple cabalmente con los requisitos de claridad, patentabilidad, novedad y nivel inventivo respecto a los compuestos expuestos el capítulo reivindicatorio adjunto. Por lo tanto, solicito comedidamente a ese despacho se sirva reconocer estos requisitos y conceder el privilegio de patente de invención a la solicitud en estudio.

En consecuencia, solicitamos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional. De igual forma, si el examinador considera que subsisten razones para objetar la presente invención ruego expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que mi mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: "*habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares*" y "*(..) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso*", respectivamente (el subrayado es nuestro).

Señor Superintendente


DILIA RODRIGUEZ D'ALEMAN
CC. 41.654.882 de Bogotá
TP 20824


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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

REF: **EXPEDIENTE No. 05.107.315**
SOLICITUD DE PATENTE A NOMBRE DE NEXMED
HOLDINGS, INC.

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53 Piso 6, atentamente digo a usted que sustituyo el poder con que obro a la doctora **DILIA RODRIGUEZ D'ALEMAN**, domiciliada en Bogotá, D.C., portadora de la tarjeta profesional No. 20.824, con las mismas facultades con que me fueron conferidas para este caso.


JIMENA ESCOBAR URIBE

C.C. 39.779.452 de Usaquén

T.P. 68.228

Acepto sustitución

DILIA RODRIGUEZ D'ALEMAN

C.C. 41.654.882 de Bogotá

T.P. 20.824

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PRESENTACION PERSONAL

El anterior escrito fue presentado ante el
NOTARIO ONCE (E) DEL CIRCULO DE BOGOTA, D.C.
personalmente por [Redacted]

quien exhibió la c.c. 2972944 de [Redacted]
y Tarjeta Profesional No. 62228 C.S.J.

Firma [Redacted]

Fecha [Redacted]

23 ABR 2009

Nelson Sánchez García



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Cód. 008

REIVINDICACIONES

1. Una composición de recubrimiento anti-hongos, de doble acción, del tipo de una sola capa para uñas que comprende en un ~~psa~~ base del total de la composición:

clorhidrato de terbinafina presente en una cantidad en el rango de 0,5 a 10 por ciento en peso;

clorhidrato de dodecil-2-(N,N-dimetilamino) isopropionato (DDAIP-HCl) presente en una cantidad en el rango de 0,1 a 25 por ciento en peso;

Bencil alcohol presente en una cantidad en el rango de 0,1 a 10 por ciento en peso;

Polivinilpirrolidona presente en una cantidad en el rango de 0,1 a 5 por ciento en peso;

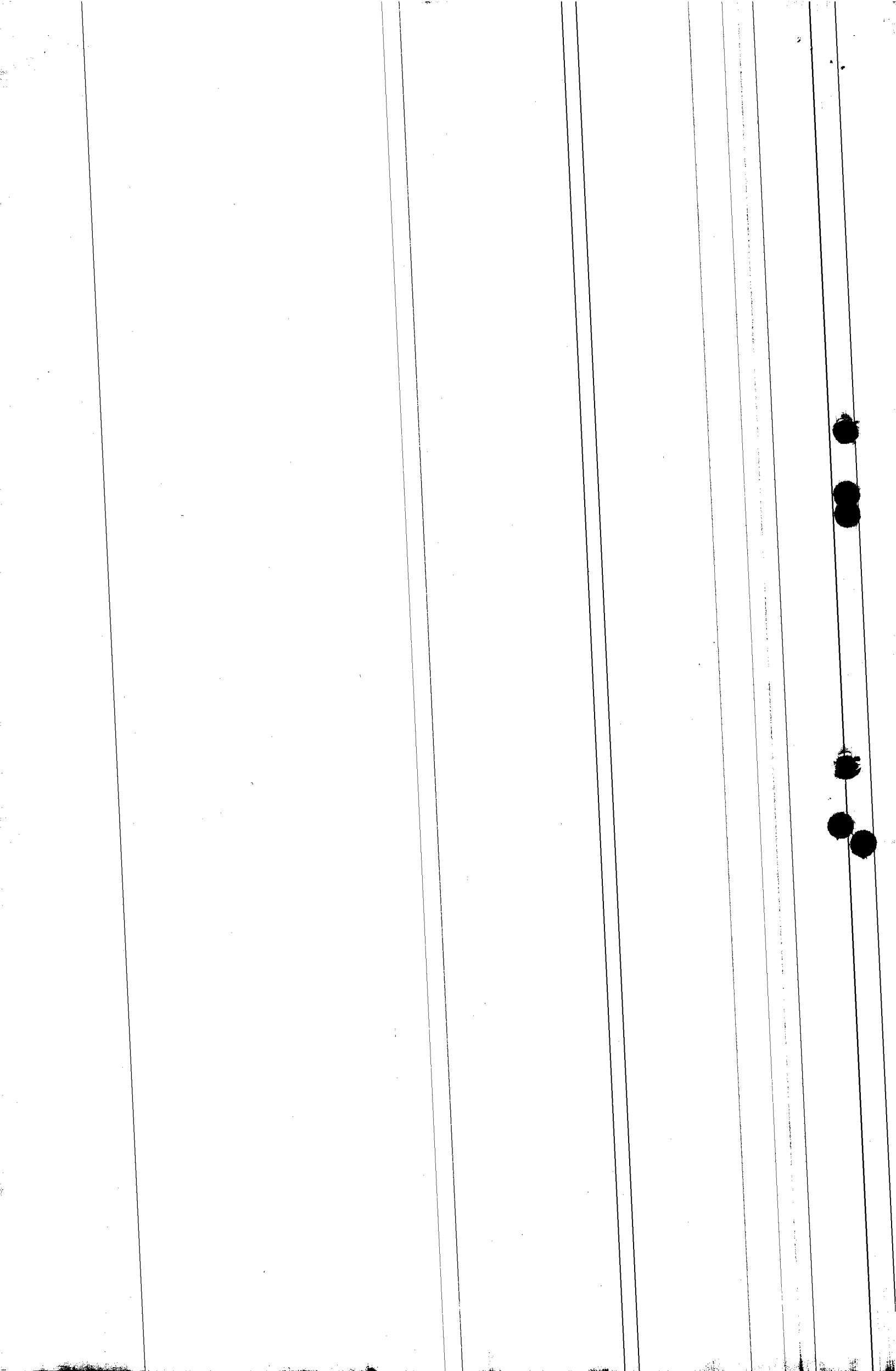
y el resto es etanol.

2. Una composición de acuerdo con la reivindicación 1 en donde el DDAIP-HCl está presente en una cantidad en el rango de 0,1 a 10 por ciento en peso.

3. Una composición de acuerdo con la reivindicación 1 en donde el bencil alcohol está presente en una cantidad en el rango de 0,5 a 1,5 por ciento en peso.

4. Una composición de acuerdo con la reivindicación 1 en donde la polivinilpirrolidona está presente en una cantidad en el rango de 0,25 a 1 por ciento en peso.

5. Una composición de acuerdo con cualquiera de las reivindicaciones precedentes, apropiada para aplicación al menos una vez al día.



6. Una composición de acuerdo con cualquiera de las reivindicaciones precedentes, para emplearse en el tratamiento de la onicomycosis. ✓

7. Una composición de acuerdo con cualquiera de las reivindicaciones precedentes, la cual es sustancialmente transparente. ✓



US005082866A

United States Patent [19]
Wong et al.

[11] Patent Number: **5,082,866**
[45] Date of Patent: **Jan. 21, 1992**

[54] BIODEGRADABLE ABSORPTION ENHANCERS

- [75] Inventors: Ooi Wong, Lawrence, Kans.;
Toshiaki Nishikata, Ibaraki, Japan;
Joseph H. Rytting, Lawrence, Kans.
- [73] Assignee: Odontex, Inc., Lawrence, Kans.
- [21] Appl. No.: 566,758
- [22] Filed: Aug. 14, 1990

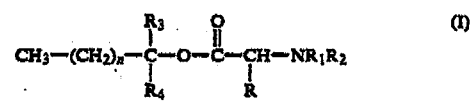
FOREIGN PATENT DOCUMENTS

- 57-88113 6/1982 Japan .
58-57309 4/1983 Japan .

Primary Examiner—Michael L. Shippen
Attorney, Agent, or Firm—Zarley, McKee, Thomte,
Voorhees & Sease

[57] ABSTRACT

Biodegradable absorption enhancers, especially useful in pharmaceutical formulations, are compounds having the formula



wherein R is hydrogen, C₁-C₇ alkyl, benzyl or 4-hydroxybenzyl; n is a whole number from 4 to 18 inclusive; R₁ and R₂ are independently selected from hydrogen and C₁-C₇ alkyl, or R₁ and R₂ together with the nitrogen atom to which they are attached are combined to form a substituted or unsubstituted heterocycloalkyl radical having a total of 5 to 7 ring atoms, optionally including a hetero ring atom selected from oxygen, sulfur and nitrogen in addition to the indicated nitrogen atom, the substituents when present being one to three C₁-C₇ alkyl radicals, which may be the same or different; and R₃ and R₄ are independently selected from hydrogen, methyl and ethyl.

7 Claims, 2 Drawing Sheets

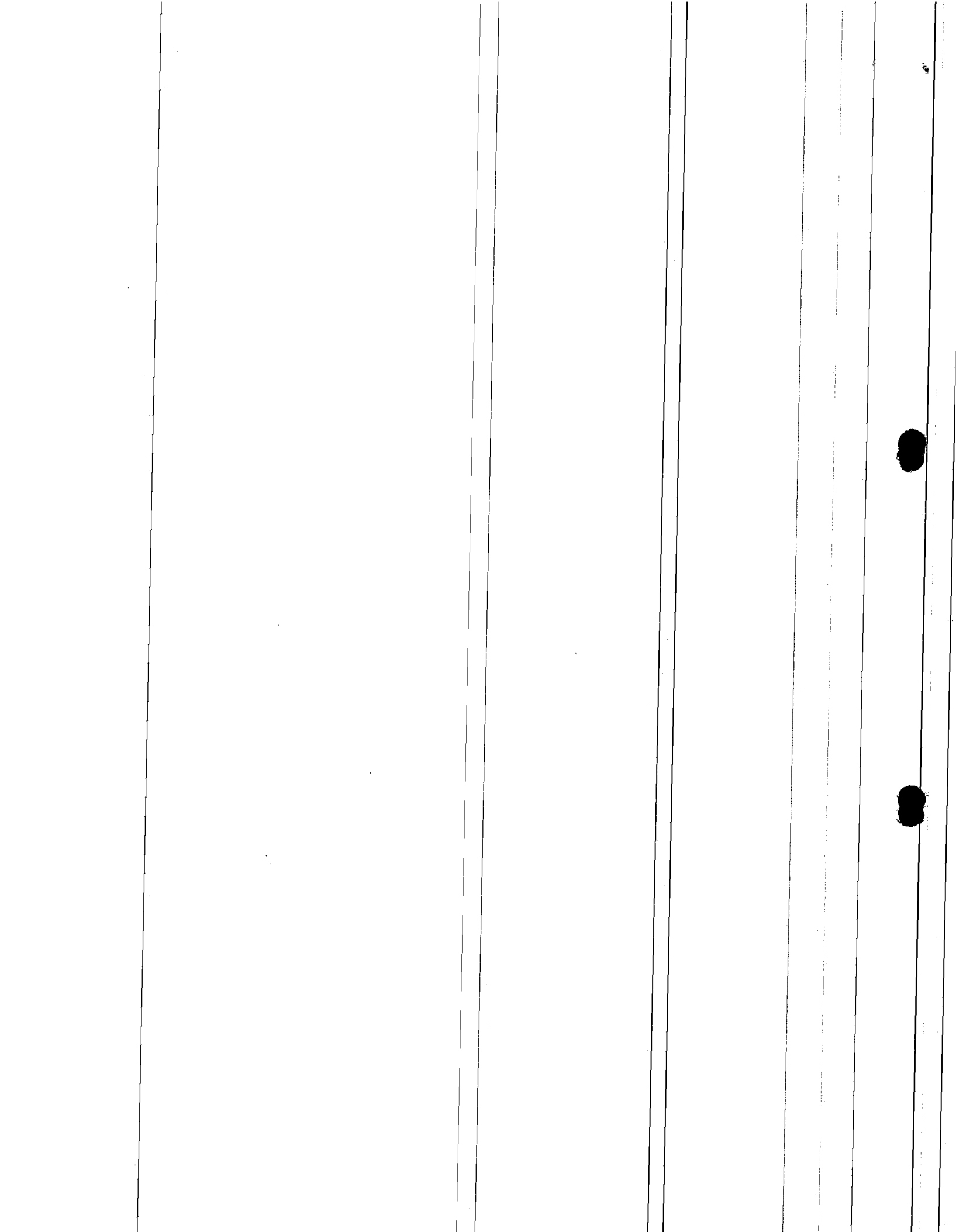
Related U.S. Application Data

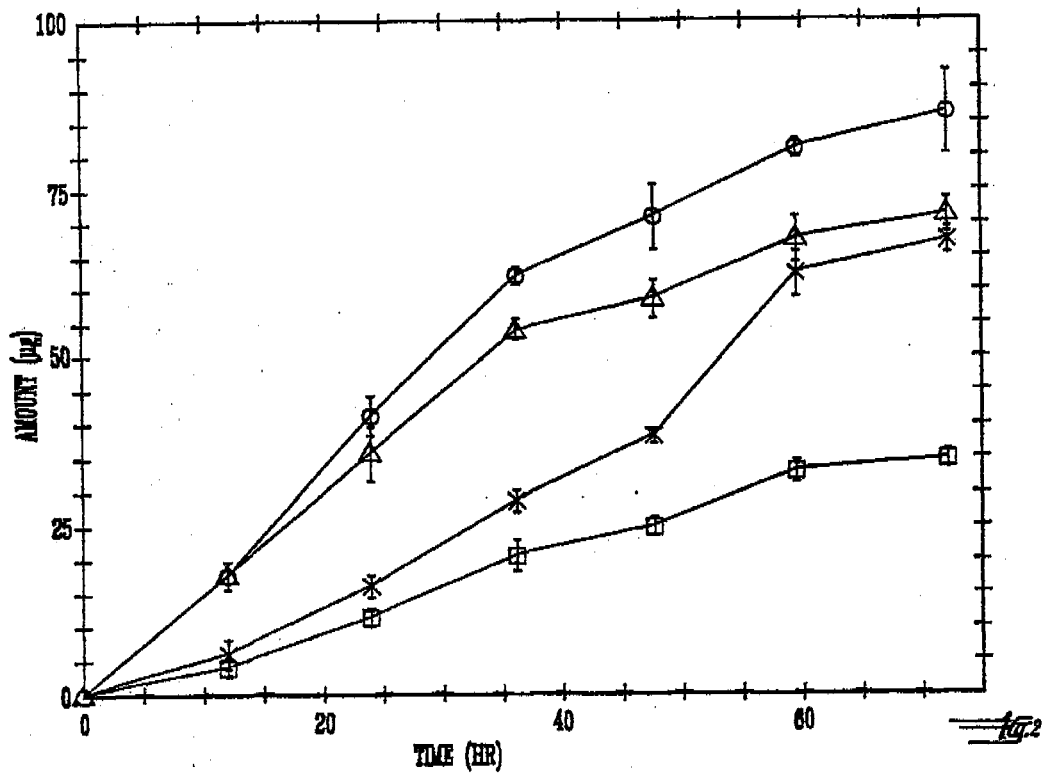
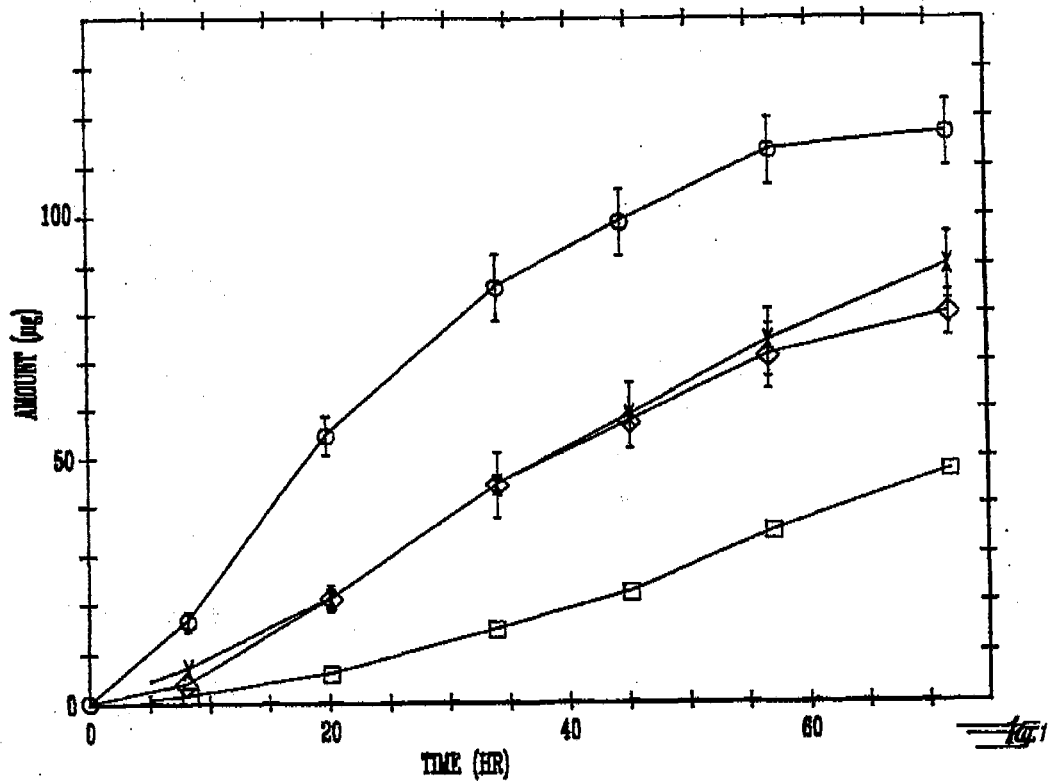
- [62] Division of Ser. No. 201,029, Jun. 1, 1989, Pat. No. 4,980,378.
- [51] Int. Cl.⁵ A61K 47/00
- [52] U.S. CL 514/785; 514/420;
514/946; 514/947
- [58] Field of Search 514/947, 785, 946, 420

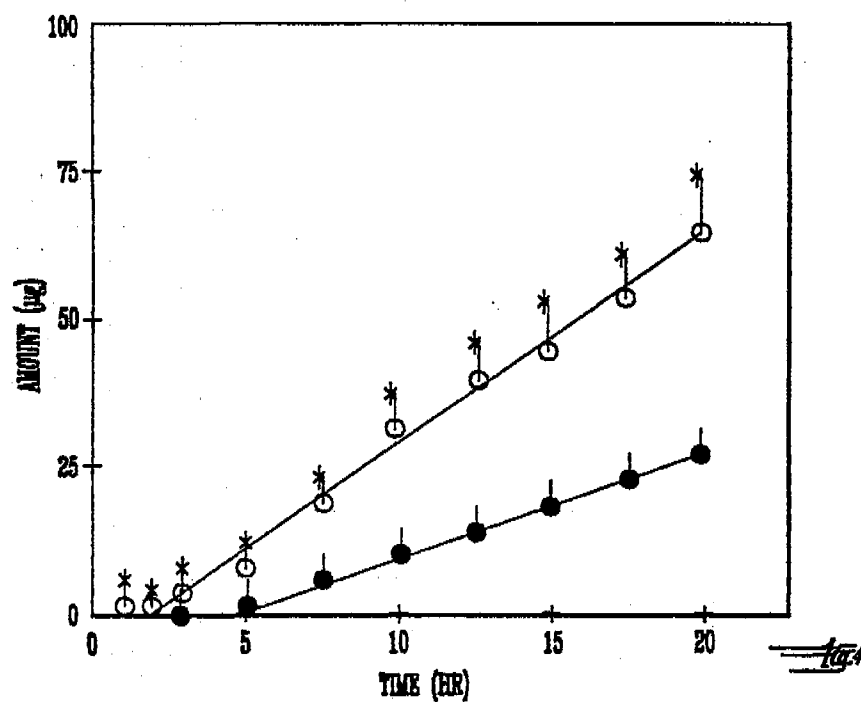
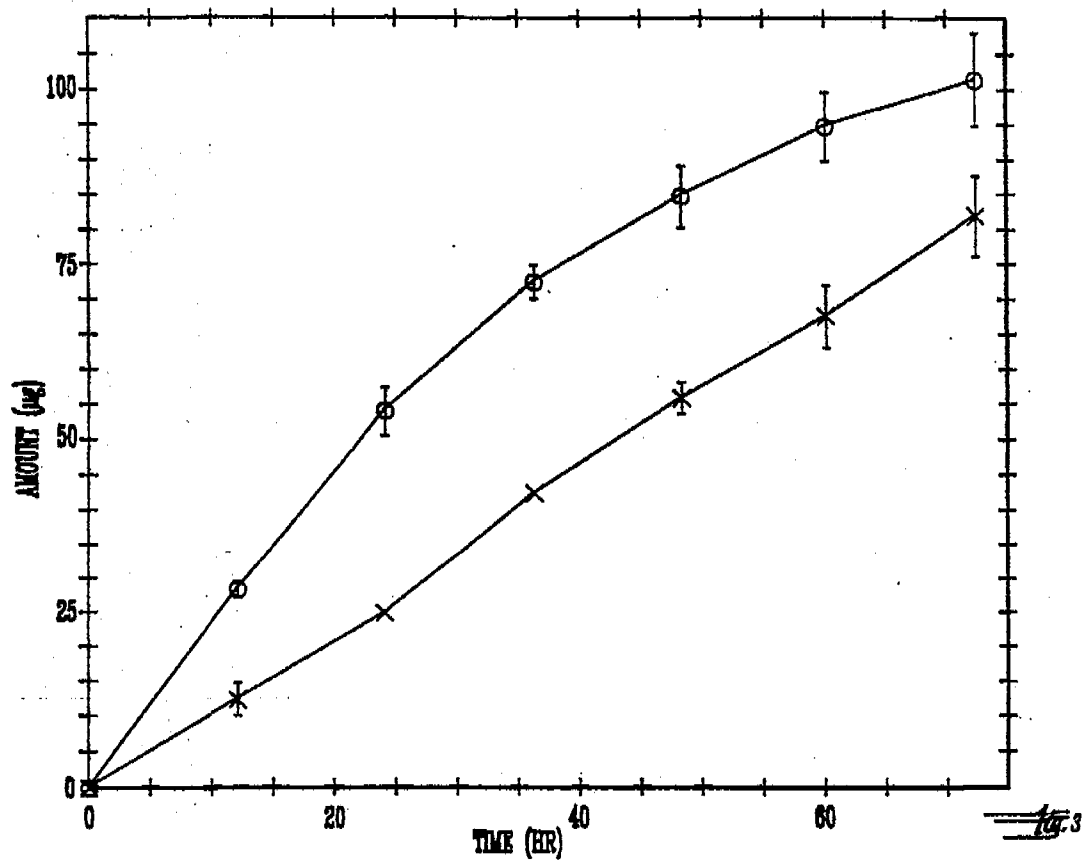
References Cited

U.S. PATENT DOCUMENTS

2,135,641	11/1938	Jacobson	560/155
2,290,174	7/1942	Epstein	560/155
2,293,026	8/1942	Day	560/155
2,293,034	8/1942	Moore	560/155
3,899,585	8/1975	Misato	514/551
4,032,325	6/1977	Kida	71/95
4,732,892	3/1988	Sarpotdar	514/947
4,822,773	4/1989	Alexander	514/947









BIODEGRADABLE ABSORPTION ENHANCERS

This is a divisional of copending application Ser. No. 201,029, filed on June 1, 1989, now U.S. Pat. No. 4,980,378.

FIELD OF THE INVENTION

The invention relates to the development of safe and effective agents which improve the rate of percutaneous and oral mucosal transport of physiologically active agents. More particularly, the present invention relates to an improved topical penetration enhancer for use in the topical delivery of a local or systemic physiologically active agent to a mammalian organism.

BACKGROUND ART

Dermal drug formulations may represent the oldest drug dosage form in human history. It is highly probable that even ancient people used resins and animal fats to treat damage to the skin resulting from injuries and burns. The use of such dermal formulations for local effect remained largely unchanged until the middle of this century. The concept of administering drugs through the skin to achieve a local or systemic effect was first seriously advocated by Dr. Alejandro Zafaroni in the early 1970's. Since that time extensive research has been undertaken in this field.

The transdermal route of drug administration offers a number of advantages over the more conventional routes of drug administration. For instance, a drug may be delivered to targeted tissues from adjacent skin areas. The transdermal route of drug administration also allows for a gradual, controlled release of drug into the systemic circulation. Since many drugs are poorly absorbed or delivered through the traditional routes of administration, the transdermal route provides an effective method of achieving improved bioavailability for those drugs. The transdermal route of drug administration is also advantageous since the administration of dermally administered drugs may be easily stopped should an undesirable side effect occur during therapy.

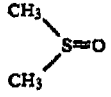
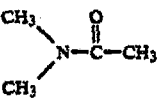
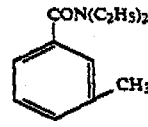
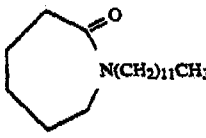
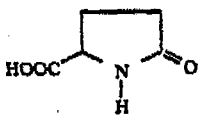
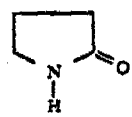
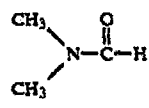
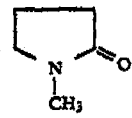
In spite of the foregoing advantages, transdermal formulations are limited. They cannot be used with most polar drugs since they tend to penetrate the skin too slowly. This characteristic is particularly crucial since most drugs are of a polar character. In addition, many drugs elicit a reaction and/or irritation at the site of topical application.

Two methods are known for improving the rate of penetration of polar drugs across the skin. The first method is to make a better formulation of the drug to increase its thermodynamic activity. The thermodynamic activity of a drug in a dermal formulation is dependent on the concentration of the drug and the choice of the vehicle. According to the laws of thermodynamics, the maximum activity of the drug is usually fixed by that of the pure state, i.e., the drug crystal. The second method involves the use of compounds or penetration enhancers to increase the permeability of the barrier membrane. The latter method is generally more practical because of its convenience and effectiveness.

Thus, in the last two decades, a wide variety of compounds have been evaluated as to their effectiveness in enhancing the rate of penetration of drugs through the skin. The classically recognized strong enhancers tend to be proton accepting solvents, e.g., dimethyl sulfoxide (DMSO) and dimethyl acetamide (DMA). Recently,

2-pyrrolidone, N,N-diethyl-m-toluidide (Deet), 1-dodecylazacycloheptane-2-one (Azone, a registered trademark of Nelson Research), N,N-dimethylformamide, N-methyl-2-pyrrolidone and calcium thioglycolate have been reported as effective enhancers. The structures of these compounds are set forth in Table I.

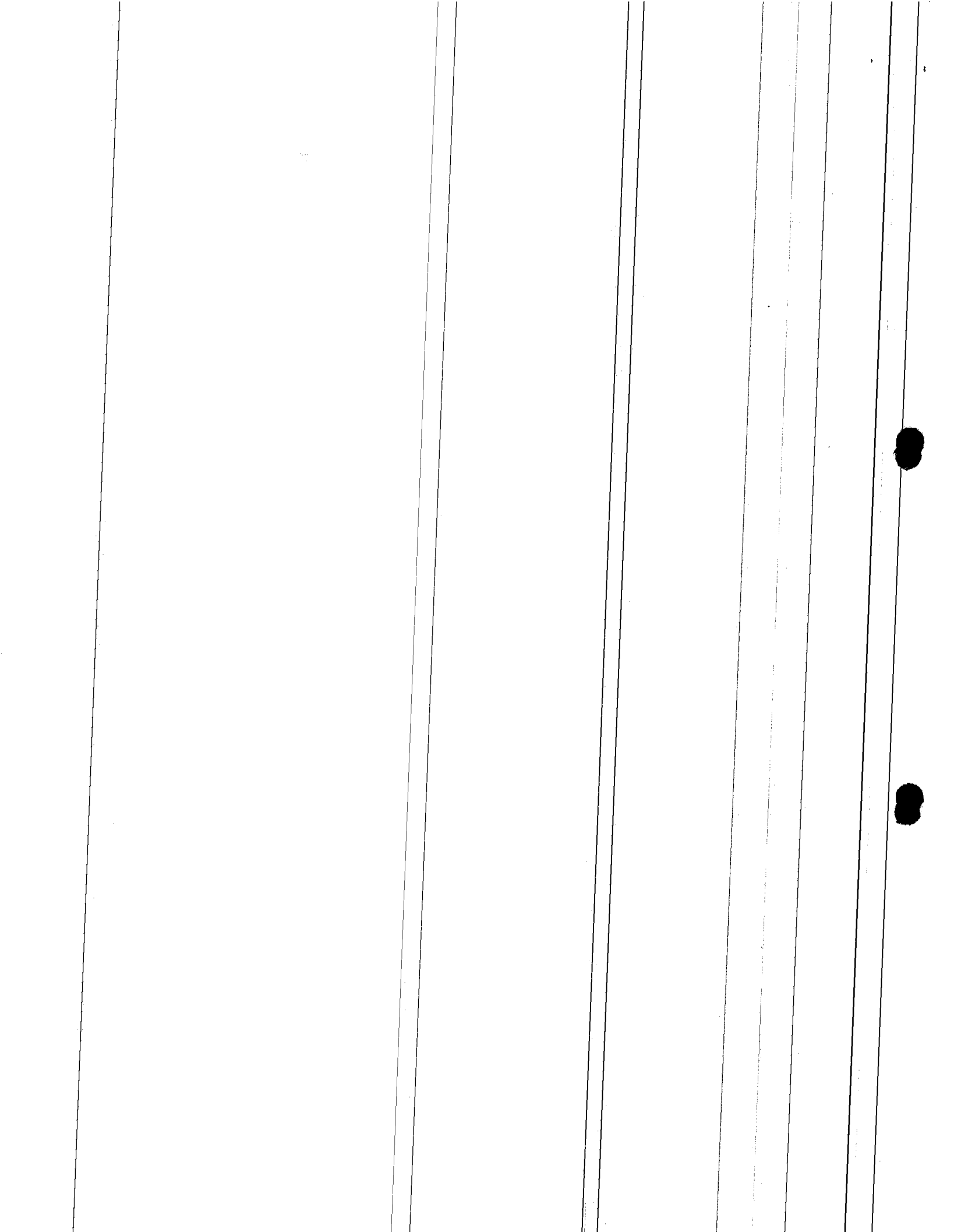
TABLE I

Dimethyl Sulfoxide (DMSO)	
N,N-Dimethyl Acetamide (DMA)	
N,N-Diethyl-m-Toluidide (Deet)	
1-Dodecylazacycloheptane-2-One (Azone or laurocapram)	
2-Pyrrolidone-5-Carboxylic Acid	
2-Pyrrolidone	
N,N-Dimethylformamide	
N-methyl-2-pyrrolidone	
calcium thioglycolate	$\text{CaCH}_2\text{COOS} \cdot 3\text{H}_2\text{O}$

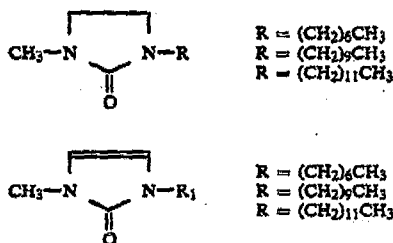
See, for example, the review article by Kenneth A. Walters entitled "Percutaneous absorption and transdermal therapy," *Pharmaceutical Technology*, March 1986, pp. 30-46, which discusses the use of surfactants and penetration enhancers to improve skin transport and their possible mechanisms of action.

Several problems have been associated with these prior art dermal enhancers. They cannot be applied to most polar drugs because they tend to penetrate the skin too slowly. And many of these prior art dermal enhancers produce reactions and/or irritation at the site of application.

In the search for new dermal penetration enhancers, Rinta Iubuki, in his Ph.D. Thesis in 1985 at the University of Kansas entitled "Use of Snake Skin as a Model



Membrane for Percutaneous Absorption Studies," investigated the use of six compounds for transdermal penetration enhancement of indomethacin in a dosage form of a petrolatum ointment. The compounds disclosed in his thesis are presented below:

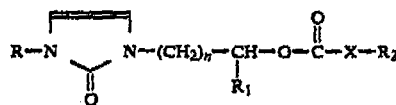


The primary problem with these compounds is their toxicity. Obviously, if a compound when used as a dermal enhancer is either toxic, irritating or allergic, then that compound is unsuitable for application to the human body. DMSO and DMA are also not clinically acceptable for those reasons. Deet and Azone have lower reported toxicities yet their toxicity is high enough such that they are not widely used.

In developing effective dermal enhancers, it would be advantageous to evaluate the potential enhancers by in vivo determination of the rate of human skin penetration of a drug administered along with the enhancer. The amount of drug could be measured in the host's circulation or in the target tissue. Unfortunately, due to the risks involved and the cost of such an evaluation, human in vivo determination is not practical. Thus, researchers have used a variety of mammals for in vivo study. Typical mammals include mice, rats, rabbits, pigs and dogs. However, significant differences have been found in the pattern of drug penetration among these mammals and humans. Although the reason for this species variation has not been well-established, the difference in the density of hair follicles is considered to be a factor.

Thus, the disadvantage of in vivo methods has encouraged wide use of various in vitro methods. Copending application U.S. Ser. No. 901,732, filed Aug. 29, 1986, incorporated by reference herein, discloses a novel method for in vitro determination of transdermal absorption. The method involves the use of shed snake skin.

In spite of the numerous attempts in the art to prepare a method for enhancing the absorption of drugs, especially polar drugs, through the skin, there still exists a clear and present need in the art for a method to enhance the absorption of drugs through the skin. This need has been addressed by co-pending application U.S. Ser. No. 096,092, filed Sept. 11, 1987, which describes a novel group of cyclic urea compounds which enhance the absorption of active substances through the skin while avoiding the significant pharmacological activities and toxicities of the prior art enhancers. The soft penetration enhancers of Ser. No. 096,092 have the formula:



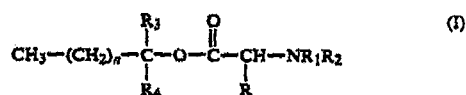
wherein R, R₁ and R₂ are independently selected from hydrogen; hydroxy; fluoride; bromine; chlorine; C₁-C₂₀ alkyl; C₂-C₂₀ alkenyl; C₂-C₂₀ alkynyl; C₃-C₁₀ cycloalkyl; C₂-C₂₀ (monohydroxy or polyhydroxy)alkyl; C₁-C₂₀ (monohalo or polyhalo)alkyl; carboxy; C₁-C₂₀ alkylcarboxy; C₁-C₂₀ alkenylcarboxy; C₁-C₂₀ carboxyalkyl; C₁-C₂₀ alkanoyl; C₁-C₂₀ alkanoyloxy; C₁-C₂₀ alkoxy; carbamoyl; carbamyl; C₁-C₂₀ alkylcarbamyl; sulfo; C₁-C₂₀ alkylsulfonyl; C₁-C₂₀ alkylsulfinyl; C₁-C₂₀ alkylsulfoxide; C₁-C₂₀ alkylthio; thio; C₁-C₂₀ alkylthio; amino; nitro; C₁-C₂₀ alkylamino; C₁-C₂₀ aminoalkyl; substituted or unsubstituted phenyl or benzyl, the substituents being selected from hydroxy, fluoride, bromine, chlorine, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ (monohydroxy or polyhydroxy)alkyl; X is methylene or oxygen and n is 0 to 20.

Improvement of transdermal drug delivery has thus been a focus of pharmaceutical research for many years. However, the stratum corneum presents a formidable barrier to percutaneous drug absorption. This barrier function is believed to be due to the ordered matrix of intercellular lipids and to the low water content in the stratum corneum. Since human gingivae also have stratum corneum, the problems besetting development of gingival formulations are much the same. There is clearly a need for additional novel compounds which enhance the absorption of active substances through the skin and mucous membranes such as the gingivae, but which are designed to have greatly reduced toxicity.

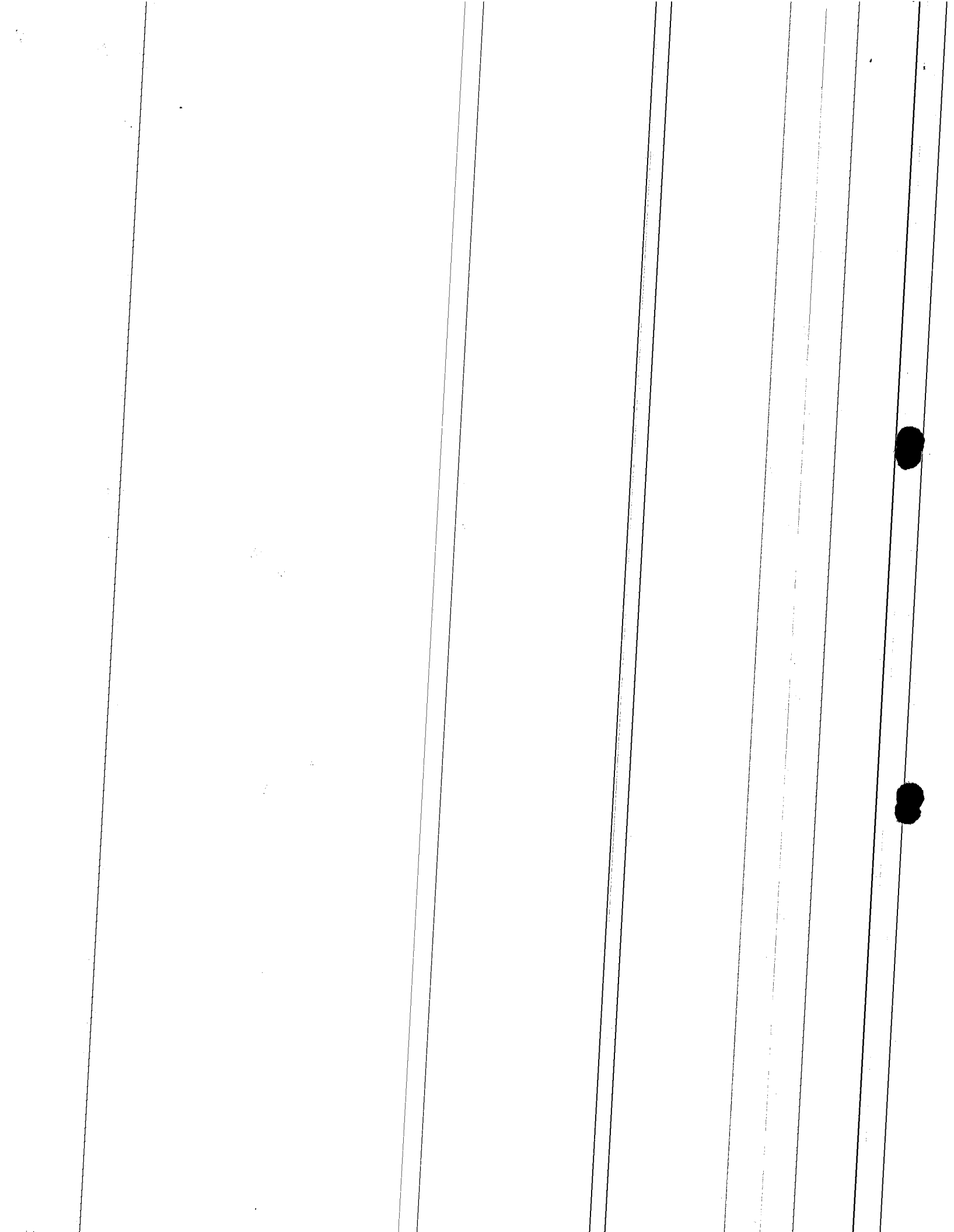
SUMMARY OF THE INVENTION

Surprisingly, the present inventors now find that a novel group of long chain alkyl (N,N-disubstituted amino)acetates and related compounds enhance the absorption of active substances through the skin and mucous membranes while avoiding the significant pharmacological activities and toxicities of the classical prior art enhancers. The present invention thus provides a new class of biodegradable soft penetration enhancers which because of their structure have less adverse or toxic effects but which are nevertheless excellent promoters of percutaneous and oral mucosal (especially gingival) absorption.

The soft penetration enhancers of the present invention have the structural formula



wherein R is hydrogen, C₁-C₇ alkyl, benzyl or 4-hydroxybenzyl; n is a whole number from 4 to 18 inclusive; R₁ and R₂ are independently selected from hydrogen and C₁-C₇ alkyl, or R₁ and R₂ together with the nitrogen atom to which they are attached are combined to form a substituted or unsubstituted heterocycloalkyl radical having a total of 5 to 7 ring atoms, optionally including a hetero ring atom selected from oxygen, sulfur and nitrogen in addition to the indicated nitrogen



atom, the substituents when present being one to three C₁-C₇ alkyl radicals, which may be the same or different; and R₃ and R₄ are independently selected from hydrogen, methyl and ethyl.

The present invention also provides a method for carrying physiologically active agents through body surfaces such as skin and mucous membranes and to compositions for use in that method. More specifically, the invention relates to a method for increasing the penetration of a physiologically active agent across the skin or mucous membrane of a mammalian organism comprising topically applying a physiologically active agent in an amount sufficient to achieve the desired local or systemic effect and the soft penetration enhancing compound described above in an amount sufficient to effectively increase penetration of the physiologically active agent. The invention further provides a pharmaceutical composition comprising same along with a pharmaceutically acceptable carrier therefor.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of the amount of indomethacin, in μ g, detected in the donor cell of a vertical diffusion cell apparatus, versus time, in hours, for an ointment composition containing the prior art enhancer Azone (Δ) or one of three representative enhancers of the invention, CH₃(CH₂)₉OCOCH₂N(CH₃)₂ (O), CH₃(CH₂)₁₁OCOCH₂N(CH₃)₂ ($\diamond$) and



($\square$).

FIG. 2 is a plot as described with reference to FIG. 1 for an ointment composition containing the prior art enhancer Azone (X) or one of three representative enhancers of the invention, CH₃(CH₂)₇OCOCH₂N(CH₃)₂ (O), CH₃(CH₂)₉OCOCH₂N(CH₃)₂ (Δ) and CH₃(CH₂)₁₁OCOCH₂N(CH₃)₂ ($\square$).

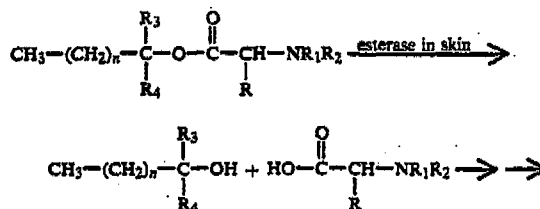
FIG. 3 is a plot as described with reference to FIG. 1 for an ointment composition containing the prior art enhancer Azone (X) or a representative enhancer of the invention, CH₃(CH₂)₁₁OCOCH₂N(CH₃)₂ (O).

FIG. 4 is a plot as described with reference to FIG. 1 for a patch containing 542 $\pm$ 31 mg indomethacin together with a representative enhancer of the invention, CH₃(CH₂)₁₁OCOCH₂N(CH₃)₂ (O), and for a patch containing 582 $\pm$ 24 mg indomethacin together with dodecyl alcohol (e).

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

The long chain alkyl (N,N-disubstituted amino)acetates of the present invention may be described as "soft" dermal penetration enhancers since subsequent to exerting their desired effect, they "cleave" via chemical and/or enzymatic hydrolysis to release nontoxic by-products. Without being bound by any particular theory, it is believed that an active ingredient and a soft penetration enhancer are released from a topical formulation and the soft enhancer would then exert its penetration enhancing effect. The soft or biodegradable penetration enhancer, either during or after penetration, would be broken down by skin enzymes, e.g. esterases, into a long chain alkanol and a substituted amino acid. In this way, the toxicity of the soft penetration enhancer

would be greatly reduced. The possible cleavage of the soft penetration enhancer is set forth below:

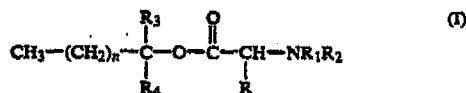


Subcutaneous tissues also contain esterases, so the esters break down during and after incorporation, but before reaching the systemic circulation. The penetration enhancers of the invention may act like biodegradable surfactants in that, after they exert their penetration enhancing effects on drug transport from the topical dosage form, they will be fragmented into smaller compounds, thus reducing toxicity.

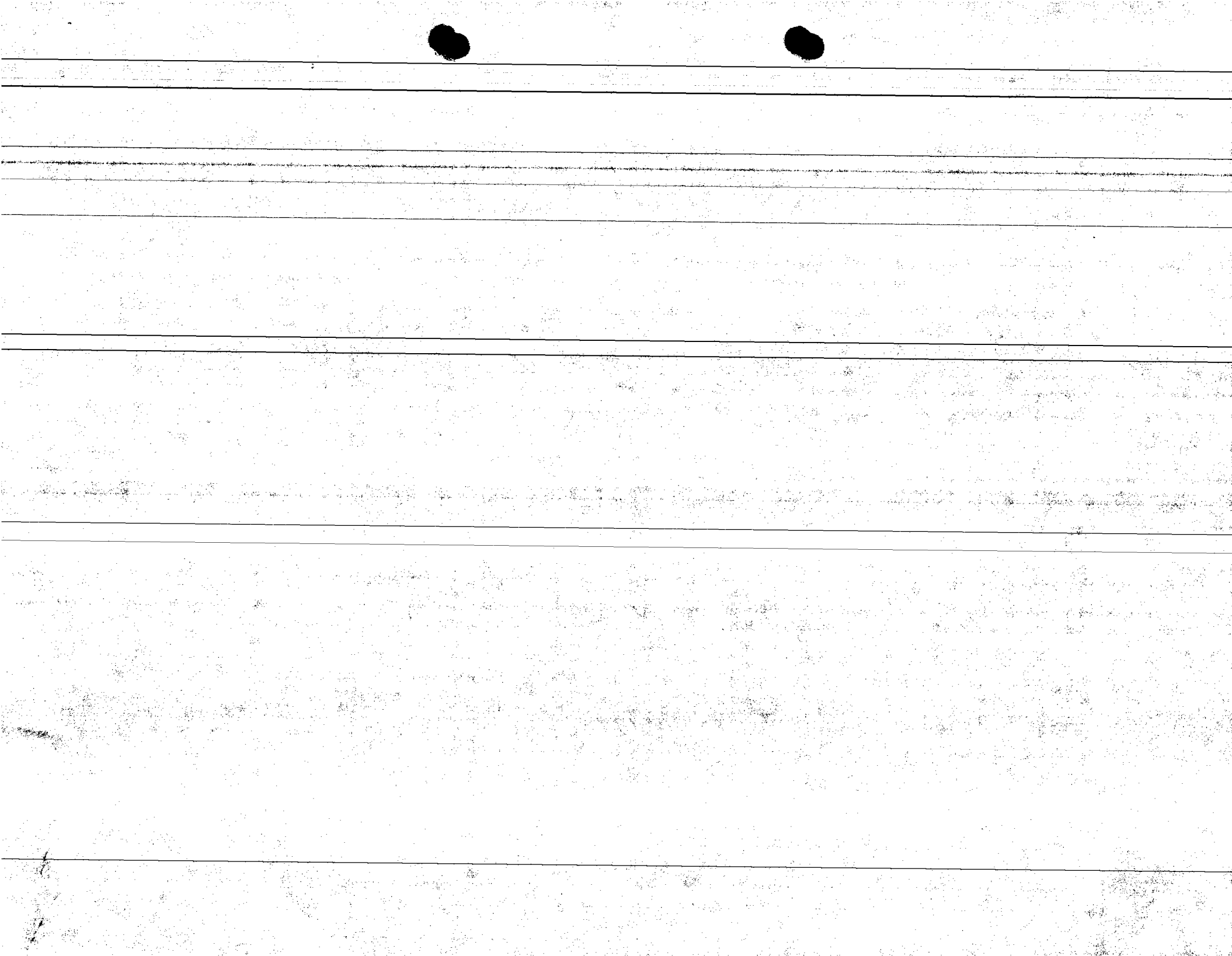
The alkanols and amino acids to which the present enhancers are initially converted by esterases may themselves act as strong enhancers. Alkanols are widely used moisturizers in the cosmetic field and are known to increase transport across the stratum corneum. However, they are weak in practical use, due to their slow incorporation into the stratum corneum. On the other hand, compounds with amino groups are rapidly incorporated into skin.

As noted earlier, the prior art absorption enhancers have significant pharmacological activities and toxicities. The compounds of the present invention, on the other hand, are a new class of enhancers which, because of their structure, do not demonstrate a significant adverse effect on the skin or mucous membranes and yet are excellent promoters of percutaneous absorption. The toxicity of known enhancers is generally due to the fact that they are not metabolized by pathways which would diminish their toxicity. To minimize toxicity, the basic structure of the synthesized enhancer should be selected to resemble those biological substances which are well-known metabolites. The enhancers of the present invention were specifically designed to be metabolized in a non-toxic fashion. Moreover, the present compounds are liquid so they can be readily incorporated into the skin.

The long chain alkyl (N,N-disubstituted amino)acetates and related compounds of the present invention have the formula:



wherein R is hydrogen; C₁-C₇ alkyl, benzyl or 4-hydroxybenzyl; n is a whole number from 4 to 19 inclusive, and R₁ and R₂ are independently selected from hydrogen and C₁-C₇ alkyl, or R₁ and R₂ together with the nitrogen atom to which they are attached are combined to form a substituted or unsubstituted heterocycloalkyl radical having a total of 5 to 7 ring atoms, optionally including a hetero ring atom selected from oxygen, sulfur and nitrogen in addition to the indicated nitrogen atom, the substituents when present being one to three C₁-C₇ alkyl radicals, which may be the same or



different; and R_3 and R_4 are independently selected from hydrogen, methyl and ethyl.

The alkyl radicals may be straight or branched, i.e. methyl, ethyl, propyl, butyl, pentyl, hexyl and heptyl, and the branched chain groups isomeric therewith.

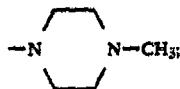
When R_1 and R_2 are combined with the adjacent nitrogen atom such that



represents a heterocycloalkyl radical, illustrative such heterocycloalkyl radicals include morpholino, 1-pyrrolidinyl, perhydro-1,2,4-oxathiazin-4-yl, 1- or 4-piperazinyl, 4-methyl-1-piperazinyl, piperidino, hexamethylenecimino, 2-methyl-1-pyrazolidinyl, 1- or 2-pyrazolidinyl, 3-methyl-1-imidazolidinyl and 1- or 3-imidazolidinyl.

In preferred embodiments of the invention, the substituents in formula (I) have one or more of the following values:

- (1) R is hydrogen;
- (2) n is 6, 8, 10 or 12; and
- (3) R_1 and R_2 are both methyl or both ethyl, or together with the adjacent nitrogen atom represent a 4-methyl-1-piperazinyl radical, i.e. a radical of the formula

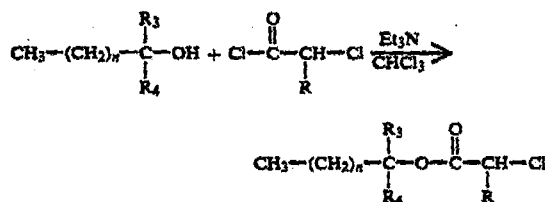


and

- (4) R_3 and R_4 are both hydrogen.

Particularly preferred compounds of the present invention include dodecyl (N,N-dimethylamino)acetate, decyl (N,N-dimethylamino)acetate and octyl (N,N-dimethylamino)acetate.

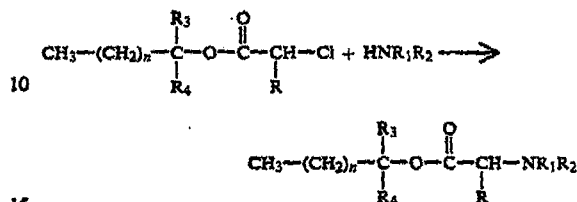
The compounds of formula (I) are readily prepared via a two-step synthesis. In the first step, long chain alkyl chloroacetates are prepared by reaction of the corresponding long chain alkanols with chloromethyl chloroformate or the like in the presence of an appropriate base such as triethylamine, typically in a suitable solvent such as chloroform. The reaction can be depicted as follows:



wherein R , R_3 , R_4 and n are as defined as above. The reaction temperature may be selected from about 10° C. to about 200° C. or reflux; however, room temperature is preferred. The use of a solvent is optional. If a solvent is used, a wide variety of organic solvents may be selected. Choice of a base likewise is not critical. Preferred bases include tertiary amines such as triethylamine,

pyridine and the like. Reaction time generally extends from about one hour to three days.

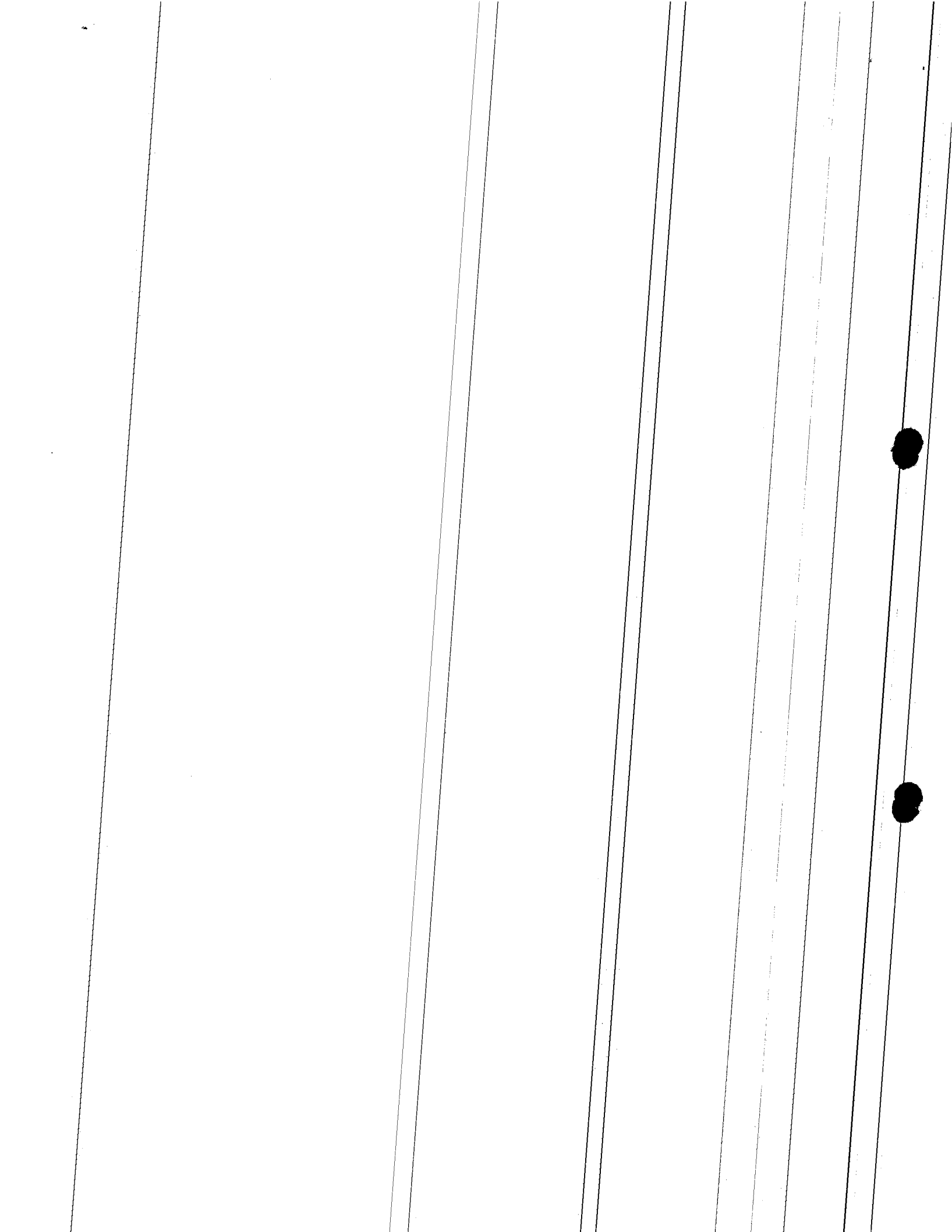
In the second step, the long chain alkyl chloroacetate is condensed with an appropriate amine according to the scheme:



wherein n , R , R_1 , R_2 , R_3 and R_4 are defined as before. Excess amine reactant is typically used as the base and the reaction is conveniently conducted in a suitable solvent such as ether. The reaction is preferably run at room temperature; however, other temperatures may be selected above or below room temperature, as in the first synthetic step. Again, reaction time usually varies from about one hour to several days.

The amount of the penetration enhancer of formula (I) which may be used in the present invention is an effective, non-toxic amount for enhancing absorption either through the skin or mucous membranes. Generally, this amount ranges from about 1 to about 95 weight percent of the topical composition. Preferably, about 0.5 to about 40 weight percent of the penetration enhancer is used in the composition.

The compounds described herein are useful in improving percutaneous or mucous membrane absorption of physiologically active agents. The term "percutaneous" means transdermal or transcutaneous; it denotes the passage of substances through unbroken skin. While the term "mucous membrane absorption" refers generally to any of the mucous membranes in the body, absorption through the mucous membranes of the oral cavity is of particular interest. Thus, buccal, sublingual, gingival and palatal absorption are specifically contemplated by the present invention. In a preferred embodiment, the instant penetration enhancers are used to improve absorption through those oral tissues which most resemble the skin in their cellular structure, i.e. the gingivae and palate. The term "physiologically active agent" is used herein to refer to a broad class of useful chemical and therapeutic agents including physiologically active steroids, antibiotics, antifungal agents, antibacterial agents, antineoplastic agents, analgesics and analgesic combinations, anorexics, anthelmintics, antiarrhythmics, antiasthma agents, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antinotion sickness preparations, antinauseants, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, including gastrointestinal and urinary; anticholinergics, sympathomimetics, xanthine derivatives, cardiovascular preparations including calcium channel blockers, betablockers, antiarrhythmics, antihypertensives, diuretics, vasodilators including general, coronary, peripheral and cerebral; central nervous system stimulants, cough and cold preparations, decongestants, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics, psychostimulants, sedatives, tranquilizers, allergens, antihistaminic agents, anti-inflammatory agents,



physiologically active peptides and proteins, ultraviolet screening agents, perfumes, insect repellents, hair dyes, and the like. The term "physiologically active" in describing the agents contemplated herein is used in a broad sense to comprehend not only agents having a direct pharmacological effect on the host but also those having an indirect or observable effect which is useful in the medical arts, e.g. the coloring or opacifying of tissue for diagnostic purposes, the screening of U.V. radiation from the tissues and the like.

For instance, typical fungistatic and fungicidal agents include thiabendazole, chloroxine, amphotericin, candidin, fungimycin, nystatin, chlordanol, clotrimazole, ethonam nitrate, miconazole nitrate, pyrrolnitrin, salicylic acid, fozatione, ticlatone, tolnaftate, triacetin, zinc pyrrithione and sodium pyrrithione.

Steroids include cortisone, cortodoxone, fluoracetone, fludrocortisone, difluorone diacetate, flurandrenolone acetone, medrysone, amcinafel, amcinafide, betamethasone and its esters, chloroprednisone, cortelone, desinolone, desonide, dexamethasone, dichlorisone, difluprednate, flucorolone, flumethasone, flunisolide, flucoronide, flucortolone, fluoromethalone, fluperolone, fluprednisolone, meprednisone, methylmeprednisolone, paramethasone, prednisolone and prednisone.

Antibacterial agents include sulfonamides, penicillins, cephalosporins, penicillinase, erythromycins, lincomycins, vancomycins, tetracyclines, chloramphenicols, streptomycins, and the like. Specific examples of antibacterials include erythromycin, erythromycin ethyl carbonate, erythromycin estolate, erythromycin gluceptate, erythromycin ethylsuccinate, erythromycin lactobionate, lincomycin, clindamycin, tetracycline, chlorotetracycline, demeclocycline, doxycycline, methacycline, oxytetracycline, minocycline, and the like.

Peptides and proteins include, in particular, small to medium-sized peptides, e.g., insulin, vasopressin, oxytocin and human growth hormone.

Other agents include iododeoxyuridine, podophylline, theophylline, isoproterenol, triamcinolone acetate, hydrocortisone, indomethacin, phenylbutazone, paraaminobenzoic acid, aminoprionitrile and penicillamine.

The foregoing list is by no means intended to be exhaustive and any physiologically active agent may be applied by the method of the present invention.

An important advantage of the present invention is that absorption of polar bioactive agents as well as non-polar drugs is also improved. The polar bioactive agents encompass a variety of therapeutic agents such as the xanthines, triamterene and theophylline, the antitumor agents, 5-fluorouridinedeoxyriboside, 6-mercaptopurinedeoxyriboside, vidarabine, the narcotic analgesics, hydromorphone, cyclazine, pentazocine, buporphine, the compounds containing organic anions, heparin, prostaglandins and prostaglandin-like compounds, cromolyn sodium, carbenoxolone, the polyhydroxylic compounds, dopamine, dobutamine, 1-dopa, α -methyl-dopa, the polypeptides, angiotensin antagonists, bradykinin, insulin, ACTH, enkaphaline, endorphin, somatostatin, secretin and miscellaneous compounds such as tetracyclines, tromocriptine, lidocaine, cimetidine or any related compounds. The quantity of these polar bioactive agents necessary for preparing the drug form could vary over a wide range, but would normally be regulated by that quantity necessary to comprise the therapeutically effective dosage form.

Agents normally applied as eye drops, ear drops or nose drops or into the membranes of the oral cavity are also more effective when applied along with the penetration enhancers of the present invention.

As indicated earlier, agents used in diagnosis may be used more effectively when applied dissolved in one of the vehicles of this invention. Patch tests to diagnose allergies may be effected promptly without scratching the skin or covering the area subjected to an allergen when the allergens are applied along with the enhancers of this invention.

This invention is also useful in topical application of cosmetic or esthetic agents. For example, compounds such as melanin-stimulating hormone (MSH) or dihydroxy acetone and the like are more effectively applied to skin to simulate a suntan when they are applied along with the enhancers of this invention. The agent is carried into the skin more quickly and in greater quantity when applied in accordance with this invention. Hair dyes also penetrate more completely and effectively when dissolved in one of the vehicles of this invention.

While the foregoing discussion describes the simultaneous administration of the physiologically active agent along with the penetration enhancer, the penetration enhancer may be applied before or after to the application of the physiologically active agent, if desired.

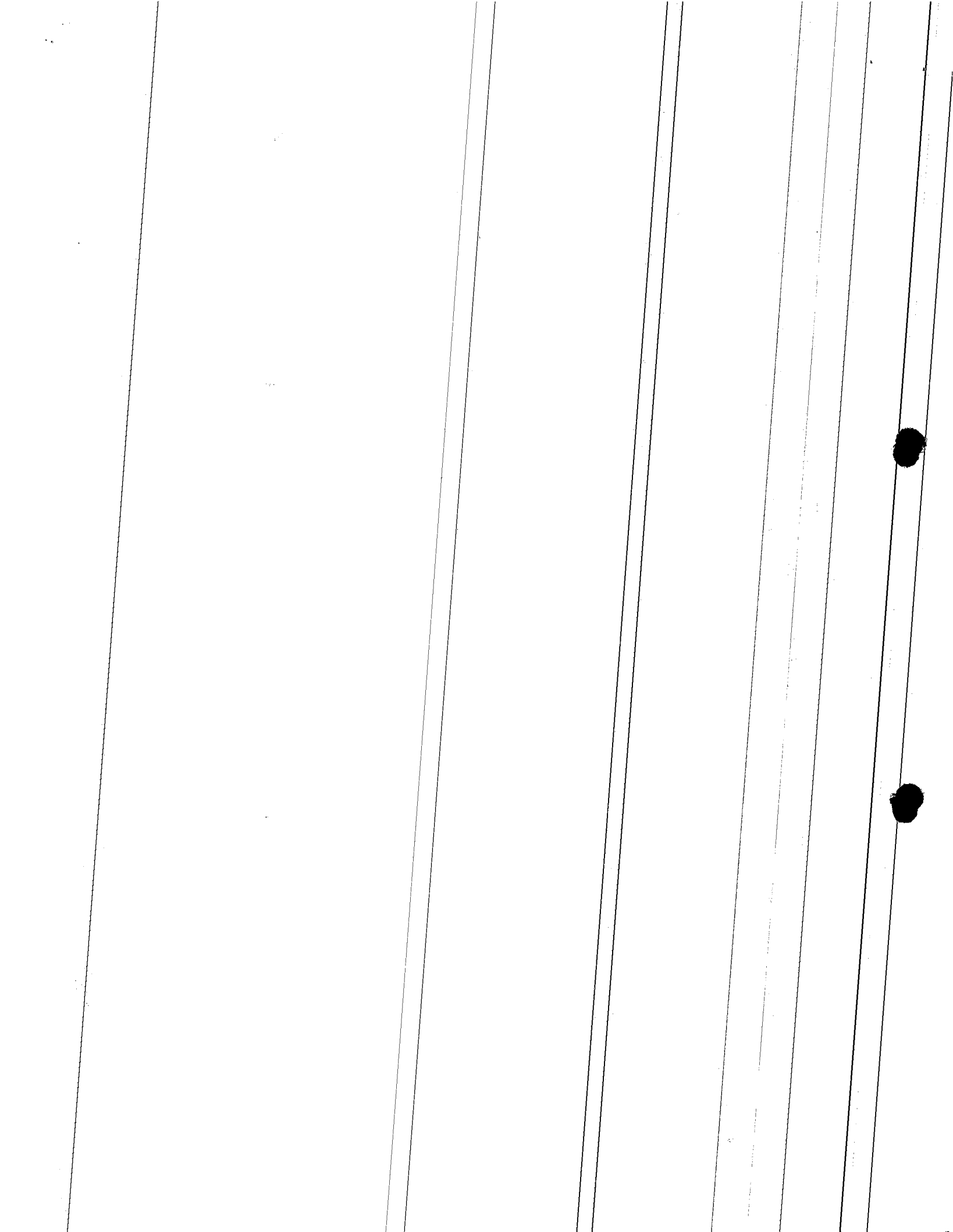
The physiologically active agents intended for use in the practice of the present invention are intended for either their systemic effect or for their local effect.

Dosage forms for topical application to the skin or mucous membranes of humans and animals include creams, lotions, gels, ointments, suppositories, sprays, for example nasal sprays, aerosols, buccal and sublingual tablets, gingival and buccal patches or any one of a variety of transdermal devices for use in the continuous administration of systemically active drugs by absorption through the skin, oral mucosa or other membranes, see for example, one or more of U.S. Pat. Nos. 3,598,122, 3,598,123, 3,731,683, 3,742,951, 3,814,097, 3,921,636, 3,971,995, 3,993,072, 3,993,073, 3,996,934, 4,031,894, 4,060,084, 4,069,307, 4,201,211, 4,230,105, 4,292,299 and 4,292,303 and U.S. Pat. No. 4,077,407. The foregoing patents also disclose a variety of specific systemically active agents which may also be useful in transdermal delivery, which disclosures are hereby incorporated herein by reference.

The usual pharmaceutical compounding agents, diluents or carriers may be included in these compositions as desirable for the particular route of administration and dosage form. The amount and type of diluent or carrier used should, of course, be consistent with the compatibility of the agent with the compound of this invention. For instance, a cosolvent or other standard adjuvant, such as a surfactant, may be necessary to maintain the agent in solution or suspension at the desired concentration.

For nasal sprays and other mucous membrane applications isotonic saline may be preferable as a diluent. The instant enhancer may be present in these forms in various concentrations, for example, from about 2% to about 75% by weight or higher.

Lotions and gels, ointments or creams, may contain the usual ingredients to provide a base, as for example cetyl alcohol, an emulsifier such as lauryl sulfate and water. Another base may be formulated by combining equal weight amounts of stearic acid, cetyl alcohol, triethanolamine and glycerol monostearate with water. Still other bases may utilize polyethylene glycols of



different viscosities, depending upon the desired consistency.

A suppository form may be made from a high viscosity polyethylene glycol 4000, water and the penetration enhancer.

Typical inert carriers which may be included in the foregoing dosage forms include conventional formulating materials, such as, for example, water, acetone, isopropyl alcohol, freons, ethyl alcohol, polyvinyl pyrrolidone, propylene glycol, fragrances, gel-producing materials such as "Carbopol", mineral oil, stearyl alcohol, stearic acid, spermaceti, sorbitan monooleate, "Polysorbates", "Tweens", sorbitol, methylcellulose, and the like. The compositions of the present invention are formulated with any suitable nontoxic pharmaceutically acceptable inert carrier material. Such carrier materials are well known to those skilled in the art of pharmaceutical formulations. For those not skill in the art, reference is made to the text entitled, "REINGTON'S PHARMACEUTICAL SCIENCES," 17th edition, 1985, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, Pa. 18042.

Any type of transdermal drug delivery system is also suitable in the practice of the present invention, for instance, the transdermal patch. A variety of transdermal drug delivery systems are disclosed and described in U.S. Pat. No. 4,624,665, herein incorporated by reference.

The amount of the composition, and thus of the physiologically active agent therein, to be administered will obviously be an effective amount for the desired result expected therefrom. This, of course, will be ascertained by the ordinary skill of the practitioner. Due to enhanced activity which is achieved, the dosage of the physiologically active agent may often be decreased from that generally applicable. In accordance with the usual prudent formulating practices, a dosage near the lower end of the useful range of the particular agent may be employed initially and the dosage increased as indicated from the observed response, as in the routine procedure of the physician.

The concentration of physiologically active agent in the various dosage forms is, of course, commensurate with that normally utilized for the particular agent in conventional formulations for effective results for the intended route. Both the amount of physiologically active agent and the amount of penetration enhancer will be influenced by the type of effect desired. To a certain degree, if a more localized effect is required, as for example, in treating a superficial infection with an antibacterial agent, lower amounts of physiologically active agents and lower concentrations of enhancer may be called for. Where deeper penetration is desired, as in the case of local anaesthesia, a higher concentration of enhancer may be desirable to promote adequate penetration. Where general systemic concentration of an agent is desired for a topical preparation, generally higher concentrations of enhancer are desirable and the amount of agent as, for example, a steroid, may be included in the composition sufficient to provide the blood level desired.

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that same are intended only as illustrative and in nowise limitative.

EXAMPLE 1

Preparation of Dodecyl Chloroacetate

A mixture of dodecanol (10 g, 0.054 mol), chloromethyl chloroformate (6 g, 0.05 mol) and triethylamine (5.5 g) in 40 ml of dry chloroform was stirred at room temperature for 16 hours. The reaction mixture was then washed twice with water (50 ml per washing) and the organic phase was dried over anhydrous magnesium sulfate. Removal of the solvent gave 13.3 g (94% yield) of liquid product, which was chromatographed through a column of Florisil using chloroform as the eluent. ¹HNMR(CCl₄) 80.90(3H, t, CH₃); 1.28[20 H, s, broad, -(CH₂)₁₀-]; 3.93(2H, s, -CH₂Cl); 4.11(2H, t, J=6 Hz, -CH₂-O). *v*_{max} (film): 2940, 2880(CH); 1765, 1745(C=O); 1180 (-C-O-C-)cm⁻¹.

EXAMPLE 2

Preparation of Dodecyl (N,N-dimethylamino)acetate

Dodecyl chloroacetate (5.5 g, 0.021 mol) was dissolved in 20 ml of ether and the resultant solution was cooled in an ice-bath. Dimethylamine (40 ml, 0.1M in ether) was added to the cooled solution of dodecyl chloroacetate. The reaction mixture was stirred at room temperature for two hours, then filtered through a filter paper to remove the white solid which formed. The filtrate was concentrated to give a liquid product which was chromatographed through a column of silica gel (60-200 mesh) using ethyl acetate as the eluent. The purity of the fractions was checked by thin layer chromatography. The pure fractions were combined and the solvent was removed by a rotary evaporator under reduced pressure to afford 5.8 g (100% yield) of dodecyl (N,N-dimethylamino)acetate. ¹HNMR(CCl₄) 80.83(3H, t, CH₃); 1.20[20 H, s, broad, -(CH₂)₁₀]; 2.23[6H, s, (CH₃)₂N-]; 3.0 (2H, s, -CH₂-N); 3.93 (2H, t, J=6 Hz, -OCH₂-). *v*_{max}(film): 2940, 2870, 2790(CH); 1760, 1740(C=O); 1200, 1170 (-C-O-C-)cm⁻¹. m/e 271; C₁₆H₃₃NO₂ requires 271.

EXAMPLE 3

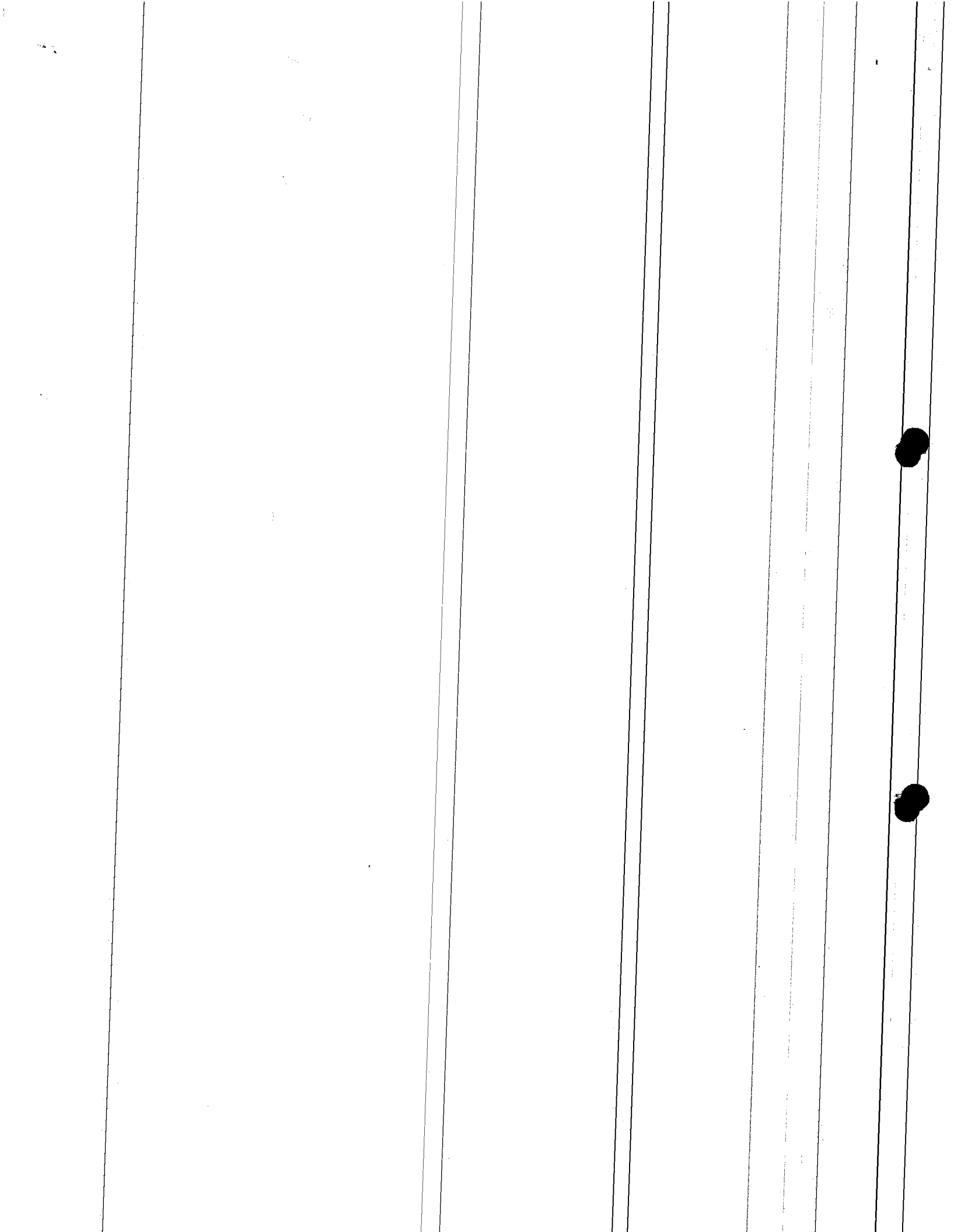
Preparation of Decyl (4-methyl-1-piperazinyl)acetate

Following the general procedure of Example 2, a mixture of decyl chloroacetate (5 g, 0.021 mol) and 1-methylpiperazine (2 equivalents) in 20 ml of ether was stirred for one and one-half days. Work-up as in Example 2 gave 6 g of a liquid product (92% yield), which was chromatographed through a column of silica gel using ethyl acetate as the eluent. ¹HNMR(CCl₄) 0.73(3H, t, CH₃); 1.13[16H, s, broad, -(CH₂)₈-]; 2.03 (3H, s, CH₃N-); 2.27(8H, multiplets, -NCH₂CH₂-); 2.91(2H, s, -CH₂N-); 3.87(2H, t, J=6 Hz, OCH₂). *v*_{max} (film): 2940, 2870, 2800, 2700(CH); 1755 (C=O); 1170 (-C-O-C-)cm⁻¹. m/e 298; C₁₇H₃₄N₂O₂ requires 298.

EXAMPLE 4

Preparation of Representative Intermediates and Final Products

Alkyl chloroacetates were prepared in almost quantitative yields by reaction of chloromethyl chloroformate with n-alkanols in the presence of triethylamine, as in Example 1. The purification of these compounds is straight-forward, by column chromatography using silica gel as the supporting material and chloroform as



the eluent. Yields are summarized in TABLE 1 below.

TABLE 1

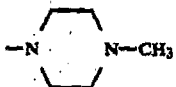
$$\text{CH}_3-(\text{CH}_2)_n-\overset{\text{R}_3}{\underset{\text{R}_4}{\text{C}}}-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\underset{\text{R}}{\text{CH}}-\text{Cl} \quad (\text{II})$$

Name of Compound	R	n	R ₃	R ₄	Yield (%)
tetradecyl chloroacetate	H	12	H	H	85
dodecyl chloroacetate	H	10	H	H	94
decyl chloroacetate	H	8	H	H	100
octyl chloroacetate	H	6	H	H	100

The penetration enhancers of formula (I) were also prepared in high yield, as in Example 2, by condensation of the alkyl chloroacetates with excess amine. Purification is also simple due to the high yields and high R_f values on thin layer chromatography using ethyl acetate as the developing solvent. Because of their low ultraviolet absorption, the purity of the products was checked by thin layer chromatography, using Analtech HPTLC-GHLF tic plates, ethyl acetate as the developing system and iodine vapor as the visualizing agent. Nuclear magnetic resonance, infrared and mass spectra were consistent with the assigned structures. Yields are summarized in Table 2 below:

TABLE 2

$$\text{CH}_3-(\text{CH}_2)_n-\overset{\text{R}_3}{\underset{\text{R}_4}{\text{C}}}-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\underset{\text{R}}{\text{CH}}-\text{NR}_1\text{R}_2 \quad (\text{I})$$

Name of Compound	R	n	—NR ₁ R ₂	R ₃	R ₄	Yield (%)
tetradecyl (N,N-dimethylamino)-acetate	H	12	—N(CH ₃) ₂	H	H	90
dodecyl (N,N-dimethylamino)-acetate	H	10	—N(CH ₃) ₂	H	H	100
decyl (N,N-dimethylamino)-acetate	H	8	—N(CH ₃) ₂	H	H	91
octyl (N,N-dimethylamino)-acetate	H	6	—N(CH ₃) ₂	H	H	72
dodecyl (N,N-diethylamino)-acetate	H	10	—N(C ₂ H ₅) ₂	H	H	95
decyl (4-methyl-1-piperazinyl)-acetate	H	8		H	H	96

EXAMPLE 5

Preparation of Ointment for Evaluation

Ointments were prepared by mixing 100 mg (1%) indomethacin, 500 mg (5%) penetration enhancer and 9400 mg (94%) petrolatum at 55°–60° C. to give a homogeneous dispersion of indomethacin. In each transport study, 30 mg of ointment containing 300 g of indomethacin was applied.

EXAMPLE 6

Preparation of Patch for Evaluation

Patches were prepared by first dissolving 300 mg indomethacin, 400 mg penetration enhancer, 300 mg polyethylene glycol 400 and 800 mg hydroxypropyl cellulose in 20 ml of ethanol. That viscous solution was spread on a backing layer, which was a film of ethoxycellulose, with 0.9 mm of thickness. After drying at 40° C. for one hour, two layer film patches were obtained. Circles with a diameter of 12 mm were used for the transport studies.

EXAMPLE 7

Preparation and Use of the Black Rat Snake Barrier Membrane to Evaluate Drug Penetration

A whole shed snake skin from the molt of adult *Elaphe obsoleta* (black rat snake) was obtained from the Animal Care Unit of the University of Kansas. Only the dorsal side of the shed snake skin was used for in vitro penetration studies. The head and tail sections of the snake skin was removed and the remainder of the skin was cut randomly into sections of approximately 2 inches by 2 inches. Each piece of snake skin was hydrated overnight by first soaking the skin in water (about 5 to 10 minutes) until it could be stretched and then placing it on a plastic pan which held some water. The pan was floated on a water-bath at 32° C. overnight.

For the transport studies using ointments, approximately 30 mg of ointment prepared as described in Example 5 was smeared evenly on an area of the 2"×2" snake skin. The ointment was smeared into an essentially circular area approximately 1.77 cm² and having a diameter of approximately 15 mm. The snake skin was then mounted on top of the receptor cell of a verticle diffusion cell assembly in which a small magnetic bar was inserted and filled with an isotonic buffer. A rubber o-ring was placed on top of the skin followed by the placement of the donor cell. The two cells were clamped together and transferred to a water-bath (32° C.) which had several magnetic stirrers placed underneath to stir the contents of the diffusion cells. Samples from the cells were withdrawn periodically by gravity by inputting fresh isotonic buffer into the cell inlets. The first five drops were discarded and the following four drops were collected for analysis. These nine drops of sample solution were approximately equivalent to about 0.20 ml.

The samples were analyzed for the concentration of indomethacin using a Perkin-Elmer ISS-100 HPLC apparatus with a Perkin-Elmer LC90 UV spectrophotometric detector and a Perkin-Elmer ISS-100 automatic sampler with the detection wavelength set at 260 nm. The peak heights of the chromatograms were recorded on a Perkin-Elmer LCI-100 Laboratory Computing Integrator. A reverse phase column, RP-8 Spheri-5, 4.6×100 mm and a guard column OD-GU, purchased from Brownlee Labs, were used in conjunction with the HPLC system. The flow rate was 1.0 ml/min and the solvent system was a mixture of acetonitrile (50%) and a 0.01M phosphate buffer (pH 3.0) (50%).

The concentration in each sample was interpreted from a standard curve which was obtained by plotting the peak areas obtained from HPL chromatograms versus four different standard solutions of indomethacin. The standard curves were linear over a range of



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concentrations from 2.5 to 10 g/ml. The receptor cell volume was calibrated by weighing the amount of water in the cell. The first sample needs no concentration correction. However, the concentration in the subsequent samples can be corrected by the following equation:

$$\left(\frac{\text{volume withdrawn}}{\text{volume of the receptor cell}} \times X_i \right) + X_{i+1} + Y_i$$

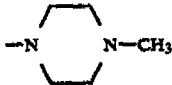
where X_i is number of microgram of indomethacin in the i^{th} with sample. Y_i is the concentration correction for $i-1$ sample. The volume withdrawn for each sampling is about 0.20 ml.

For the transport studies using patches, the same procedures were used as described above for the ointments, except that patches were prepared as described in Example 6 and the studies were performed using a new diffusion cell in which receptor medium was recirculated through the spectrophotometer to assay automatically at 265 nm.

Statistical analyses were performed using the Student's t-test.

Table 3 below summarizes the transdermal penetration results for representative enhancers of the invention in the ointment studies.

TABLE 3

Compound No.	Name of Compound	R	n	$-\text{NR}_1\text{R}_2$	$\text{R}_3 \quad \text{R}_4$		Relative Enhancement %
1	tetradecyl (N,N-dimethyl-amino)acetate	H	12	$-\text{N}(\text{CH}_3)_2$	H	H	100
2	dodecyl (N,N-dimethyl-amino)acetate	H	10	$-\text{N}(\text{CH}_3)_2$	H	H	200
3	decyl (N,N-dimethyl-amino)acetate	H	8	$-\text{N}(\text{CH}_3)_2$	H	H	380
4	octyl (N,N-dimethyl-amino)acetate	H	6	$-\text{N}(\text{CH}_3)_2$	H	H	250
5	dodecyl (N,N-diethyl-amino)acetate	H	10	$-\text{N}(\text{C}_2\text{H}_5)_2$	H	H	70
6	decyl (4-methyl-1-piperazinyl)-acetate	H	8		H	H	40

Relative penetration enhancements (%) were calculated by

$$\frac{\text{Penetration enhancement by the new enhancer}}{\text{Penetration enhancement by Azone}} \times 100\%$$

Azone was selected as the standard for comparison since it is claimed to be an excellent enhancer although it is too toxic; it was assigned a value of 100% enhancement. It has been reported by that the LD_{50} of Azone by intraperitoneal administration is approximately 232 mg/kg.

Penetration that was equal to the penetration of Azone was reported as 100% relative penetration. All

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of the relative enhancements listed in Table 3 are based on the early stage or hours of the penetration studies.

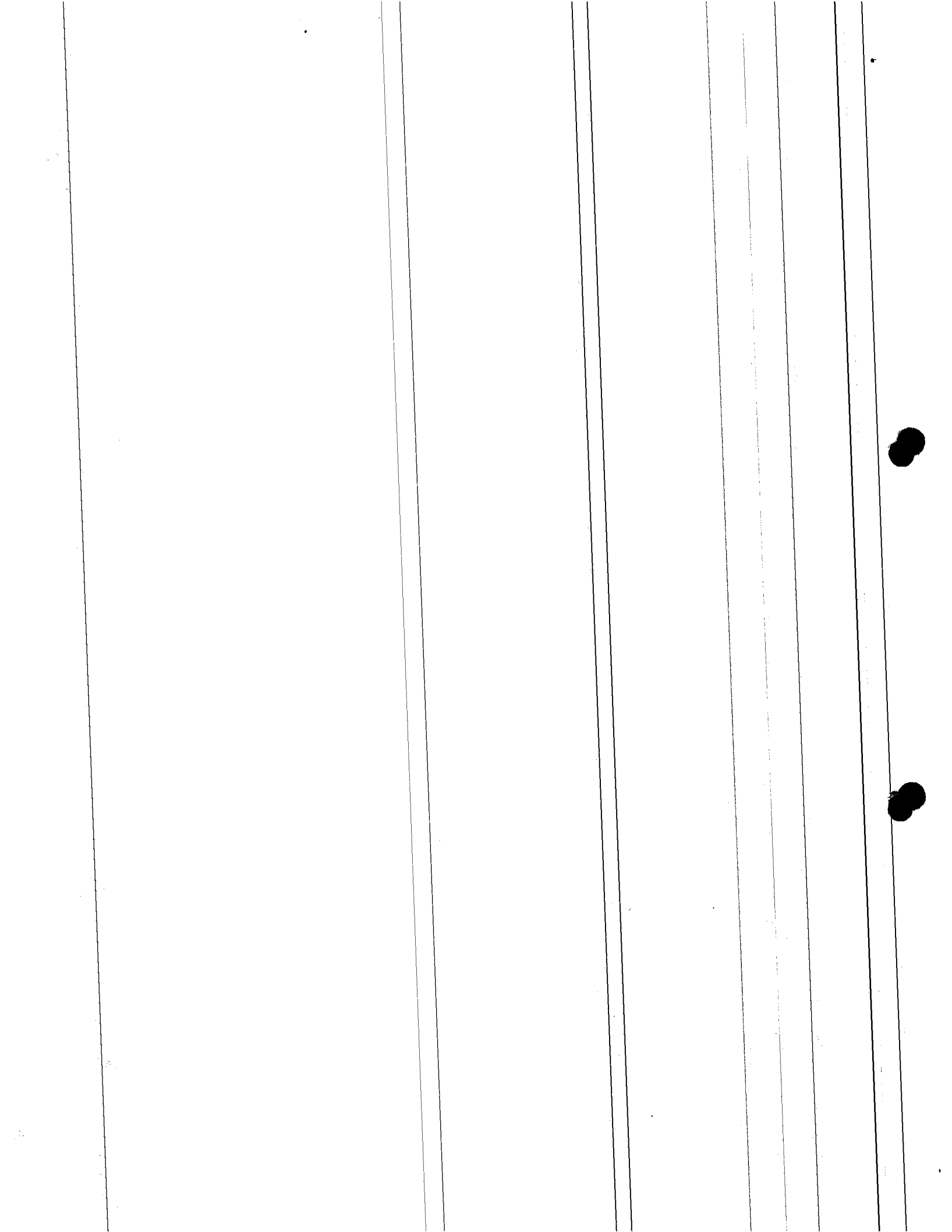
Results of the ointment studies are shown in FIGS. 1, 2 and 3. At least 3 or 4 diffusion cells were used for each enhancer and mean values for amounts (μg) of indomethacin in the receptor cells are plotted versus time in hours.

In FIG. 1, results are depicted for tests of ointments containing Azone (Δ) or one of three enhancers of the invention, namely Compound No. 3 (O), Compound No. 1 ($\diamond$) and Compound No. 6 ($\square$). In FIG. 2, results are depicted for tests of ointments containing Azone (X) or one of three enhancers of the invention, namely Compound No. 4 (O), Compound No. 3 (Δ) and Compound No. 5 ($\square$). In FIG. 3, results are depicted for tests of ointments containing Azone (X) or a preferred enhancer of the invention, Compound No. 2 (O), also referred to hereinbelow as NDMA.

As can be seen from FIGS. 1 to 3, the new enhancers of the present invention show quick action and exhibit a leveling profile after 24 hours. The fact that the instant enhancers are several times better than Azone at the early time points suggests that the onset of these compounds is short, i.e. they exhibit quick action. This is particularly important in the preparation of topical formulations since one of the most important criteria for enhancers is to have quick action. In receptor cells in

which ointments containing enhancers of the present invention were tested, as much as 25 μg of indomethacin were detected in the early stage of less than 12 hours. However, at the same stage, only a few μg of indomethacin were detected in the cells for which Azone was used as the enhancer. The final amounts of indomethacin which penetrated the snake skin in the presence of these enhancers was also high. As high as 117 μg of indomethacin was detected after 72 hours, representing about 40% of the total indomethacin incorporated into the petrolatum ointment.

The effect of Compound No. 2, or NDMA, in ointment on the transport of indomethacin compared with



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that of Azone is depicted in FIG. 3. The transport of indomethacin accelerated by NDMA was twice that accelerated by Azone during the first 24 hours. The percent of indomethacin across the membrane was $18.2 \pm 0.9\%$ ($n=4$, $p<0.01$ versus Azone) for 24 hours and $34.1 \pm 2.1\%$ ($n=4$, $p<0.01$ versus Azone) for 72 hours when NDMA was present in the ointment, while the values were $8.3 \pm 0.9\%$ ($n=4$) for 24 hours and $26.4 \pm 1.8\%$ ($n=4$) for 72 hours when Azone was present. The effect of NDMA appeared to be faster than that of Azone. In the absence of either adjuvant, the percent of indomethacin transported was less than 1% for 72 hours ($n=4$).

The effect of dodecyl (N,N-dimethylamino)acetate (NDMA) on the transport of indomethacin from a film patch compared to the effect of dodecyl alcohol is shown in FIG. 4. The NDMA (o) patch contained 542 ± 31 mg indomethacin, while the dodecyl alcohol patch contained 582 ± 24 mg indomethacin. The transport of indomethacin enhanced by the presence of 20 NDMA reached steady state flux at about 2 hours, while transport enhanced by dodecyl alcohol reached steady state at about 5 hours. The steady state flux for indomethacin was 3.84 ± 0.57 $\mu\text{g}/\text{hour}$ ($n=4$, $p<0.01$ versus dodecyl alcohol) in the presence of NDMA, which was 2.5 times greater than that in the presence of dodecyl alcohol (1.49 ± 0.21 $\mu\text{g}/\text{hour}$, $n=4$).

EXAMPLE 8

Chronic Toxicity Study

Dodecyl (N,N-dimethylamino)acetate or NDMA (10% w/w) was dispersed in saline (0.85% NaCl in deionized boiled water) with 2% Tween 80. Seven male CF-1 white mice were injected subcutaneously (dorsal site) with the NDMA dispersion at a dose of 1 g/kg daily for seven days. Six control mice were injected with an equivalent volume of 2% Tween 80 saline solution daily for seven days. All mice survived after 14 days.

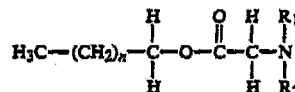
While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions,

omissions and changes may be made without departing the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims.

What is claimed is:

1. A pharmaceutical composition for topical administration of a pharmacologically active topical medicament, said composition comprising:

- (a) a pharmacologically active topical medicament in an amount sufficient to achieve a desired pharmacological effect; and
- (b) a skin penetration enhancer compound of the formula:



wherein n is a whole integer and is 6, 8, 10, or 12, and R₁ and R₂ are both methyl or both ethyl.

- 2. A pharmaceutical composition as claimed in claim 1, wherein the penetration enhancing compound of the formula is tetradecyl (N,N-dimethylamino) acetate.
- 3. A pharmaceutical composition as claimed in claim 1, wherein the penetration enhancing compound of the formula is dodecyl (N,N-dimethylamino) acetate.
- 4. A pharmaceutical composition as claimed in claim 1, wherein the penetration enhancing compound of the formula is decyl (N,N-dimethylamino) acetate.
- 5. A pharmaceutical composition as claimed in claim 1, wherein the penetration enhancing compound of the formula is octyl (N,N-dimethylamino) acetate.
- 6. A pharmaceutical composition as claimed in claim 1, wherein the penetration enhancing compound of the formula is dodecyl (N,N-dimethylamino) acetate.
- 7. A pharmaceutical composition as claimed in claim 1, said composition being formulated as a cream, lotion, gel, ointment, suppository, spray, aerosol, buccal tablet or sublingual tablet, or as a buccal, gingival, sublingual or palatal patch.

* * * * *

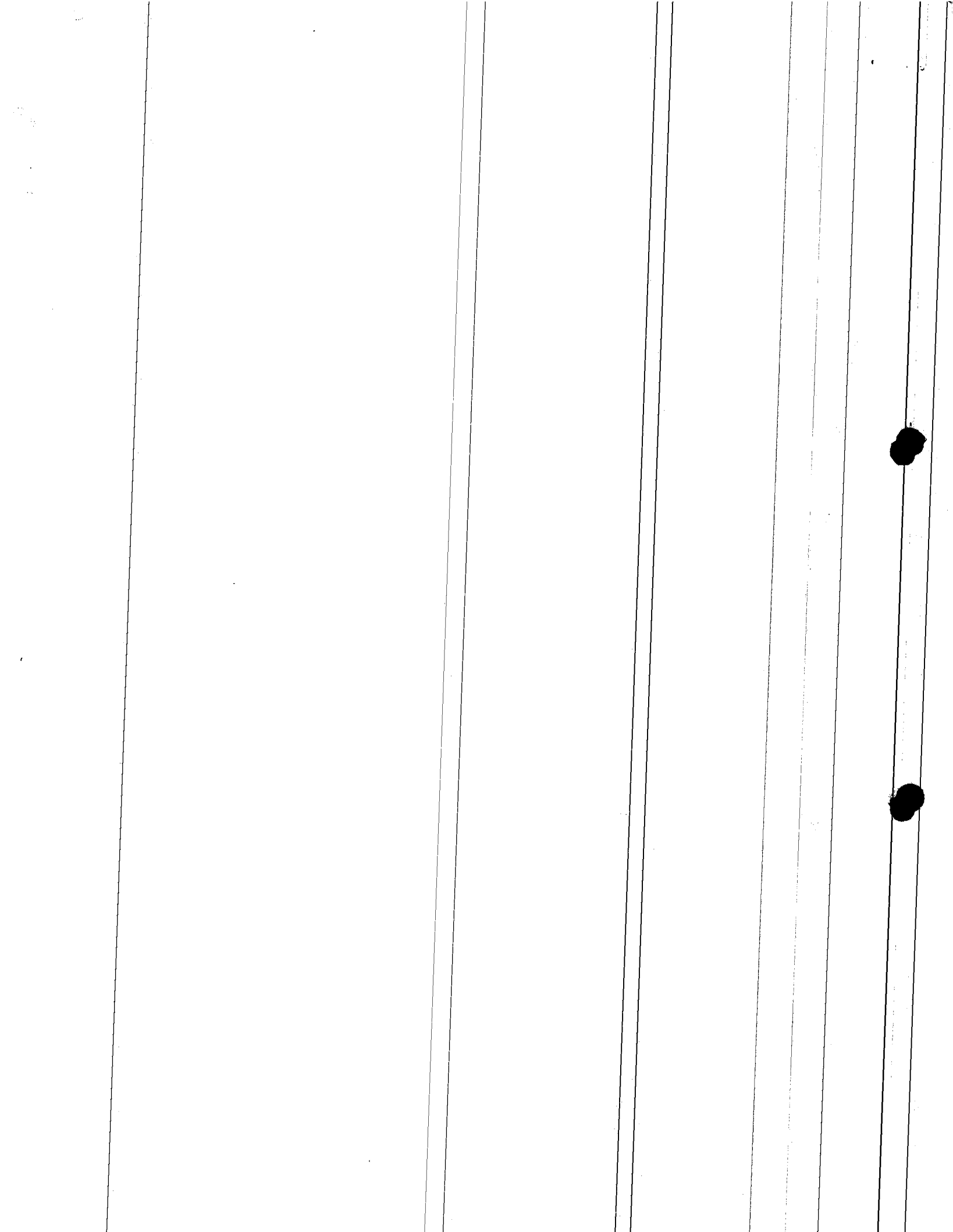
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
DILIA RODRIGUEZ D'ALEMAN

ASUNTO	Radicación	05-107315
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	6971
	Folios	016

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☐
No. Sol. Internacional	<u>PCT/US2004/008618</u>		
Fecha de Presentación Internal.	<u>22/03/2004</u>		

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:

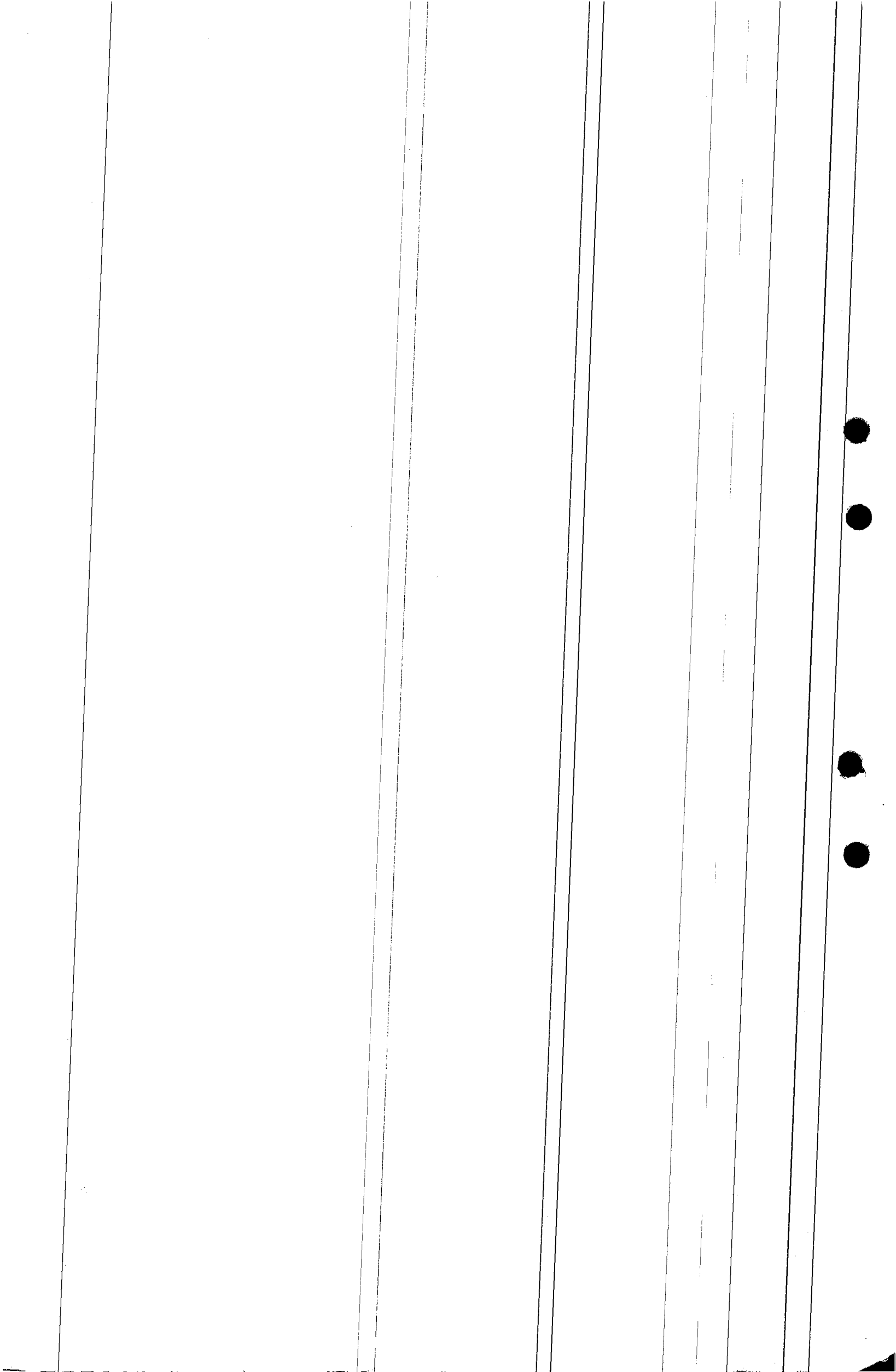
1. Documentos estudiados

<u>Descripción:</u>	Folios <u>5-69 y 88-91</u> como se radicó inicialmente
<u>Reivindicaciones:</u>	Folios <u>70-87</u> como se radicó inicialmente
	Folios <u>161-162</u> como se radicó el 27-04-2009
<u>Prioridad:</u>	Folio <u>1</u> 21-03-2003, US, 60/456684
<u>Respuesta del solicitante:</u>	Folios <u>154-158</u> como se radicó el 27-04-2009

2. Objeto de la invención

Título de la solicitud: REVESTIMIENTO ANTI-FUNGICO PARA UÑAS Y METODO DE USO (folio 1).

El problema técnico planteado en esta solicitud esta relacionado con la necesidad de obtener una composición antifúngica para uñas y piel adyacente, soluble en agua, que permita una mejor biodisponibilidad tópica del fármaco dentro de la uña y piel circundante, mediante una mayor difusión (por aumento de la permeación); que sea útil en el tratamiento de infecciones fúngicas de uñas y piel circundante (folio 6-7 y 10; pág. 1-2 y 6).



Para solucionar este problema técnico la solicitud en estudio proporciona en:

Reivindicaciones 1-7: una composición de recubrimiento antifúngico para uñas, que comprende en peso clorhidrato de terbinafina (0,5-10)%, clorhidrato de dodecil-2-(N,N-dimetilamino)isopropionato -DDAIP_HCl- (0,1-25)%, bencil alcohol (0,1-10)%, polivinilpirrolidona (0,1-5)% y el resto etanol.

Clasificación Internacional de Patentes (IPC): A61K 47/14, A61K 47/16, A61K47/10, A61K31/135, A61P31/10.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

Las reivindicaciones 5-7 caracterizan inapropiadamente una composición por resultados a alcanzar (ser apropiada para usarse una vez al día en la 5, ser transparente en la 7) y por usarse en un tratamiento en la 6. Ya que una composición debe caracterizarse por los elementos esenciales que la conforman, como son el principio activo, los excipientes y proporciones si es necesario.

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de tener claridad, de acuerdo con las exigencias del artículo 30 de la Decisión 486.

4. 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 21-03-2003, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación
D1	EP0515312	Pharmaceutical composition containing terbinafine as an anti-mycotic agent.	25-11-1992
D4	US5082866	Biodegradable absorption enhancers	21-06-1992

Anterioridad D1 en folios 134-137 y D3 en folios 163-174.

5. Análisis de patentabilidad (artículo 14 D486)

5.1 Nivel inventivo (artículo 18 D486)

En las reivindicaciones 1-7, se solicita una composición de recubrimiento anti-hongos para uñas, que comprende en peso clorhidrato de terbinafina (0,5-10)%, clorhidrato de dodecil-2-(N,N-dimetilamino)isopropionato -DDAIP_HCl- (0,1-25)%, bencil alcohol (0,1-10)%, polivinilpirrolidona (0,1-5)% y el resto etanol.

SOLICITUD	D1	D4
Composición de recubrimiento anti-hongos para uñas.	Composición de revestimiento antifúngico para uñas.	Composiciones de aplicación tópica (folio 174, col. 18)
Clorhidrato de terbinafina (0,5-10)%	Clorhidrato de terbinafina (0,5-30)% (folios 135-137; pág. 2-3 y 6, ej. 8)	Un antifúngico Entre otros, por ej. un derivado de azol como miconazol, clotrimazol (folios 169-170, col. 8-9)
Clorhidrato de dodecil-2-(N,N-dimetilamino) isopropionato (0,1-25)%	Aumentadores de permeación Por ej. dimetilsulfoxido, alcoholes, surfactantes, propilenglicol, isopropil miristato. (folios 136-137; pág. 3, lín. 29; pág. 6, ej. 8).	Dodecil-2-(N,N-dimetilamino) isopropionato (0,05-40)% (folio 169; col. 8) Excelente aumentador de permeación biodegradable y no toxico (folio 167-168; col. 4, 6) Logra rápida absorción del fármaco y mayor cantidad absorbida del mismo a través de la piel y tejidos queratinizados como el cabello (folio 170; col. 10)
bencil alcohol (0,1-10)%		En un vehículo farmacéuticamente aceptable, conteniendo excipientes como alcoholes, polivinilpirrolidona, etc., adecuados y conocidos en el arte de la formulación farmacéutica (folio 170-171; col. 10-11)
polivinilpirrolidona (0,1-5)%	Polivinilpirrolidona ó copolimeros de vinilpirrolidona (folios 135, 137; pág. 2, lín. 55, pág. 6 ej. 8)	
etanol	etanol u otros alcoholes como solventes orgánicos en el sistema solvente. (folio 136, pág. 3, lín. 15)	

El estado de la técnica más cercano es D1 que divulga composiciones de clorhidrato de terbinafina para revestimiento antifungico de uñas, tal como se enseña arriba en el cuadro comparativo (folios 135-137; pág. 2,3 y 6).

Además, D1 explica que las formulaciones obtenidas poseen una eficacia elevada y tienen beneficios como: formar un deposito después de la aplicación a partir del cual el fármaco puede difundir libremente hacia el tejido de las uñas, liberar fácilmente el fármaco, ser de fácil aplicación, ser de fácil remoción y ser bien toleradas (folio 135, pag.2, lín. 40-48); aclarando que tanto las uñas como los dedos pueden ser tratados con tales composiciones cuando están infectados por hongos causantes de onicomycosis (folio 136, pág. 3, lín. 47-48).

La solicitud se diferencia de D1 en que señala como aumentador de permeación el clorhidrato de dodecil-2-(N,N-dimetilamino)isopropionato.

El Efecto Técnico que logra la diferencia es aumentar la permeación del fármaco antifúngico a través de la uña y piel circundante.

Así que, El Problema Técnico Objetivo de esta solicitud esta relacionado con la necesidad de obtener una composición antifúngica, que permita una mejor biodisponibilidad tópica del fármaco dentro de la uña y piel circundante, mediante una mayor difusión (por aumento de la permeación).

No obstante, D4 señala que en composiciones de aplicación tópica, donde el activo puede ser un antifúngico, el dodecil-N,N-dimetil amino isopropionato es un excelente aumentador de permeación, puesto que es biodegradable, no tóxico y tiene la capacidad de lograr una más rápida absorción del fármaco y una mayor cantidad absorbida del mismo a través de la piel y tejidos queratinizados como el cabello (y las uñas) (folio 170; col. 10).

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De manera tal, que un experto en la materia estaría motivado a combinar las enseñanzas de D1 y D4 para lograr una composición de terbinafina como la reivindicada que incluye el excelente aumentador de permeación dodecil-N,N-dimetil amino isopropionato, con el fin de lograr una mejor biodisponibilidad tópica (aumentar la velocidad de absorción y la cantidad) del fármaco antifúngico dentro de la uña y piel circundante; por lo que la composición reivindicada no tiene nivel inventivo.

6. Respuesta al solicitante

El solicitante anexa un nuevo capítulo reivindicatorio (folios 161-162) con 7 reivindicaciones en el que ha concretado la materia solicitada, capítulo que es aceptado por esta Oficina.

- En cuanto novedad el solicitante plantea no estar de acuerdo con la afectación de la misma puesto que el examinador consideró los aspectos generales de la invención, sin tener en cuenta que son las particularidades las que conceden la novedad (folio 156; pág. 3 de respuesta).

Al respecto, se aclara que tal como estaba el primer capítulo reivindicatorio (amplio y general, especialmente reivindicación 1, folio 70; pág. 65) si era posible afectar la novedad con D1; sin embargo, dado que el nuevo capítulo reivindicatorio solicita una composición concreta D1 ya no le afecta la novedad.

- En cuanto a nivel inventivo el solicitante plantea que el técnico con habilidad en la materia no podría determinar a partir de D2 cual es el mejorador de permeabilidad más apropiado para la composición de la invención, ni se proporcionan argumentos que demuestren que el clorhidrato de dodecil-2-(N,N-dimetilamino)isopropionato es mejor que otros mejoradores mencionados (folio 157; pág. 4 de respuesta)

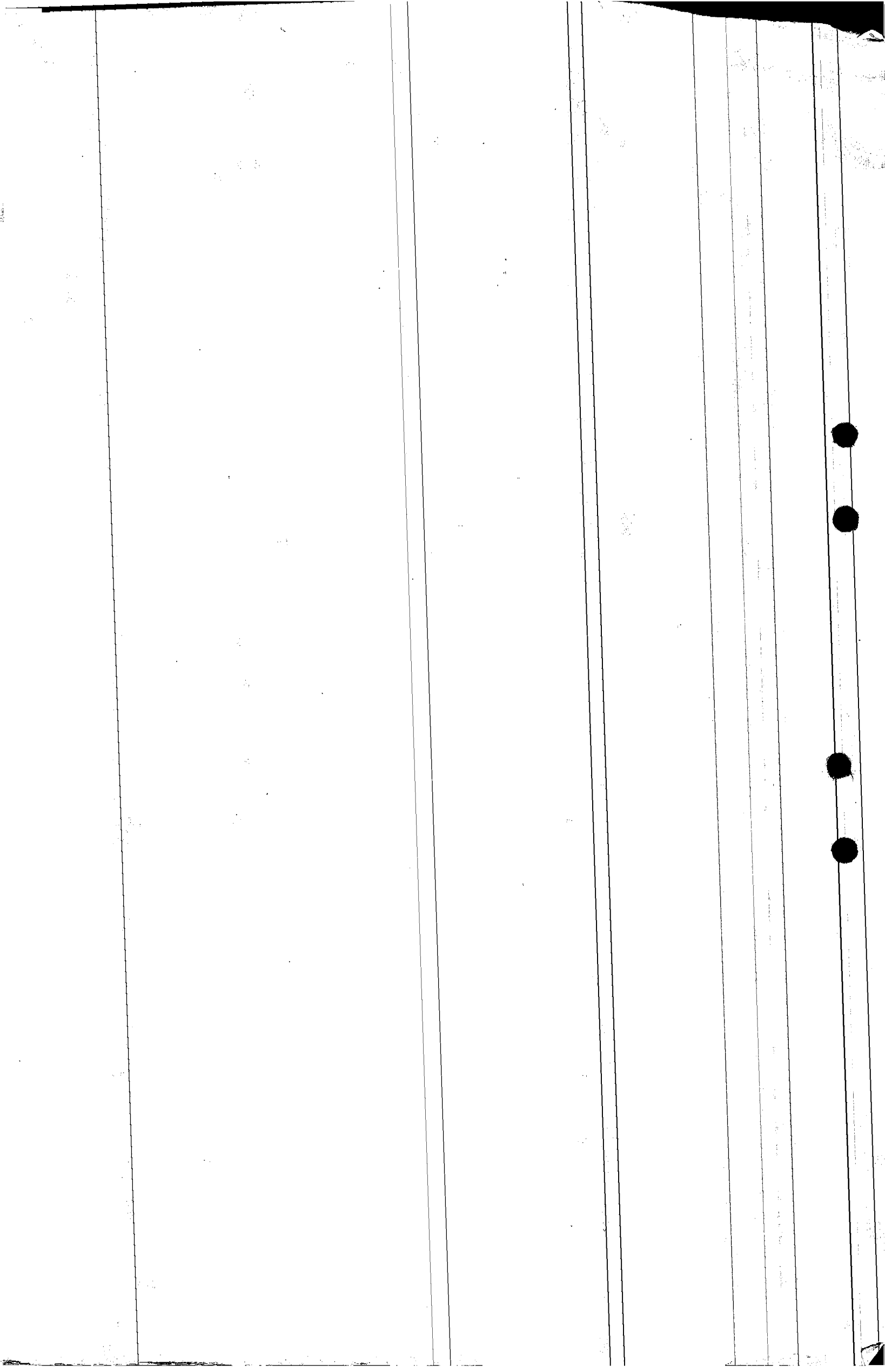
Al respecto, se aclara que el documento D4 introducido al nivel inventivo en este concepto, permite demostrar que el dodecil-2-(N,N-dimetilamino)isopropionato es un excelente mejorador de la permeabilidad en composiciones tópicas que contienen un agente antifúngico, tal como se explica en el aparte de nivel inventivo, para lograr una mejor biodisponibilidad del fármaco tanto en la uña como en la piel circundante, logrando así resolver el problema propuesto junto con la información de D1.

7. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	EP0515312	1-7	Nivel inventivo
D4	US5082866	1-7	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 sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso



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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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

19 JUN 2001

CONCEPTO TECNICO No. 10668	EXAMINADOR TECNICO Código No. 202079
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2003

