

ESTTA Tracking number: **ESTTA575099**

Filing date: **12/06/2013**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

Proceeding	92052897
Party	Plaintiff Thomas SkÅ¶ld
Correspondence Address	ARTHUR E JACKSON MOSER IP LAW GROUP 1030 BROAD STREET, SUITE 203 SHREWSBURY, NJ 07702 UNITED STATES docketing@mtiplaw.com, ajackson@mtiplaw.com
Submission	Plaintiff's Notice of Reliance
Filer's Name	Arthur E Jackson
Filer's e-mail	ajackson@mtiplaw.com, docketing@mtiplaw.com
Signature	/Arthur E Jackson/
Date	12/06/2013
Attachments	SkdNoticeReliance.pdf(4904079 bytes)

differentiated portfolio of topical dermatological pharmaceuticals.

“The technology is based on the ability of certain lipid compositions to enhance the natural skin barrier and facilitate the dermal and transdermal delivery of known active ingredients. The **Restoraderm technology** is currently still under development, and CollaGenex anticipates that the first products to be developed using the technology will be available in late 2002.

“In exchange for the rights to the technology, CollaGenex will pay the inventor milestone fees upon the achievement of certain objectives as well as royalties on future sales of products based on the technology.

“ ‘The **licensing** of the **Restoraderm drug delivery technology** is an important element of our strategy to build a diversified portfolio of products for the dermatology market,’ noted Brian M. Gallagher, PhD, chairman, president and chief executive officer of CollaGenex. ‘We anticipate that our future business in dermatology will include three key elements. Our first sales in this area will come from established, under-promoted products that we in-license, and we expect to complete the first of these agreements in the near future. The second key business element will be composed of dermatology products based on the **Restoraderm technology**, the first of which we hope to launch later this year. * * * ’”

The document is particularly relevant in that Registrant admits that the technology it licensed from Petitioner is one and the same as what it referred to as “Restoraderm”, and hence that the “Restoraderm” mark is most clearly part of the goodwill relating to the “Restoraderm Intellectual Property” (which includes know-how) as set forth in the 2004 Asset Purchase and Product Development Agreement . The Registrant further admits that the technology is licensed.

<p>Exhibit T144</p>	<p>pp. 1-3, 5-6 and 10 of the meeting program of the American Contact Dermatitis Society, 16th Annual Meeting, February 17, 2005 (New Orleans, LA)(avail. at http://www.contactderm.org/files/public/programbook2005.pdf). The meeting program includes the abstract of a Fowler et al. poster entitled "A Comparator Study of an Adjunctive Dermal Lipid Replacement Foam (Restoraderm®) in the Management of Refractory Hand Contact Dermatitis." The Abstract is particularly relevant in noting that the research was sponsored by Registrant, and in using the term "Restoraderm" to describe a technology that is "composed of an exclusive non-alcohol, water-based formulation of lipids that mimics the body's own natural skin barrier system. It contains ceramides, cholesterol, palmitic acid and two biologic precursors, mevalonic acid and hydroxycholecalciferol." This description is consistent with the technology described in US Pat. No. 8,029,810, which is the Restoraderm technology licensed to Registrant (see, e.g., Col. 2, lines 20-24; Col. 3, lines 24-27).</p>
<p>T151</p>	<p>A web page obtained at http://business.highbeam.com/industry-reports/equipment/electron-tubes on 10 May 2013, as a first page result of a Google search of "size of the vacuum tube market". The relevance is to assist in distinguishing the cited case law: <u>Westrex Corp. v. New Sensor Corp.</u>, 83 U.S.P.Q.2d 1215, 1217 (T.T.A.B. 2007). The particularly relevant text is found in the 4th paragraph on p. 1 and reads "U.S. Census data, the [electron tube] industry shipped \$1.05 billion in electron tubes and tube parts in 2009 followed by \$1.2 billion in 2010."</p>
<p>T152</p>	<p>A web page obtained at http://en.wikipedia.org/wiki/Tube_sound. The relevance is to assist in distinguishing the cited case law: <u>Westrex Corp. v. New Sensor Corp.</u>, 83 U.S.P.Q.2d 1215, 1217 (T.T.A.B. 2007). The particularly relevant text is in the first paragraph reciting "Tube amplifiers have retained a loyal following amongst some audiophiles and musicians."</p>
<p>T153</p>	<p>A web page obtained at http://hometheater.about.com/od/vacuumtubeaudio/a/vacuumtubeaudio.htm. The particularly relevance is to assist in distinguishing the cited case law: <u>Westrex Corp. v. New Sensor Corp.</u>, 83 U.S.P.Q.2d 1215, 1217 (T.T.A.B. 2007). The most relevant text is in the 2nd and 3rd paragraphs noting the demand for vacuum tubes, and the numerous manufacturers of vacuum tube audio equipment.</p>

Submitted Under §704.07 TTAB Manual of Procedure – Official Records

<p>Exhibit T129</p>	<p>Collagenex Form 10-K for the fiscal year ended December 31, 2001, p. 17 (from www.sec.gov/Archives/edgar/data/1012270/000090310002000094/form10k_123101.txt). In this official record available from the Securities and Exchange Commissions EDGAR database, Respondent states (emphasis</p>
--------------------------------	--

	<p>added):</p> <p>“In February 2002 we announced that we had <i>licensed</i> a dermal and transdermal drug delivery technology, <i>named Restoraderm</i>(TM), from its inventor. <i>Restoraderm</i> is designed to enhance the dermal delivery of a variety of active ingredients and we intend that it will form the basis for a portfolio of topical dermatological pharmaceuticals.</p> <p>“The <i>Restoraderm technology</i> is based on the ability of certain lipid compositions to enhance the natural skin barrier and facilitate the dermal and transdermal delivery of known active ingredients. The <i>Restoraderm technology</i> is currently still under development, and we anticipate that the first products to be developed using the technology will be available in late 2002. In exchange for the rights to the technology, we will pay the inventor milestone fees upon the achievement of certain objectives as well as royalties on future sales of products based on the technology.”</p> <p>The document is particularly relevant in that Registrant admits that the technology it licensed from Petitioner is one and the same as what it referred to as “Restoraderm”, and hence that the “Restoraderm” mark is most clearly part of the goodwill relating to the “Restoraderm Intellectual Property” (which includes know-how) as set forth in the 2004 Asset Purchase and Product Development Agreement . The Registrant further admits that the technology is licensed.</p>
<p>Exhibit T130</p>	<p>U.S. Patent 8,029,810, resulting from the patent Petitioner filed in collaboration with Collagenex to cover Restoraderm technology. The patent is particularly relevant to understanding the asset which Registrant was obligated to return to Petitioner pursuant to the 2004 Asset Purchase and Product Development Agreement.</p>

Submitted Under §704.11 TTAB Manual of Procedure – Interrogatory Answers; Admissions

<p>Exhibit T154</p>	<p>Registrant’s Supplemental Response to Petitioner Sköld’s First Request for Admissions. The particularly relevant portion is Registrant’s admissions (Nos. 1 – 3) on lack of use of “Restoraderm” in early 2002 and in 2001.</p>
<p>Exhibit T155</p>	<p>Registrant’s Supplemental Response to Petitioner Sköld’s First and Second Sets of Interrogatories and Requests for Production of Documents and Things. The particularly relevant portion is the response to Interrogatory No. 6, noting use of the mark in commerce only as early as May 27, 2005.</p>

Submitted Under §704.11 TTAB Manual of Procedure – Produced Documents

Exhibit T156	Exhibit B to Declaration of Cindy Kee, filed with Registrant's Motion for Partial Summary Judgment of April 27, 2012. As stated in the declaration, The exhibit "comprises materials Registrant currently distributes or presents to dermatologists in the United States to educate dermatologists about Registrant's RESTORADERM products." The particularly relevant text is the line on p. 25 (of 34) which states that the product is "steroid free", which indicates that the product does not contain the cholesterol of the Restoraderm technology.
-------------------------	--

Respectfully submitted,

Date: December 6, 2013

By: 

Arthur E. Jackson, Esq.
New Jersey Bar No. 00288-1995
ajackson@mtiplaw.com
MOSER TABOADA
1030 Broad Street, Suite 203
Shrewsbury, NJ 07702
(732) 935-7100
(732) 935-7122
Attorney for Petitioner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

Thomas Sköld,
Petitioner,

v.

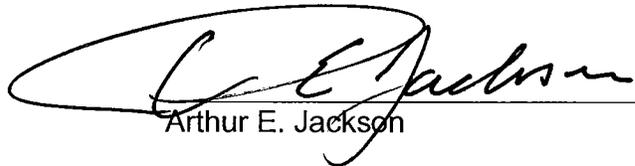
Galderma Laboratories, Inc.,
Registrant

Cancellation No. 92052897

CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing Sköld Notice of Reliance and the Exhibits referred to therein were sent by email on this 6th day of December, 2013 to:

Jeff.Becker@haynesboone.com


Arthur E. Jackson

NON-CONFIDENTIAL - Initial Disclosure



1. Products & Services
2. Knowledge Center
3. Browse News Releases
4. Contact PR Newswire

See more news releases in: Cosmetics and Personal Care, Household, Consumer & Cosmetics, Health Care & Hospitals, New Products & Services



Cetaphil® Brand Launches Cetaphil® Restoraderm® -- a new Line of Products to Help Soothe the Symptoms of Eczema and Atopic Dermatitis

Introducing Cetaphil® Restoraderm® Skin Restoring Body Wash and Skin Restoring Moisturizer Specially Formulated for the Management of Eczema and Atopic Dermatitis

FORT WORTH, Texas, Sept. 14 /PRNewswire/ -- The Cetaphil® brand, the #1 dermatologist-recommended brand of cleansers and moisturizers today announced the launch of Cetaphil® Restoraderm® products, formulated specifically for the needs of eczema and atopic dermatitis skin. Cetaphil® Restoraderm® Skin Restoring Body Wash and Skin Restoring Moisturizer soothes itching associated with skin affected by eczema and atopic dermatitis. Both products enhance the skin's ability to restore hydration and help repair the epidermal barrier as part of a dermatologist-recommended daily routine for the management of eczema.

Symptoms of eczema include severe itching, scratching, bleeding skin and sleep disturbance. The most common form of eczema is atopic dermatitis, a disorder of the skin's immune system that most often appears in infancy. Up to 85% of children are diagnosed with eczema before the age of 5. The discomfort of eczema can be particularly distressing for children who are irritable, want to be held and experience pain while being bathed. Their parents are also affected by the emotional demands these children may have.

"Cetaphil Restoraderm Moisturizer and Body Wash have been awarded the National Eczema Association Seal of Acceptance," says Julie Block, President & CEO of the National Eczema Association. "The Seal of Acceptance is awarded to products that have been created or intended for use by persons with eczema or severe sensitive skin conditions," adds Block.

Click here to hear board-certified dermatologist Dr. Doris Day discuss the common skin condition eczema and skin care tips to help manage symptoms if you or someone you know is a sufferer.

People suffering with eczema and atopic dermatitis lack the production of natural moisturizing factors that serves as a barrier against viruses and bacteria and may have a deficiency in ceramides which hold skin cells together to form a healthy skin barrier. The lack of

NON-CONFIDENTIAL - Initial Disclosure

natural moisturizing factors and ceramides is what may exacerbate eczema and atopic dermatitis symptoms, leaving the skin dry, itchy and painful.

"As the leader in the dermatology category, Galderma is committed to advancing options for the management of eczema and atopic dermatitis and other skin conditions that can have a significant emotional and physical impact on sufferers," says Francois Fournier, President of U.S. & Canadian operations of Galderma Laboratories.

Cetaphil® Restoraderm® skin care products work to help restore the skin's natural ability to retain moisture utilizing exclusive Filaggrin Technology™. The Skin Restoring Moisturizer is the only product on the market to contain a unique combination of filaggrin breakdown products and ceramides which help restore natural moisturizing factors in the skin and help rebuild a healthy skin barrier. The Skin Restoring Body Wash contains the unique Miracare® technology which works to replenish moisture, restore filaggrin breakdown products and rebuild lipid bilayer during bathing.

Both products are intended to fit into the dermatologist-recommended daily management for eczema. Patients are advised to take lukewarm baths using Cetaphil® Restoraderm® Skin Restoring Body Wash, followed by the application of a Cetaphil® Restoraderm® Skin Restoring Moisturizer to the still-damp skin to help retain and replenish the moisture.

Cetaphil® Restoraderm® products extend the Cetaphil® brand into disease-specific collections of products and builds upon a legacy of being the #1 recommended brand of cleansers and moisturizers by dermatologists. Learn more about Cetaphil® products and join the Cetaphil Skin Care Club™ by visiting www.cetaphil.com.

About Galderma

Galderma, created in 1981 as a joint venture between Nestle and L'Oreal, is a fully-integrated specialty pharmaceutical company dedicated exclusively to the field of dermatology. The Company is committed to improving the health of skin with an extensive line of products across the world that treat a range of dermatological conditions with a research and development center in Sophia Antipolis, France, Galderma has one of the largest R&D facilities dedicated exclusively to dermatology. Leading worldwide dermatology brands include Differin®, MetroGel® 1%/Rozex®, Clobex®, Tri-Luma®, Loceryl®, Vectical®, Epiduo® Gel and Cetaphil®. For more information on Galderma, visit www.galdermaUSA.com.

About Cetaphil®

The family of Cetaphil® Cleansers and Moisturizers is a line of dermatologist-recommended skin care products specially formulated for all skin types and conditions. Cetaphil® products are developed to provide effective, gentle skin care and include: Cetaphil® Gentle Skin Cleanser, Cetaphil® Daily Facial Cleanser, Cetaphil® Gentle Cleansing Bar, Cetaphil® Antibacterial Gentle Cleansing Bar, Cetaphil® Moisturizing Lotion, Cetaphil® Moisturizing Cream, Cetaphil DailyAdvance Ultra Hydrating Lotion®, Cetaphil® Daily Facial Moisturizer SPF 15, Cetaphil® UVA/UVB Defense SPF 50, Cetaphil® Therapeutic Hand Cream. www.cetaphil.com.

Copyright© 2010 Galderma Laboratories, L.P. All trademarks are the property of their respective owners. Galderma Laboratories, L.P. 14501 N. Freeway, Fort Worth, TX 76177 CETA-175 A, B; Printed in the USA 08/10

SOURCE Cetaphil

[Back to top](#)

RELATED LINKS

<http://www.galdermausa.com>

Featured Video



#264;

Page 17 - Collagenex Form 10-K or the fiscal year ended December 31, 2001

limited disease stabilization, with one patient, suffering from an hemangioendothelioma (an unusual type of lung tumor), remaining on Metastat for over two years without progressive disease. The studies established a maximum tolerated dose, with phototoxicity proving to be the dose-limiting toxicity.

On May 18, 2000, we announced positive findings from an 18-patient, National Cancer Institute sponsored Phase I dose-escalating study of Metastat, administered once daily to patients with Kaposi's sarcoma, a disfiguring and potentially deadly malignancy frequently associated with human immunodeficiency virus (HIV). In such Phase I clinical trials, Metastat demonstrated an overall tumor response rate of 44% in patients with Kaposi's sarcoma and the National Cancer Institute has elected to continue testing Metastat in Phase II clinical trials. This trial is an open-label, two-dose study to establish clinical efficacy in patients with HIV-related Kaposi's sarcoma. The trial began recruitment in summer 2001 and presently is approximately 50% recruited.

Preclinical and Other Research and Development Activities

We have an active preclinical program in place to identify and characterize IMPACS that exhibit enhanced biological activities compared to Periostat and Metastat. In collaboration with the University of Rochester, we have synthesized over thirty new IMPACS. These are being evaluated in a variety of in vitro and in vivo assay systems under a three-year research agreement with SUNY, which concluded in May 2001.

We receive certain proprietary rights to inventions or discoveries that arise as a result of this research. Our current research and development objective is to develop additional products utilizing our IMPACS technology, preferably in conjunction with development partners.

In February 2002 we announced that we had licensed a dermal and transdermal drug delivery technology, named Restoraderm(TM), from its inventor. Restoraderm is designed to enhance the dermal delivery of a variety of active ingredients and we intend that it will form the basis for a portfolio of topical dermatological pharmaceuticals.

The Restoraderm technology is based on the ability of certain lipid compositions to enhance the natural skin barrier and facilitate the dermal and transdermal delivery of known active ingredients. The Restoraderm technology is currently still under development, and we anticipate that the first products to be developed using the technology will be available in late 2002. In exchange for the rights to the technology, we will pay the inventor milestone fees upon the achievement of certain objectives as well as royalties on future sales of products based on the technology.

Our research and development expenditures were approximately \$5.0 million, \$3.1 million and \$3.8 million in 1999, 2000 and 2001, respectively. See "Management's Discussion and Analysis of Financial Condition and Results of Operations - Results of Operations."



US008029810B2

(12) **United States Patent
Skold**

(10) **Patent No.: US 8,029,810 B2**
(45) **Date of Patent: Oct. 4, 2011**

(54) **WATER-BASED DELIVERY SYSTEMS**

(75) Inventor: **Thomas Skold, Norrtalje (SE)**

(73) Assignee: **Thomas Skold, Norrtalje (SE)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 297 days.

(21) Appl. No.: **12/290,455**

(22) Filed: **Oct. 30, 2008**

(65) **Prior Publication Data**

US 2009/0226491 A1 Sep. 10, 2009

Related U.S. Application Data

(63) Continuation of application No. 10/957,320, filed on Sep. 30, 2004, now abandoned, which is a continuation-in-part of application No. PCT/US03/07752, filed on Mar. 13, 2003, and a continuation-in-part of application No. 10/388,371, filed on Mar. 13, 2003, now abandoned.

(60) Provisional application No. 60/365,059, filed on Mar. 13, 2002.

(51) **Int. Cl.**

A61K 9/00 (2006.01)
A61K 31/74 (2006.01)
A61K 47/00 (2006.01)

(52) **U.S. Cl.** 424/400; 424/78.02; 514/784

(58) **Field of Classification Search** 424/400, 424/78.02; 514/784

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,508,703 A 4/1985 Redziniak et al.
4,610,868 A 9/1986 Fountain et al.
5,196,190 A 3/1993 Nangia et al.
5,206,020 A 4/1993 Critchley et al.

5,298,246 A 3/1994 Yano et al.
5,320,906 A 6/1994 Eley et al.
5,468,475 A 11/1995 Shaku et al.
5,534,499 A 7/1996 Ansell
5,593,622 A 1/1997 Yoshioka et al.
5,628,936 A 5/1997 Wallach
5,631,012 A 5/1997 Shanni
5,643,899 A * 7/1997 Elias et al. 514/171
5,665,379 A 9/1997 Herslof et al.
5,733,572 A * 3/1998 Unger et al. 424/450
5,776,480 A 7/1998 Candau et al.
5,817,856 A 10/1998 Tirosh et al.
5,820,873 A 10/1998 Choi et al.
5,942,245 A 8/1999 Katinger et al.
5,993,830 A 11/1999 Freij
6,132,763 A 10/2000 Fisher
6,153,209 A 11/2000 Vega et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CA 2281430 * 9/1999

(Continued)

OTHER PUBLICATIONS

Database CA Chemical Abstracts Service: XP002341829. Assn. #134:168089.

(Continued)

Primary Examiner — Blessing Fubara

(74) *Attorney, Agent, or Firm* — Moser Taboada

(57) **ABSTRACT**

The invention relates to a water-based delivery system for an active substance, characterized by enhancing skin barrier restoration in the stratum corneum comprising water, a fatty acid, cholesterol, a ceramide and at least one skin lipid precursor.

73 Claims, 7 Drawing Sheets

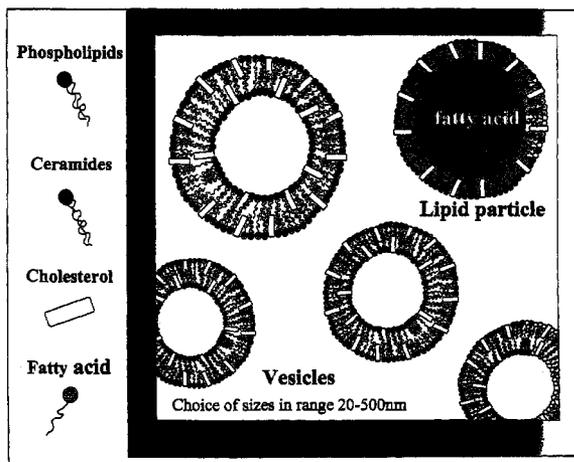


Exhibit **T 130**
Skold v. Galderma
Cancellation No. 92052897

U.S. PATENT DOCUMENTS

6,238,694	B1	5/2001	Gasco
6,419,949	B1	7/2002	Gasco
6,497,888	B1	12/2002	Morancais et al.
6,586,000	B2	7/2003	Luo et al.
6,730,288	B1	5/2004	Abram
6,824,785	B1	11/2004	Kitson et al.
6,932,963	B2	8/2005	Perricone
6,936,272	B2	8/2005	Martin et al.
2002/0048596	A1	4/2002	Cevc
2002/0064524	A1	5/2002	Cevc
2003/0099694	A1	5/2003	Cevc et al.
2004/0009213	A1	1/2004	Skold
2004/0071767	A1	4/2004	Cevc et al.
2005/0123897	A1	6/2005	Cevc et al.
2005/0129722	A1	6/2005	Skold
2007/0031483	A1	2/2007	Cevc
2007/0042030	A1	2/2007	Cevc
2007/0184114	A1	8/2007	Cevc
2009/0081139	A1	3/2009	Skold

FOREIGN PATENT DOCUMENTS

CA	2281430	A	9/1999
EP	0087993	A	9/1983

EP	0711558	A1	5/1996
EP	0711588	A1	5/1996
EP	1092428	A	4/2001
FR	2794366	A	12/2000
JP	2001-048721	*	2/2001
JP	200104874	A	2/2001
JP	2001048721		2/2001
NZ	254392		7/1997
NZ	254392	A	7/1997
WO	9637192	A	11/1996
WO	9637192	A1	11/1996
WO	9817253	A	4/1998
WO	9817253	A1	4/1998

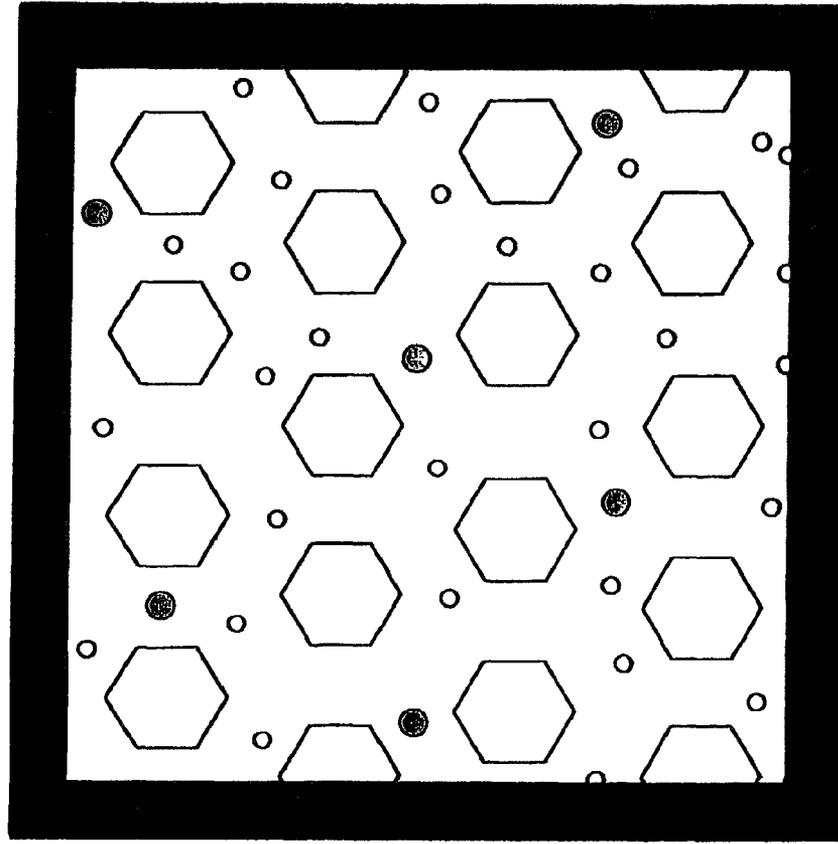
OTHER PUBLICATIONS

Silvander, et al. "A Method to Detect Leakage of DNA Intercalators through Liposome Membranes" Analytical Biochemistry 242, 40-44 (1996) Article No. 0425, May 6, 1996.

Igarashi, et al. (Advanced Drug Delivery Reviews 20, p. 147-154, 1996).

* cited by examiner

Lipoid micro compartments



Hydro phase

Gas Spheres

Lipid particles

Vesicles

FIGURE 1

Lipid Monolayer Gas Spheres

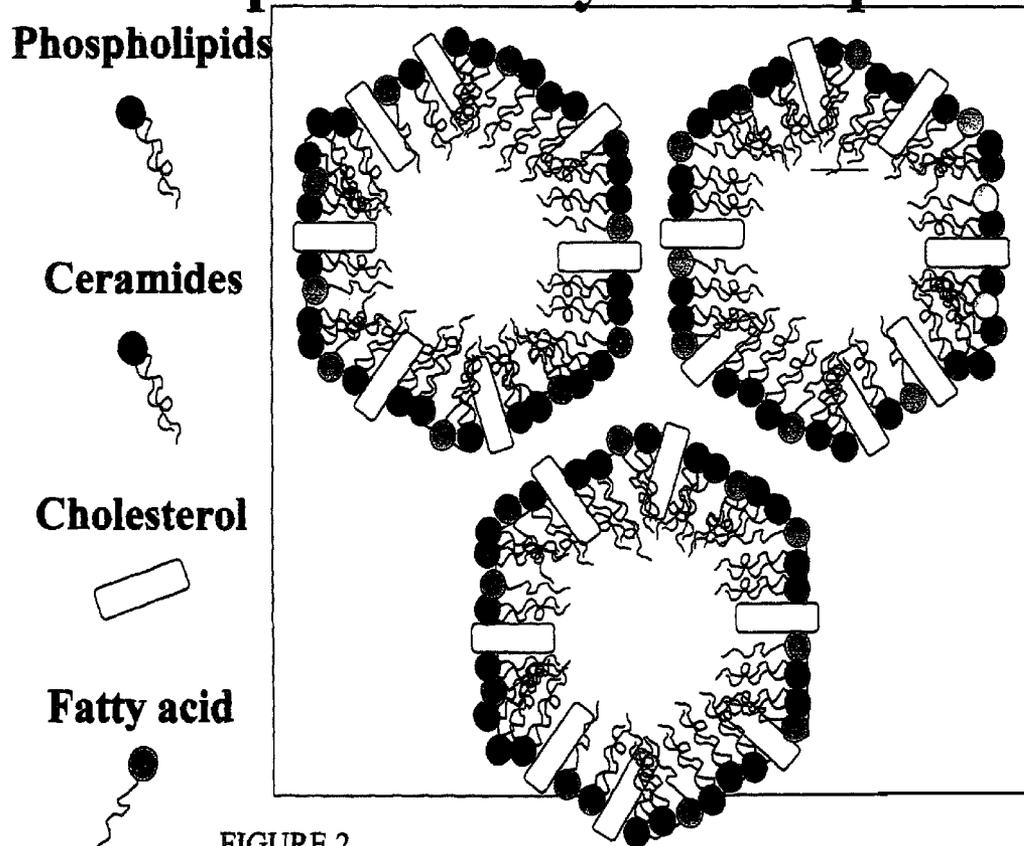
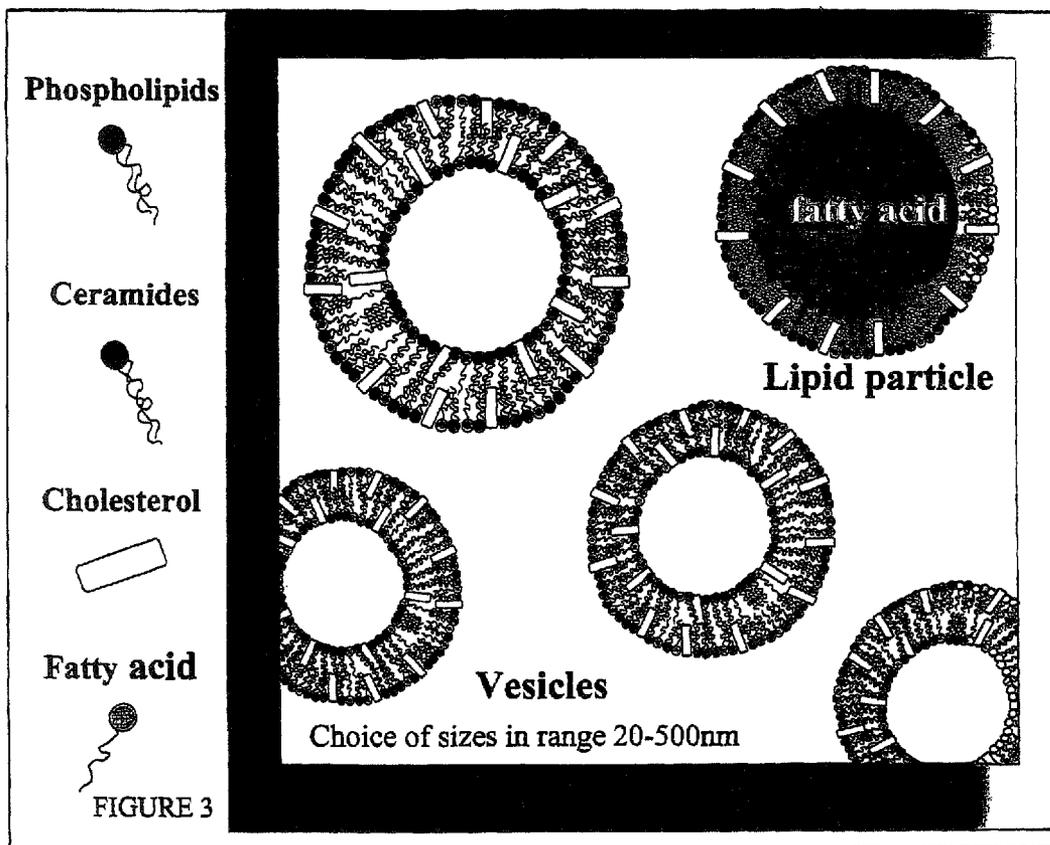


FIGURE 2



Delivery of Actives

Water Soluble Active ◆

Fat Soluble Active ●

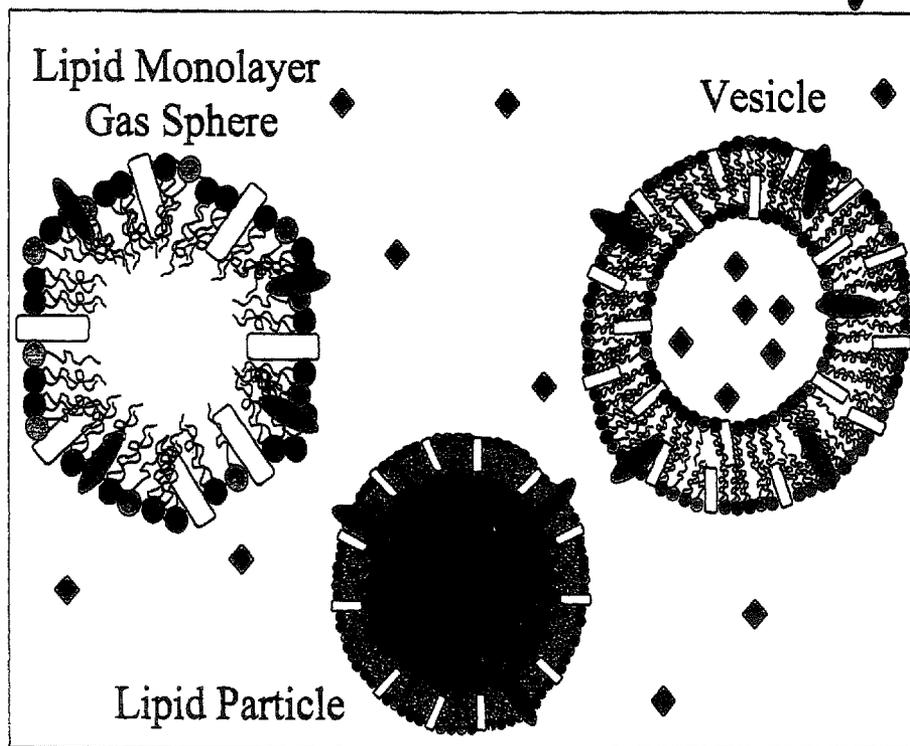


FIGURE 4

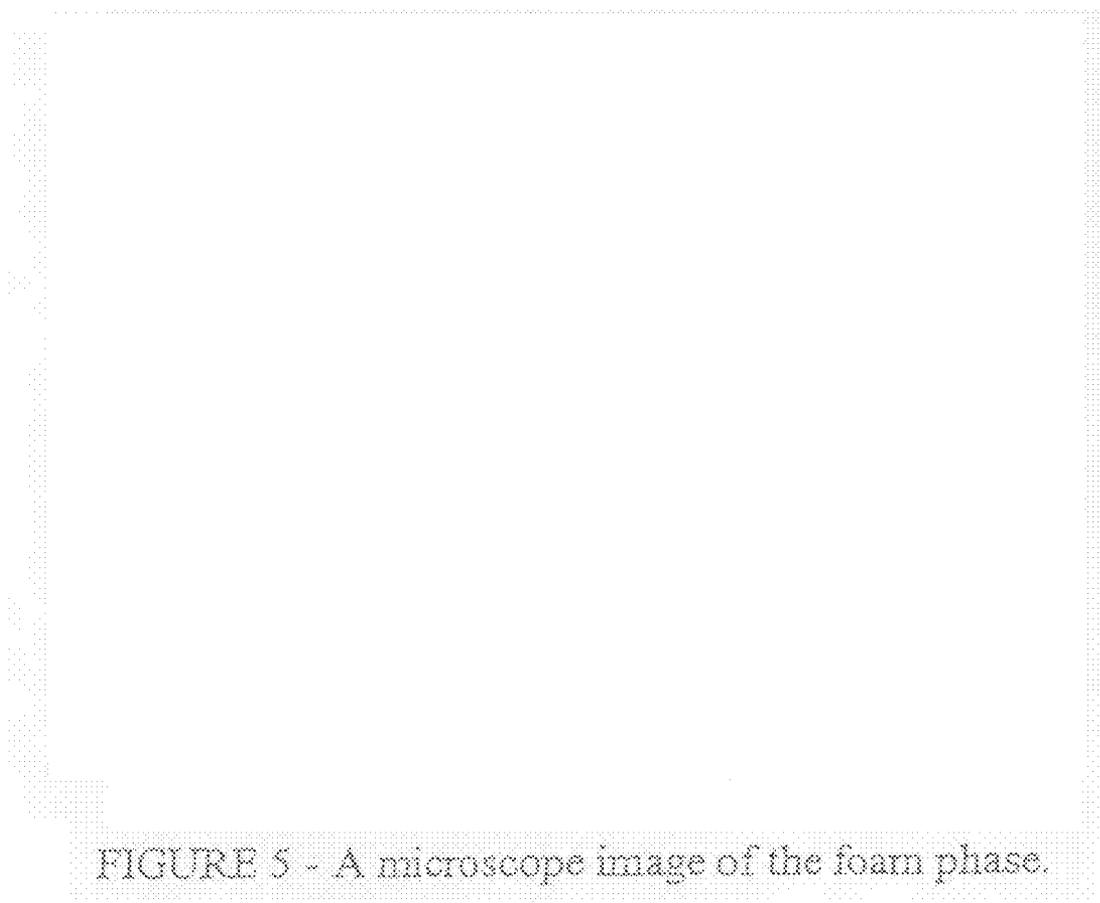


FIGURE 5 - A microscope image of the foam phase.

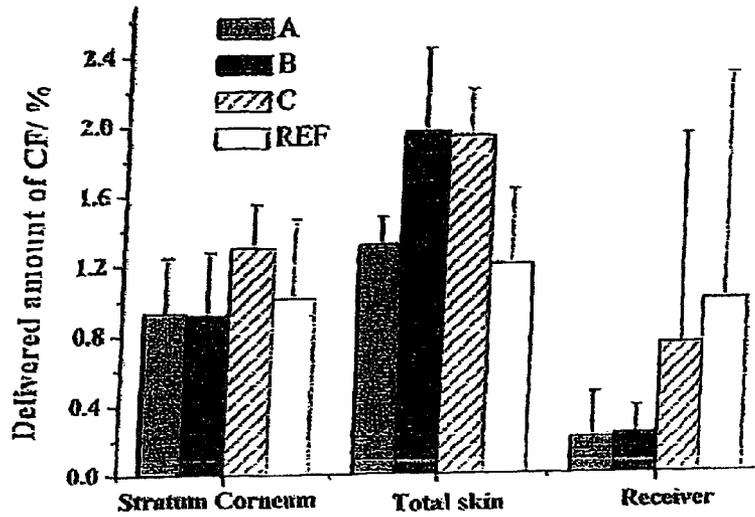


FIGURE 6 - Amount of CF detected in stratum corneum, total skin and the receiver compartment.

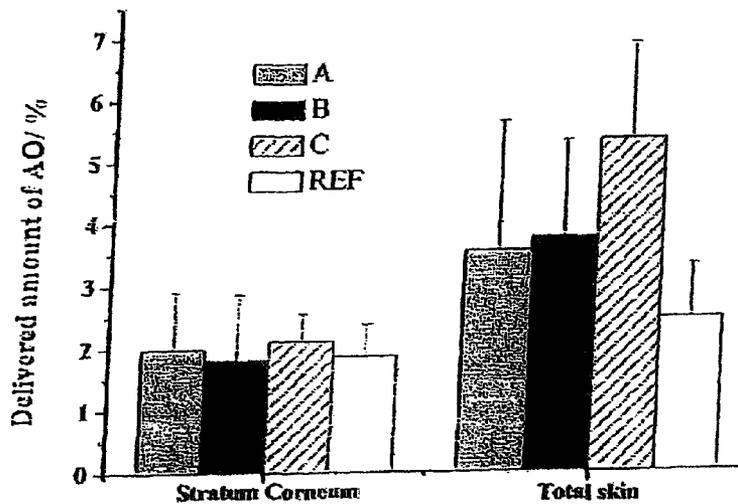


FIGURE 7 - Amount of AO detected in stratum corneum and total skin.

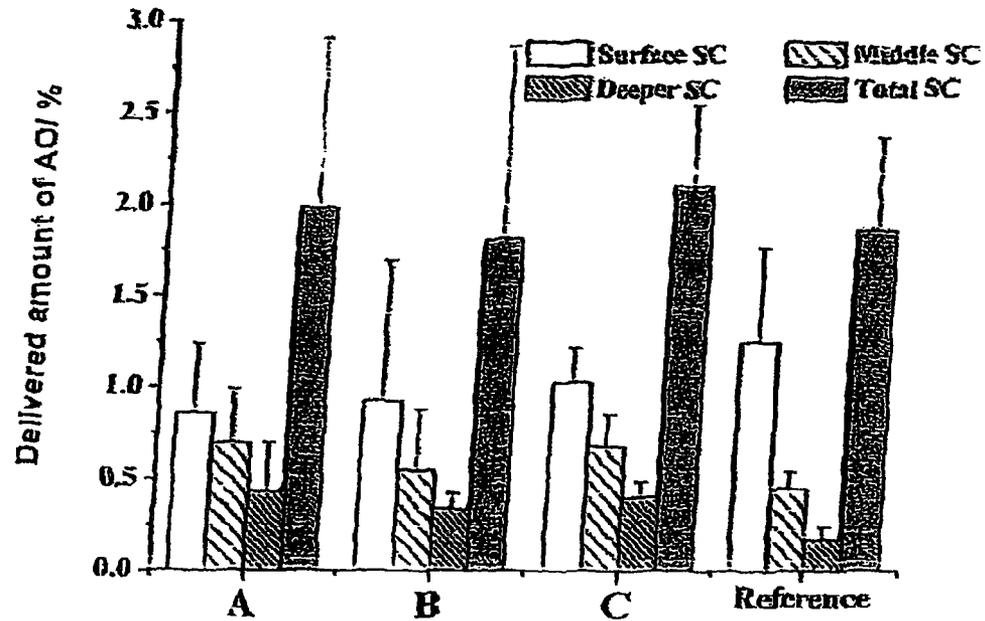


FIGURE 8 - Amount of AO detected at different depth of stratum corneum.

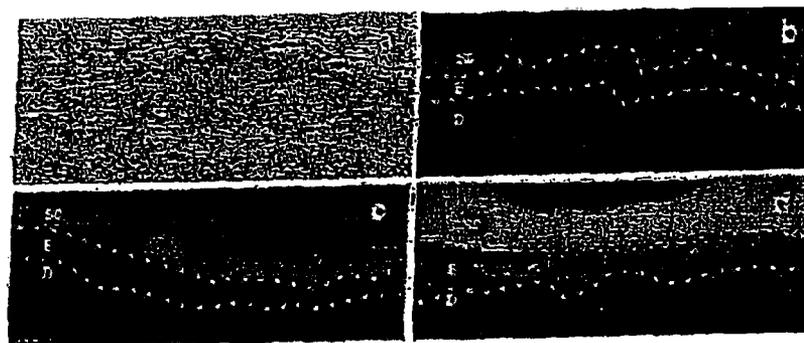


FIGURE 9 - Fluorescence microscopy images.

WATER-BASED DELIVERY SYSTEMS**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of U.S. patent application Ser. No. 10/388,371, filed Mar. 13, 2003; and U.S. Provisional Application No. 60/365,059, filed Mar. 13, 2002, both of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a novel topical and mucosal delivery systems for drugs or any other active substance.

BACKGROUND OF THE INVENTION

The main demands on human skin are to prevent loss of water, and to prevent water and other matter of the environment from entering the body indiscriminately. The human skin thus forms a selectively permissible physical barrier between the human body and its surroundings.

The barrier function has been shown to reside in the stratum corneum. The stratum corneum is the topmost layer of the skin, and is built of corneocytes. Corneocytes are cells that contain extensively cross-linked proteins, surrounded by a highly resistant cell envelope. The corneocytes are embedded in a bed of specific lipid structures of long chain lipids. These long chain lipids are organized as bilamellar structures stacked on top of each other. The bilamellar structures fill the intercellular spaces between the corneocytes.

To account for the skin's barrier properties, and for its selective hydrophilic and hydrophobic pathways, the skin has been described as a mosaic barrier model. This model envisages barrier lipids to exist predominantly in crystalline (gel) form. Such a form provides water impermeable domains, which are surrounded by so-called grain borders of lipids in a liquid crystalline state. This arrangement provides an effective, water tight barrier that still allows a minute but controlled loss of water through the liquid crystalline interdomains. This controlled water loss is enough to keep the keratin of the stratum corneum hydrated. The liquid character of the interdomain grain borders allows passage of hydrophilic and hydrophobic molecules on down-hill gradients, i.e. passage by passive diffusion.

Dermal delivery systems are compositions which deliver active substances to, or through, the skin. These compositions typically contain skin permeation enhancers. Permeation enhancers may induce structural transformations of the bilamellar structure in the liquid crystalline interdomain regions, and thus promote transdermal delivery of, for example, pharmacological substances.

Typical dermal delivery systems have an alcohol or petroleum base, with little consideration given to the biological properties of the vehicle itself. For example, emulsified fatty acids can inherit certain detergent properties if their structure is significantly altered from those in the normal skin. The detergent properties can lead to disruption of the normal barrier function, which is counteractive to the potential benefit of the delivery system. Disruption of the normal barrier function often causes the stratum corneum to lose its natural potential to function properly as a barrier. As a result, the skin becomes either too dry or too permeable to environmental substances.

Other conventional delivery systems that are thought to protect the skin from harmful substances are barrier oint-

ments. The purpose of barrier ointments is to provide a film, and thereby create a layer which is impermeable to environmental substances. Due to the impermeability, though, these ointments both increase the body temperature of the treated body part, as well as prevent perspiration, and thus render an uncomfortable sensation.

The dermal delivery systems described above are not formulated to deliver a substance to, or through, the human skin without permanently disrupting the stratum corneum's natural barrier function.

SUMMARY OF THE INVENTION

In one embodiment, the invention relates to a water-based delivery system for an active substance, characterized by enhancing skin barrier restoration in the stratum corneum comprising water, a fatty acid, cholesterol, and a ceramide. In another embodiment, the delivery system also comprises at least one skin lipid precursor.

In an additional embodiment, the invention relates to delivery system for an active substance comprising water and lipophilic components, wherein the lipophilic components comprise fatty acids, cholesterol, and a ceramide/phospholipid portion, and wherein the lipophilic components are in the form of lipid particles, and gas spheres or vesicles. This delivery system can also comprise at least one skin lipid precursor.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a diagram showing the gas spheres, lipid particles, vesicles and hydrophilic phase of the delivery systems.

FIG. 2 is a diagram showing the components of the gas spheres of the delivery systems.

FIG. 3 is a diagram showing the components of the lipid particles and of the vesicles of the delivery systems.

FIG. 4 is a diagram showing the location of active substances within the various microcompartments of the delivery systems.

FIG. 5 is a microscopic image of the foam phase.

FIG. 6 is a graph showing the amount of 5(6)-carboxyfluorescein (CF) detected in the stratum corneum, total skin and the receiver compartment for four different formulations, CF-A, CF-B, CF-C and the reference.

FIG. 7 is a graph showing the amount of acridine orange 10-nonyl bromide (AO) detected in the stratum corneum, total skin and the receiver compartment for four different formulations, AO-A, AO-B, AO-C and the reference.

FIG. 8 is a graph showing the amount of AO detected at different depths of the stratum corneum.

FIG. 9 are fluorescent microscope images showing in vivo results for the penetration of active ingredients into the skin using the delivery systems: a) frozen section of normal skin stained with hematoxylin viewed by light microscopy, b) auto fluorescence of untreated epidermis, c) auto fluorescence of petrolatum with penetration only into stratum corneum, d) auto fluorescence of the total lipid formulation (variation A) with penetration into the viable epidermis and dermis.

DETAILED DESCRIPTION OF INVENTION

The present invention provides an improved topical delivery system (skin preparation) formulated to deliver a substance to, or through, the human skin without permanently disrupting the stratum corneum's natural barrier function. Additionally, the topical delivery system of the present invention provides unique skin barrier restoration properties.

All percentages given below are indicated in percent by weight. All numbers are approximate.

The topical delivery system of the present invention is a water-based formulation comprising hydrophilic and lipophilic components. In a preferred embodiment, the delivery system comprises a water content exceeding 50%, such as more than 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 85%, 87%, 90%, 94%, 95% and 98%. Preferably, the water content is between 60-80%, more preferably, between 70 and 80%.

The topical delivery system is preferably designed, in its choice and composition of lipids, to resemble the normal lipid organization of the stratum corneum (horny layer), as much as possible. Upon administration, the system (formulation) blends with the lipids naturally present in the stratum corneum, and easily penetrates the lipid bilayer of the skin. In doing so, the system carries along with it one or more active substances to be administered. The system enhances penetration of active substances into and/or through the stratum corneum, while the normal barrier properties of the stratum corneum are left intact, and/or are even functionally enhanced.

The lipophilic component (i.e. lipids) of the system comprises fatty acids, cholesterol and a ceramide/phospholipid portion. The lipids are similar to those which make up the normal stratum corneum. The preferred ratio of the ceramide/phospholipid portion:cholesterol:fatty acid is in the range of approximately 2:1:1.5 to approximately 2.95:0.5:0.5. Preferably, for example, the ratio is approximately 2:1:1; more preferably the ratio is approximately 2.35:1:1.

The fatty acids of the present invention can be any fatty acid, mixtures of fatty acids, salts of fatty acids, or mixtures of fatty acids and salts of fatty acids. The fatty acids can be saturated or unsaturated. Additionally, the fatty acids can comprise precursors of fatty acids. In a preferred embodiment, the fatty acids comprise ten, twelve, fourteen, sixteen, eighteen, twenty, twenty-two, or twenty-four carbon atoms, or any mixture of such fatty acids. A fatty acid mixture with a predominant portion of fatty acids which comprise a chain of sixteen or eighteen carbon atoms is most preferred.

For example, the delivery system can be prepared from a mixture of fatty acids of the following composition: at most about 2% of a component comprising a chain of fourteen carbon atoms, between about 47 and about 52% of a component comprising a chain of sixteen carbon atoms, between about 43 and about 48% of a component comprising a chain of eighteen carbon atoms, and at most about 1% of a component comprising a chain of twenty carbon atoms.

Examples of suitable saturated fatty acids for use in the delivery system include lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, and lignoceric acid. Examples of suitable unsaturated fatty acids include oleic acid, palmitoleic acid, linoleic acid, linolenic acid, and arachidonic acid. Preferably, the delivery system contains an essential portion, such as about 90%, of such fatty acids.

The preferred fatty acids are the essential fatty acids (EFAs). EFAs are essential for the plasma membrane formation of all cells. In keratinocytes, EFA deficiency makes cells hyperproliferative. Supplementation of EFAs reverses the hyperproliferation. EFAs also enhance lipid biosynthesis of the epidermis and provide lipids for the barrier formation of the epidermis. The essential fatty acids are preferably chosen from linoleic acid, γ -linolenic acid, homo- γ -linolenic acid, columbinic acid, eicosa-n-6,9,13-trienoic acid, arachidonic acid, timnodonic acid, hexaenoic acid, and mixtures thereof.

The delivery system also comprises cholesterol, or derivatives of cholesterol such as, for example, lipid esters of cholesterol.

The ceramide/phospholipid portion can comprise 100% ceramide, 100% phospholipids, or any other percent combination of ceramide and phospholipids. For example, the ceramide/phospholipid portion can comprise 95% ceramide and 5% phospholipids, 90% ceramide and 10% phospholipids, 85% ceramide and 15% phospholipids, or 80% ceramide and 20% phospholipids.

Since the system preferably resembles the lipid composition of the skin as much as possible, it is desirable to use 100% ceramide in the ceramide/phospholipid portion. However, from an economic point of view, the addition of phospholipid to the ceramide/phospholipid portion may be a more suitable choice.

The ceramide component of the delivery system can be any ceramide or any mixture of ceramides. In this specification, ceramides include pseudoceramides and neoceramides.

For example, the ceramide may be any of ceramide 1-7; and/or mixtures thereof. Some specific examples of ceramides include ceramide 1, ceramide 3, ceramide 4, ceramide 5, ceramide 6A, cerebrosides and ceramide 6B. Preferably, the ceramides used in the systems are ceramides 1, 3 and 6. An example of a formulation that comprises these ceramides is SK-Influx® (Cosmoferm).

Some examples of pseudoceramides include:

N-(2-hydroxyoctadecyl)-N-(2-hydroxyethyl)hexadecanamide
 N-(2-hydroxyoctadecyl)-N-(2-hydroxyethyl)propanamide
 N-(2-hydroxyhexadecyl)-N-(2-hydroxyethyl)butanamide
 N-(2-hydroxyhexadecyl)-N-(2-hydroxyethyl)heptanamide
 N-(2-hydroxyoctadecyl)-N-(2-hydroxyethyl)ethanamide
 N-(2-hydroxyoctadecyl)-N-2-O-glucopyranosyl)ethylpentanamide
 N-(2-hydroxydodecyl)-N-(2-hydroxyethyl)hexanamide
 N-(2-hydroxydodecyl)-N-(2-hydroxyethyl)-2butylhexanamide
 N-(2-hydroxyhexadecyl)-N-(2-hydroxyethyl)ethanamide
 N-(2-hydroxydodecyl)-N-(2-hydroxyethyl)-2-hydroxyhexanamide
 N-(2-hydroxytetradecyl)-N-(2-hydroxyethyl)propanamide
 N-(2-hydroxyhexadecyl)-N-(2-sulfoethyl)hexadecanamide
 N-(2-hydroxyoctadecyl)-N-(2-phosphoethyl)butanamide
 N-(2-hydroxyoctadecyl)-N-(2-hydroxyethyl)-2-hydroxypropanamide
 N-(2-hydroxy-3-octadecyloxypropyl)-N-(2-hydroxyethyl)hexadecanamide
 N-(2-hydroxy-3-nonanyloxypropyl)-N-(2-hydroxyethyl)propanamide
 N-(2-hydroxyoctadecyl)-N-(2-hydroxyethyl)-2-hydroxypropanamide
 N-(2-hydroxy-3-hexadecyloxypropyl)-N-(2-hydroxyethyl)hexadecanamide
 N-(2-hydroxy-3-octadecyloxypropyl)-N-(2-hydroxyethyl)butanamide
 N-(2-hydroxy-3-hexadecyloxypropyl)-N-(2-hydroxyethyl)ethanamide
 N-(2-hydroxy-3-dodecyloxypropyl)-N-(2-sulfohydroxyethyl)decanamide
 N-(2-hydroxy-3-decyloxypropyl)-N-(2-hydroxyethyl)hexanamide
 N-(2-hydroxy-3-octadecyloxypropyl)-N-(2-hydroxyethyl)hexadecanamide
 N-(2-hydroxy-3-dodecyloxypropyl)-N-(2-hydroxyethyl)butanamide

5

N-(2-hydroxy-3-octadecyloxypropyl)-N-(2-hydroxyethyl) co-o-linoleoyldocosanamide
 N-(2-hydroxy-3-dodecyloxypropyl)-N-(2-hydroxyethyl) propanamide
 N-(2-hydroxy-3-hexadecyloxypropyl)-N-(2-hydroxyethyl)-2-methylpropanamide
 N-(2-hydroxy-3-tetraadecyloxypropyl)-N-(2-hydroxyethyl) ethanamide
 N-(2-hydroxy-3-dodecyloxypropyl)-N-(2-hydroxyethyl) heptanamide
 N-(2-hydroxy-3-hexadecyloxypropyl)-N-(2-phosphoethyl) hexadecanamide
 N-(2-hydroxy-3-dodecyloxypropyl)-N-(2-hydroxyethyl) propanamide
 N-(2-hydroxy-3-octadecyloxypropyl)-N-(2-)-glucopyranosyl)ethyl-2-hydroxy pro-panamide
 N-(2-hydroxy-3-octyloxypropyl)-N-(2-hydroxyethyl)pentanamide
 Some examples of neoceramides include:
 N-(2,3-dihydroxypropyl)-N-(hexadecyl)butanamide
 N-(2,3-dihydroxypropyl)-N-(tetradecyl)ethanamide
 N-(2,3-dihydroxypropyl)-N-(hexadecyl)-2-hydroxypropanamide
 N-(2,3-dihydroxypropyl)-N-(octadecyl)butamide
 N-(2,3-dihydroxypropyl)-N-(2-ethylhexadecyl)hexanamide
 N-(2,3-dihydroxypropyl)-N-(hexadecyl)-2-hydroxyoctanamide
 N-(2,3-dihydroxypropyl)-N-(3-methylhexadecyl)ethanamide
 N-(2,3-dihydroxypropyl)-N-(dodecyl)butanamide
 N-(2,3-dihydroxypropyl)-N-(hexadecyl)-2-hydroxyhexanamide
 N-(2-hydroxy-3-O-glucopyranosylpropyl)-N-(hexadecyl) octanamide
 N-(2-hydroxy-3-phosphopropyl)-N-(octadecyl)ethanamide
 N-(2-hydroxy-3-sulfopropyl)-N-(hexadecyl)butanamide
 N-(2-hydroxy-3-O-glucopyranosylpropyl)-N-(hexadecyl) decanamide
 N-(2,3-dihydroxypropyl)-N-(heptadecyl)ethanamide
 N-(2,3-dihydroxypropyl)-N-(3-methylhexadecyl)ethanamide
 N-(2,3-dihydroxypropyl)-N-(heptadecyl)butanamide
 N-(2,3-dihydroxypropyl)-N-(6-dodeceny)hexadecanamide
 N-(2,3-dihydroxypropyl)-N-(2-methylhexadecyl)-2-hydroxy-ethanamide
 N-(2,3-dihydroxypropyl)-N-(cctadecyl)-2-hydroxypropanamide
 N-(2-hydroxy-3-O-glucopyranosylpropyl)-N-(heptadecyl)-ethanamide
 N-(2-hydroxy-3-sulfopropyl)-N-(dodecyl)heptanamide
 N-(2,3-dihydroxypropyl)-N-(tetradecyl)-4-hydroxybutanamide
 N-(2,3-dihydroxypropyl)-N-octadecyl)-(t)-O-linoleoyl-docosanamide
 N-(2,3-dihydroxypropyl)-N-(linoleyl)ethanamide
 N-(2,3-dihydroxypropyl)-N-(oleyl)-2-hydroxy-heptanamide
 N-(2,3-dihydroxypropyl)-N-iyiodecyl)-(t)-O-linoleoyl-docosanamide
 N-(2,3-dihydroxypropyl)-N-(octadecyl)-3-hydroxybutanamide
 N-(2-phospho-3hydroxypropyl)-N-(heptadecyl)butanamide
 N-(2,3-dihydroxypropyl)-N-(2-methylheptadecyl)propanamide
 N-(2,3-dihydroxypropyl)-N-(3-ethylheptadecyl)butanamide
 N-(2-sulfo-3-hydroxypropyl)-N-(1-octadecyl)ethanamide
 N-(2,3-dihydroxypropyl)-N-octadecyl)propanamide

6

N-(2,3-dihydroxypropyl)-N-(dodecyl)decanamide
 N-(2,3-dihydroxypropyl)-N-(3-ethyl-dodecyl)butanamide
 N-(2-O-glucopyranosyl-3-hydroxy propyl)-N-(heptadecyl) butanamide
 N-(2,3-dihydroxypropyl)-N-(oleyl)-2-hydroxypropanamide
 N-(2,3-dihydroxypropyl)-N-(linoleyl)-2-hydroxyheptanamide
 N-(2,3-dihydroxypropyl)-N-(dodecyl)-2-hydroxyoctanamide
 N-(2,3-dihydroxypropyl)-N-(hexadecyl)-2-methylheptanamide
 N-(2,3-dihydroxypropyl)-N-(octadecyl)-2-hydroxypentanamide
 N-(2,3-dihydroxypropyl)-N-(2-methylhexadecyl)-2-hydroxyheptanamide
 N-(2,3-dihydroxypropyl)-N-(linoleyl)-2-hydroxypropanamide
 N-(2,3-dihydroxypropyl)-N-(tetradecyl)ethanamide.
 The phospholipid component may contain any phospholipid or mixtures of phospholipids. Preferably the phospholipid component comprises phosphatidylcholine (PC). Other examples of phospholipids include distearoylphosphatidylcholine (DSPC 18), phosphatidic acid, inositol phosphate, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, and phosphatidylethanolamine.
 Additionally, the phospholipid component can comprise one or more lysophospholipids. Lysophospholipids are single chain phospholipids. Examples of lysophospholipids include lysophosphatidylcholines, such as monopalmitoylphosphatidylcholine (MPPC); lysophosphatidylglycerols; lysophosphatidylethanolamines; lysophosphatidylinositols; lysophosphatidylserines; and lysophosphatidic acid. Mixtures of different types of phospholipids and/or lysophospholipids can also be used.
 Examples of phospholipid components include formulations which are sold by Degussa BioActives under the following names: Epikuron 200SH, Epikuron 200 and Epikuron 170. All these formulations comprise phospholipids, e.g., soya phosphatidylcholines (PC), and fatty acids. These formulations differ in the saturation and chain length of their constituent phospholipids and fatty acids.
 EPIKURON® 200 SH comprises about 95% PC and 1.2% lysophosphatidylcholine. The phospholipids used in this formulation are saturated, long-chain phospholipids. Saturated phospholipids prevent leakage of active substances through the vesicular bilayer to a greater extent than unsaturated phospholipids do. Also, saturated phospholipids are more stable, both mechanically and chemically. The fatty acids in EPIKURON® 200 SH are all saturated fatty acids, and are mainly stearic fatty acid.
 EPIKURON® 200 comprises about 95% PC and 3% lysophosphatidylcholine. The phospholipids used in this formulation are mainly unsaturated. Also, about 85% of the fatty acids are unsaturated. The fatty acids are mainly linoleic acid.
 This formulation provides enhanced penetration.
 EPIKURON® 170 comprises PC and other phospholipids such as phosphatidylethanolamine (PE). The phase behaviour of PE is different from PC because of the smaller head group area in PE. In particular, PE forms reversed hexagonal phases instead of lamellar phases in excess water and at high temperatures. Also, about 85% of the fatty acids in EPIKURON® 170 are unsaturated. The fatty acids are mainly linoleic acid.
 The chain melting temperature for phospholipids is the temperature at which the transition from solid phase to liquid crystalline phase of the lipid bilayers occurs. The chain melting temperature decreases with increasing unsaturation and decreasing chain length of the phospholipid. In the case of

saturated long-chained phospholipids, the addition of cholesterol lowers this temperature. In the case of highly unsaturated phospholipids, the addition of cholesterol has the opposite effect than for saturated phospholipids.

If there is a need to change the properties of the formulation, the choice of phospholipid is an important component to consider, since different phospholipids give rise to varying characteristics of the formulation.

In a preferred embodiment, the present system also comprises skin lipid precursors. The lipid precursors include any compound that promotes in situ cholesterol, ceramide or sphingolipid synthesis. The preferred lipid precursors are mevalonic acid, which promotes in situ cholesterol synthesis; and 25-hydroxycholecalciferol, which promotes in situ ceramide synthesis in the skin. Other preferred precursors are palmitoyl CoA and serine, which together are converted to 3-ketosphinganine, which promotes in situ ceramide synthesis in the skin.

By the promotion of in situ cholesterol and ceramide synthesis in the skin, the overall content of lipid in the system can be maintained in a range as low as approximately 2-20%. Therefore, the water content of the delivery system can be as high as 80-98%. The high water content enables the skin to "breathe" normally, and enhances its ability to restore its normal barrier function rapidly.

Other lipid precursors useful in the present invention include, for example: acylceramides; deoxyacetin cimifugoside, adopalene, adenosine, aloe derived lectins, 3-aminopropyl dihydrogen phosphate, anise extracts, ascorbic acid and derivatives thereof, ascorbyl palmitate, asiatic acid, benzoic acid derivatives, biotin, butanoyl betulonic acid, catecholamines, coenzyme Q10, dehydrocholesterol, dehydroascorbic acid and derivatives thereof, estrogen and derivatives, erythroic acid, genistein, lipoic acid, 4-methoxysalicylic acid, N-acetylcysteine, panthetine, pregnenolone and derivatives, retinal, retinoates, retinal, retinyl acetate, retinyl glucuronate, retinyl linoleate, retinyl palmitate, retinyl propionate, phytosphingosine, sphingosine, and others.

Preferably, an alkaline compound, or buffer system, is included in the formulation to adjust the pH. Examples of alkaline compounds include triethanolamine (TEA), sodium hydroxide, sodium acetate, and sodium bicarbonate. Examples of buffer systems include carbonic acid/potassium carbonate, phosphoric acid/potassium phosphate, and acetic acid/sodium acetate.

The fatty acids of the final delivery system can be in a free state or can form a salt. The portion of fatty acids which is in a free state is partially dependent on the pH of the formulation. In general, the level of free fatty acid increases as the pH of the formulation decreases. Depending upon the particular use of the formulation, the pH of the formulation can vary. Preferably, the pH of the formulation is about 6.5 to 7.8.

In a preferred embodiment, the delivery system comprises triethanolamine (TEA). It is preferred to adapt the molar ratio between the fatty acids and triethanolamine to enable a certain portion of the fatty acids in the final delivery system to form a triethanolaminium salt, while another portion of the acid exists as free fatty acid. Preferably, the delivery system is prepared from fatty acids and triethanolamine in which the molar ratio of the fatty acids to the triethanolamine is higher than about 2:1, preferably higher than about 3:1.

In a preferred embodiment, the delivery system comprises a combined content of a fatty acid, cholesterol, a ceramide/ phospholipid portion, and skin lipid precursors between about 2-20%. A preferred low end of this range is about 2%,

3%, 4%, 5%, 6%, 7% or 8%. A preferred high end of this range is about 13%, 14%, 15%, 16%, 17%, 18%, 19% and 20%.

In another preferred embodiment, the amounts of the components of the delivery system are as follows: fatty acid: 0.5-10%; cholesterol: 0.5-10%; a ceramide/phospholipid portion: 0.005-20%; and lipid precursors: 0.000001-10%.

In a preferred embodiment, the formulation does not contain any irritating ingredients. Examples of irritating ingredients include alcohols, such as isopropanol and ethanol; short chain fatty acids; and detergents. Preferably, the formulation contains less than 10% alcohol, more preferably less than 5% alcohol, most preferably less than 1% alcohol, and optimally no alcohol.

Without the intention to limit the scope of the invention, a possible theory explaining the mechanical properties of the delivery system follows. The administered formulation easily penetrates the lipid bilayer of the skin. In doing so, the system creates a temporary and reversible state of enhanced atrophy among the lipid components of the bilayer. The enhanced atrophy in itself then gives rise to either a) enhanced energy levels, wherein the energy could promote active transport of the to-be-carried substances into the skin, and/or b) creates naturally and reversibly occurring holes and disorganized patches in the lipid bilayer through which the active substances could then pass more easily. It is very well feasible that the temporary disarray in the lipid bilayer will temporarily break up the organized structure of the bilayer and create micelles of lipids with areas between them, or surrounding them, through which lipophobic/hydrophilic substances and/or compositions can enter through the stratum corneum. As the lipid composition of the formulation resembles the natural lipid composition of the skin, the so introduced new lipids will after a short time of creative chaos easily blend in with the natural lipid building stones of the lipid bilayer, and thus not permanently damage the barrier function of the skin.

Following the temporary disarray in the lipid bilayer, the normal barrier function of the cornea stratum rapidly returns. (That is, the skin barrier restoration is rapid.) The rapid return may be enhanced by the lipid precursors of the formulation. For example, the in situ promotion of cholesterol synthesis in the stratum corneum, the in situ promotion of ceramide synthesis in the stratum corneum, and/or the in situ promotion of sphingolipid synthesis in the stratum corneum may allow for the rapid skin barrier restoration.

A delivery system according to the present invention preferably comprises a combination of:

Fatty Acid (C16-24)	0.5-10%
Phospholipid	0.5-10%
Cholesterol	0.5-7%
Lipid precursor:	0.000001-10%
Mevalonic acid and/or 25-Hydroxycholecalciferol	
Ceramide	0.005%-7%

(Not all components are present are 0%.)

Another preferred embodiment of the delivery system comprises:

Fatty Acid (C16-24)	0.5-10%
Phospholipid	0.5-10%
Cholesterol	0.5-7%

-continued

Lipid precursor:	0.000001-10%
Mevalonic acid and/or	
25-Hydroxycholecalciferol	
Ceramide	0.005%-7%
Glycerine	0-5%
Propylene glycol	0-48%
PVP (e.g., M weight 40,000)	0-5%
TEA	0-3%

(Not all components are present are 0%.)

An even more preferred embodiment of the delivery system comprises:

Fatty Acid (C16-24)	2%
Phospholipid	4.5%
Cholesterol	2%
Lipid precursor:	0.000001-10%
Mevalonic acid and/or	1% or 0.01%
25-Hydroxycholecalciferol	0.015% or 0.0015%
Ceramide 3	0.015%
Glycerine	3%
Propylene glycol	4%
PVP (M weight 40,000)	2%
TEA	0.5%

An even more preferred embodiment of the delivery system comprises:

Fatty Acid (C16-24)	2%
Phospholipid	4.5%
Cholesterol	2%
Lipid precursor:	0.000001-10%
Mevalonic acid and/or	1% or 0.01%
25-Hydroxycholecalciferol	0.015% or 0.0015%
Ceramide 3	0.015%
Glycerine	3%
Propylene glycol	4%
PVP (M weight 40,000)	2%
TEA	0.5%
Ceramide 1	0.025%

For delivery systems formulated for dry skin conditions, such as, for example, eczema, psoriasis and shingles, the amount of the lipid precursors are preferably increased by a factor of about three to about six, more preferably by a factor of about four to five, vis-à-vis systems not formulated for dry skin conditions. For example, a system for a dry skin condition can comprise about four to five times as much mevalonic acid and/or 25-hydroxycholecalciferol as a system not made for a dry skin condition. For example, a dry skin system can comprise about 0.01% mevalonic acid and about 0.0015% 25-hydroxycholecalciferol vis-à-vis about 0.002% mevalonic acid and about 0.0003% 25-hydroxycholecalciferol in other type of systems.

The topical delivery system according to the present invention further comprises one or more cosmetically and/or therapeutically active substances. Active substances are defined as agents other than emollients and other than ingredients that merely improve the physical characteristics of the formulation.

Some general examples of active substances include sunscreens, tanning agents, skin anti-wrinkling agents, anti-dandruff agents, anti-acne agents, hair growth stimulants and vitamins. Therapeutically active substances include, but are not limited to, substances which treat conditions such as eczema, dry skin, itchy skin, fungal infection, acne, skin

cancer, hair loss, louse infection, psoriasis, and skin lesions (i.e. wounds). Therapeutically active substances also include substances for transdermal delivery, for example, interleukin, hormones, vaccines, nicotine, interferon, pain killers, peptides, proteins and vitamins.

Active substances also include steroid hormones. Steroid hormones inhibit inflammation and hyperproliferation of the epidermis thus resulting in normalization of hypersensitive skin conditions. Examples of steroid hormones include, but are not limited to, glucocorticoids, androgens and estrogens.

Examples of sunscreens include those materials commonly employed to block ultraviolet light. Illustrative compounds are derivatives of PABA, cinnamate and salicylate. For example, octyl methoxycinnamate and 2-hydroxy-4-methoxybenzophenone (also known as oxybenzone) can be used. Octyl methoxycinnamate and 2-hydroxy-4-methoxybenzophenone are commercially available under the trademarks, Parsol MCX and Benzophenone-3, respectively. The exact amount of sunscreen employed in the systems can vary depending upon the degree of protection desired from the sun's UV radiation.

Examples of vitamins include vitamin A and vitamin E, preferably in the form of an ester of a fatty acid, such as vitamin A palmitate (retinyl palmitate) and vitamin E linoleate (tocopheryl linoleate). Other esters of vitamins A and E may also be utilized, such as any of the fatty acids mentioned above and below.

Preservatives may also be included in the formulations of the present invention. Suitable preservatives include alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, propionate salts, and a variety of quaternary ammonium compounds. Particularly preferred preservatives of this invention are methyl paraben, propyl paraben, imidazolidinyl urea, sodium dehydroxyacetate and benzyl alcohol. Preservatives are typically used in amounts up to about 2% by weight of the formulation. An example of a preservative is Phenonip®.

Other adjunct minor components may also be incorporated into the formulations of the present invention. These components may include thickeners, coloring agents, opacifiers and perfumes. For example, any thickening agent can be included in the formulation to adjust the viscosity of the formulation. Examples of suitable thickening agents include glycerol and xanthan gum. Some additional adjunct minor components include chalk, talc, Fullers earth, kaolin, starch, smectites clays, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, aluminium starch octenyl succinate and mixtures thereof. Amounts of these adjunct minor components may range anywhere from 0.001 up to 20% by weight of the formulation (i.e. composition). Additionally, to adjust the pH, bases can be included in the systems, e.g., sodium hydroxide and triethanolamine.

The delivery system can be in any form, such as a cream, a lotion, a gel, and an aerosol foam. The amount of certain adjunct minor components used in a particular formulation varies depending on the desired form of the delivery system, as would be known by a skilled artisan. For example, the amount of thickening agent used to prepare an aerosol foam formulation is about 10 to 20% of the amount used to prepare a cream formulation. Additionally, emulsifiers are added to an aerosol foam formulation, such as, for example, laureth 4.

In another embodiment, the present invention provides a mucosal delivery system formulated to deliver a substance to, or through, a human mucous membrane without permanently disturbing the integrity of the mucous membrane. The mucous membrane is the moist tissue that lines some organs and body cavities (such as nose, mouth, lungs, rectum, stom-

ach and vagina) and secretes mucous. The mucosal delivery system comprises the lipophilic and hydrophilic components, as described above. The particular formulations of the mucosal delivery systems are varied to accommodate the particular environment of the mucosa, as would be known by a skilled artisan.

In a preferred embodiment, the lipophilic components of the topical or mucosal delivery system form three types of particles: gas spheres, vesicles, and lipid particles. These three types of particles are within a hydrophilic phase (i.e. aqueous medium). See FIG. 1.

The gas spheres are lipid monolayers that enclose air bubbles. These monolayers are formed from the lipophilic components. Negatively charged carboxylate groups stud the outer surfaces of these gas spheres. See FIG. 2. Preferably, these gas spheres are approximately 1 μm to approximately 500 μm in diameter.

The vesicles are lipid bilayers enclosing a hydrophilic core. These bilayers are formed from the lipophilic components. Negatively charged carboxylate groups stud the inner and outer surfaces of the vesicles. See FIG. 3. The vesicles can range from approximately 0.02 μm to approximately 0.5 μm in diameter, or from approximately 0.5 μm to approximately 2 μm in diameter, or from approximately 1 μm to approximately 2.5 μm in diameter. The diameter of a vesicle increases as the amount of an active ingredient incorporated into the vesicle increases.

The lipid particles are lipid monolayers enclosing fatty acids. These monolayers are formed from the lipophilic components. See FIG. 3. The lipid particles are less than approximately 1 to approximately 150 μm in diameter. The lipid particles may be in the form of individual lipid particles, or the lipid particles may aggregate to form crystals.

The various particles of the delivery system provide micro-compartments with different properties. Due to these different micro-compartments, the delivery system can be used to deliver both hydrophilic and lipophilic active substances. For example, a water soluble active substance can be located in the hydrophilic core of the vesicles, or can be located in the hydrophilic phase of the system. A lipid soluble active substance can be located within the monolayer of the gas spheres, within the bilayer of the vesicles, or within the monolayer or within the core of the lipid particles. See FIG. 4.

Preferably, the delivery systems comprise three phases, i.e. a foam phase, a vesicle phase and a hydrophilic phase. The foam phase comprises the gas spheres and the lipid particles. The vesicle phase comprises the vesicles and the lipid particles. The hydrophilic phase comprises water and hydrophilic components.

In a preferred embodiment, the delivery system is produced from three portions (i.e. fractions), in particular a hydrophilic portion and two lipophilic portions. The two lipophilic portions comprise the lipophilic components as defined above. Both lipophilic portions are immersed in aqueous media. One portion is made into the foam phase. The other portion is made into the vesicle phase. The foam phase portion and the vesicle phase portion can be in a ratio from about 1:7 to about 7:1. Preferably, the foam phase portion and the vesicle phase portion are approximately equal in amount.

Preferably, the foam phase is formed by mixing the foam phase portion at about 65 to 85° C. The pH is set to the range of about 5.5 to 8.2. The mixing is performed under conditions so as to allow gas spheres to form. Mixing can be performed by using an mixing apparatus, such as, for example, an Ultra Turrax® (Ultra Turrax T 25, Janke & Kunkel IKA-Labortechnik).

The time and speed of mixing can vary. For example, Ultra-turraxing can be performed for one minute at a speed of 9500 rpm.

Preferably, the vesicle phase is formed by gently mixing the vesicle phase portion at about 65 to 85° C. More preferably, the vesicle phase is formed by homogenizing or sonicating the vesicle phase portion at about 65 to 85° C. The pH is set to the range of about 5.5 to 8.2. Preferably, the vesicle phase is produced under conditions which do not allow any gas to enter the formulation, such as in a vacuum.

Homogenization can be accomplished with, for example, a high pressure homogenizer or a sonicator. An example of a homogenizer is a Rannie homogenizer from APV. The pressure of the homogenizer can be set, for example, from about 10,000 to 40,000 psi. An example of a sonicator is Soniprep 150, manufactured by Sanyo Gallencamp Plc. Ultrasound radiation is transmitted by high frequency vibrations via a titanium alloy probe from a transducer that converts electrical energy to mechanical energy. The diameter of the probe tip can vary. An example of a diameter of a probe tip is about 9.5 mm. The amplitude at which the sonication can be performed can vary. An example of an amplitude is 10 microns for 30 minutes.

The lipid particles, and/or lipid particle crystals, form as a by-product of the formation of the foam phase and vesicle phase. In either the foam phase or vesicle phase, up to 30% of the lipophilic components can be in the form of lipid particles and/or lipid particle crystals.

The hydrophilic phase is formed by mixing together water soluble components with water (i.e. hydrophilic portion). Examples of water soluble components include propylene glycol, glycerol, polyvinylpyrrolidone, and thickeners, e.g., xanthan gum.

The foam phase, vesicle phase and hydrophilic phases are mixed together. Preferably, an equal amount of each phase is used in the formulation.

The foam phase, vesicle phase and hydrophilic phases can be mixed together in any order. For example, the foam phase and the vesicle phase can be first mixed together, and then the resulting mixture can be mixed with the hydrophilic phase. As another example, the foam phase can be first mixed with the hydrophilic phase, and then the vesicle phase can be added.

One or more active substances can be added to the foam phase portion, the vesicle phase portion, the hydrophilic portion, or a combination of these portions.

The specific components of a formulation, and the formulation process, can be varied to obtain delivery systems which allow for different rates of the release, and degrees of penetration, of active substance(s). For example, the phase of the system in which an active substance is placed affects release and penetration rates. For instance, to enhance penetration rates of either a hydrophilic or lipophilic active substance, a major portion of the active substance is placed within the vesicle phase portion.

Another factor which affects release and penetration rates is the size of the micro-compartments. The size of the vesicles can be controlled via the formulation process. For example, during processing, as the homogenizing pressure and duration increases, the vesicle size decreases.

An additional factor which affects release and penetration rates is the type of phospholipids used in the formulation. For example, penetration can be enhanced by including a greater portion of unsaturated phospholipids within the formulation. Preferably, greater than about 90%, greater than about 95%, or greater than about 99% of the phospholipids used in the formulation are unsaturated phospholipids.

Also, phospholipids which include elevated levels of surface active single chain agents enhance penetration. Surface active single chain agents at about a level of 2% to 10% of the phospholipids are considered to be at an elevated level. Examples of surface active agents are lysophospholipids.

Examples of phospholipid formulations that enhance penetration include EPIKURON® 200SH and EPIKURON® 200, and are described above.

The concentration of free fatty acid is also an important parameter affecting penetration rates. A relatively high level of free fatty acid enhances penetration of hydrophilic active substances.

Penetration rates can also be enhanced by the addition of certain adjuvants. For example, an anionic surfactant can be added to the foam phase portion. Also, incorporation of glyceryldilaurate into the vesicle bilayers creates more flexible vesicles which can enhance penetration.

Penetration rates can also be enhanced by the addition of non-ionic adjuvants. In a preferred embodiment, the delivery systems of the present invention further comprise non-ionic adjuvants.

Unlike ionic surfactants, non-ionic adjuvants do not carry a charged species. Instead non-ionic adjuvants comprise a hydrophilic group (e.g. a short, water-soluble polymer chain). The polymers used in non-ionic adjuvants are preferably 10 to 100 units long. These adjuvants are mild on the skin even at high loadings and long-term exposure.

Non-ionic adjuvants are known in the art. Examples of non-ionic adjuvants can be found, for instance, in "Non-ionic Surfactants: Organic Chemistry," edited by Nico M. van Os, published by Marcel Dekker (1998), and "Non-ionic Surfactants: Chemical Analysis (Surfactant Science Series, Vol 19)" by John Cross, published by Marcel Dekker (Oct. 1, 1986). Some non-ionic adjuvants can be divided into classes depending on the type of hydrophilic group appearing in the adjuvant.

Two classes of non-ionic adjuvants that comprise poly (ethylene oxide) groups as their hydrophilic groups are alcohol ethoxylates and the alkylphenol ethoxylates. Examples of non-ionic adjuvants of these classes include tetraethylene glycol monododecyl ether; polyoxyethylene 23 glycol monododecyl ether, polyethylenoxide-polypropylenoxide (PEO-PPO) block-copolymers (such as the commercially available PEO-PPO-PEO triblockcopolymers, called Synperonics F108 and F127), polyoxyethylene alkylphenols; polyoxyethylene alcohols; polyoxyethylene esters of fatty acids; polyoxyethylene mercaptans; and polyoxyethylene alkylamines.

Another class of non-ionic adjuvants is the alkyl polyglycosides. In these molecules, the hydrophilic group is a sugar molecule, such as a polysaccharide, disaccharide, trisaccharide, maltose, etc. Preferably, the polyglycosides have one or two sugar groups in their chains. Examples of non-ionic adjuvants of this class include alkyl glucoside and a glucose ester.

Another class of non-ionic adjuvants is sorbitan ester surfactants. Examples of non-ionic adjuvants of this class include polysorbate 20 (i.e. polyoxyethylene (20) sorbitan monolaurate, sold as Tween 20™); polysorbate 60 (i.e. polyoxyethylene (60) sorbitan monostearate); polysorbate 80 (i.e. polyoxyethylene (20) sorbitan monooleate); and polysorbate 65 (i.e. polyoxyethylene (20) sorbitan tristearate).

The delivery systems of the invention can comprise one non-ionic adjuvant or a combination of non-ionic adjuvants.

Preferably, approximately 0.1% to approximately 15% of a delivery system of the present invention is comprised of a non-ionic adjuvant. Preferred lower boundaries of this range include approximately 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 1% and 2%. Preferred upper boundaries of this range include

approximately 0.3%, 0.4%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, and 15% of the delivery systems. Each lower boundary can be combined with each upper boundary to define a range. The lower and upper boundaries should each be taken as a separate element.

The non-ionic adjuvant can be added to the hydrophilic portion, either lipophilic portion, or combinations of these portions. Preferably the non-ionic adjuvant is added to all the portions. During the production of the hydrophilic portion or either lipophilic portion, the non-ionic adjuvant is preferably added before the mixing step.

In addition to increasing the rates of penetration of active ingredients, the inclusion of non-ionic adjuvants in the delivery systems also increases the diameter of the vesicles vis-à-vis the delivery systems without these adjuvants (while keeping the amount of active ingredient constant). The vesicle can range from approximately 0.02 μm to approximately 2.5 μm in diameter with the addition of the adjuvants. The size of the other particles are not significantly affected by the addition of the non-ionic adjuvants.

Additional factors which affect release and penetration rates include: the ratio between the different lipid components; the ratio between the foam phase, the vesicle phase and the hydrophilic phase; and the ratio between the amounts of active substances within each phase.

In one embodiment of the present invention, the lipophilic components of the delivery system form only two of the above-defined particles. That is, the formulation comprises only the gas spheres and lipid particles; or the formulation comprises only the vesicles and lipid particles.

In this embodiment, the delivery system is produced from a hydrophilic portion and a lipophilic portion. The lipophilic portion is made either into the foam phase or the vesicle phase, as described above. Preferably, the vesicle phase is produced under conditions which do not allow any gas to enter the formulation, such as in a vacuum. The foam phase or vesicle phase is mixed with the hydrophilic phase. Preferably, an equal amount of either the foam phase or vesicle phase, and the hydrophilic phase is used in the formulation.

Thus, while there have been described what are presently believed to be the preferred embodiments of the present invention, other and further embodiments, modifications, and improvements will be known to those skilled in the art, and it is intended to include all such further embodiments, modifications, and improvements and come within the true scope of the claims as set forth below.

EXAMPLES

Example 1

A General Method of Making

The phospholipid, cholesterol, palmitic acid and ceramide components are mixed together with water, and agitated at a temperature of 70-80° C. The following additional components are added: mevalonic acid lactone, 25-hydroxycholecalciferol, propylene glycol, glycerine, PVP, TEA added along with water, and sodium hydroxide. Sodium hydroxide is added to adjust viscosity and stabilize the formulation. Water is then added, and the formulation is agitated well. The formulation is then cooled down.

An active substance can be dissolved in both the lipid phase and/or the water phase, depending on the solubility and concentration of the active substance.

15
Example 2

Formulation of a Preferred Embodiment of the Topical Delivery System

(An active ingredient is excluded from this formulation.)

Component	Total amount
Water	79.5% of formulation
Epikuron 200SH	3.5% of formulation
Palmitic acid	1.5% of formulation
Cholesterol	1.5% of formulation
Mevalonic acid	0.01% of formulation or 0.1% of formulation
Triethanolamine	0.5% of formulation
Phenonip ®	0.4% of formulation
Xanthan gum	2.0% of formulation
Skinflux	2.0% of formulation
25-hydroxycholecalciferol	0.0015% of formulation or 0.015% of formulation
Propylene glycol	4.0% of formulation
Glycerol	3.0% of formulation
Polyvinylpyrrolidone	2.0% of formulation

Epikuron 200SH are hydrogenated lecithins, i.e. phosphatidylcholine (PC).
 "Skinflux" is a blend product obtainable from Degussa Goldschmidt which contains: Ceramide 1, 3, 6II; Phytosphingosine; Cholesterol; Sodium Lauroyl Lactylate; Carbomer; and Xanthan Gum.
 Mevalonic acid lactone is a lipid precursor for cholesterol/fatty acids.
 25-Hydroxycholecalciferol is a lipid precursor for ceramides
 Xanthan Gum is a thickener (polysaccharide).
 PHENONIP ® is a preservative and a blend of parabens.

Three fractions, a vesicle fraction, a foam fraction and a hydrophilic fraction, are first prepared separately, as described below. Each fraction weighs 3.3 kg. Then the three fractions are mixed together. The following tables show the percent amount of each component contributed by each fraction to the final formulation. Thus, for each component, the sum of the percent amounts of all the fractions is 100%.

1: Vesicle Fraction

Component	Percent Amount in Final Formulation
Water	33% of total water
Hydrogenated lecithins	50% of total amount
Palmitic acid	50% of total amount
Cholesterol	50% of total amount
Mevalonic acid	50% of total amount
Triethanolamine	50% of total amount
Preservative (e.g., Paraben mixture)	50% of total amount
Xanthan gum	15% of total amount
Skinflux	33% of total amount
25-hydroxycholecalciferol	50% of total amount
5M sodium hydroxide	1.3 ml per 1000 grams of water

The "Percent Amount in Final Formulation" indicates the percentage of each component which is contributed by the vesicle fraction to the final formulation.

In forming the vesicle fraction, the components are mixed and heated to the temperature range of 65 to 85° C. while gently stirring. The pH is set to the range of 5.5 to 8.2 by the use of sodium hydroxide. The resulting mixture is then homogenized. Homogenization can be accomplished by, for example, a homogenizer set at a high pressure (e.g. 10,000 to 40,000 psi); or by a sonicator. The size of the vesicles is partially dependent upon how long the resulting mixture is agitated. For example, to obtain an average vesicle size of 0.140 µm, the resulting mixture is agitated for 60 minutes at about 70° C. The mixture is then allowed to cool to below 40° C.

16

2: Foam Fraction

Component	Percent Amount in Final Formulation
Water	33% of total water
Hydrogenated lecithins	50% of total amount
Palmitic acid	50% of total amount
Cholesterol	50% of total amount
Mevalonic acid	50% of total amount
Triethanol amine	50% of total amount
Preservative (e.g. a paraben mixture)	50% of total amount
Xanthan gum	7.5% of total amount
SK-influx ®	33% of total amount
25-hydroxycholecalciferol	50% of total amount
5M sodium hydroxide	1.3 ml per 1000 g of water

The "Percent Amount in Final Formulation" indicates the percentage of each component which is contributed by the foam fraction to the final formulation.

In forming the foam fraction, the components are mixed and heated to the temperature range of 65 to 85° C. while stirring. The pH is set to the range of 5.5 to 8.2 by the use of sodium hydroxide. The composition is mixed vigorously for 1 minute. Mixing can be done with ULTRATURRAX® from IKA Werke, Janke & Kunkel GmbH & Co KG (Staufen, Germany). The composition is then allowed to cool to below 40° C.

3: Hydrophilic Fraction

Component	Percent Amount in Final Formulation
Water	34% of total water
Propylene glycol	100% of total amount
Glycerol	100% of total amount
Polyvinylpyrrolidone	100% of total amount
Xanthan gum	77.5% of total amount
Skinflux	34% of total amount
5M sodium hydroxide	3.0 ml per 1000 g of water

The "Percent Amount in Final Formulation" indicates the percentage of each component which is contributed by the hydrophilic fraction to the final formulation.

In forming the hydrophilic fraction, the components are mixed and heated to the temperature range of 65 to 85° C. while stirring. The pH is set to the range of 5.5 to 8.2 by use of sodium hydroxide. Once homogeneous, the composition is then allowed to cool to below 40° C.

In forming the final formulation, after all the fractions are cooled down (below 40° C.), the three fractions are mixed together in any order. For example, the foam fraction is added to the vesicle fraction and gently mixed. Then the hydrophilic fraction is added. The resulting mixture is gently blended for several minutes to obtain a homogeneous solution.

The delivery system of this example is in the form of a cream. In order to produce a delivery system in an aerosol foam form, the total amount of xanthan gum in the final formulation is reduced from 2% to about 0.3%. Additionally, an emulsifier is added, such as laureth 4. Preferably, the emulsifier makes up about 0.7% of the final formulation.

Example 3

Formulation of Example 2 with Lidocaine as an Active Ingredient

An example of a 48 kg batch of a formulation of the delivery system follows. The three fractions used to prepare this formulation each contain 16 kg.

INCI Name	Trade Name	Supplier	CAS	Amount
Hydrogenated Lecithines	Epikuron 200SH	Degussa		1.7 kg
Cholesterol		Goldschmidt		
Palmitic acid		Vendico	57-88-5	0.8 kg
Ceramide 1, 3, 6II,	Skin Flux	Karlshamn	57-10-3	0.8 kg
Phytosphingosine, Cholesterol, Sodium Lauroyl Lactylate, Carbomer, Xanthan Gum.		Degussa		1.0 kg
Mevalonic acid lactone		Goldschmidt		
25-Hydroxy-cholecalciferol		Sigma Aldrich	674-26-0	4.8 g
Propylene glycol		Solvay	19356-17-3	0.72 kg
Glycerin, 99.5%		MB-Sveda	57-55-6	2.0 kg
Polyvinylpyrrolidone		Vendico	56-81-5	1.5 kg
Xanthan gum		Apoteket	9003-39-8	1.0 kg
Triethanolamine, 85%		Sigma Aldrich	11138-66-2	1.0 kg
Phenonip ®		MB-Sveda	102-71-6	0.3 kg
Lidocain Purified Water	USP-grade	Vendico Chemical Apoteket		2.4 kg Up to 48 kg

Example 4

Measurement of Skin Barrier Restoration

In the present context enhancing skin barrier restoration can be measured by tape and/or acetone stripping of stratum corneum skin lipid content before, during and after a treatment period with the present invention and other systems. Then HPLC analysis of skin lipid content of stratum corneum is conducted.

Example 5

In Vivo Model and Skin Penetration Results

Tracer amounts of the fluorescent dye NBD C6-ceramide were added to the formulation of Example 2 and to a reference (Vaseline®). The formulation and the reference were each applied to hairless mice epidermis. Skin biopsies from three mice in each experimental group were taken two hours after application for fluorescence microscopy (Zeiss Axioplan 2).

FIG. 9 is a fluorescent microscope image. This image clearly shows that the uptake of the fluorescent probe is more enhanced for the formulation of Example 2 than for the reference. Remarkably, the effect was seen as soon as two hours after application.

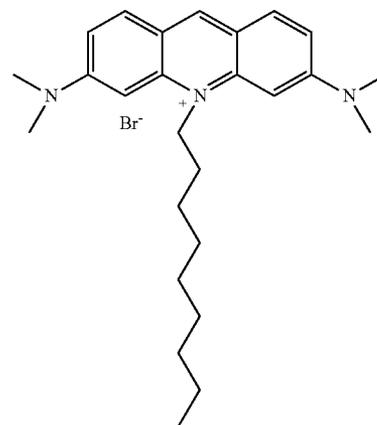
Example 6

Addition of Non-Ionic Adjuvants into the Formulation of Example 2

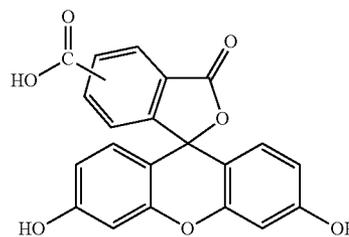
This example demonstrates how the addition of non-ionic adjuvants to the formulations of the present invention, in particular the formulation in Example 2, affects the characteristics of the formulation. This example also demonstrates a preferred distribution of active ingredients in the vesicle and foam phases.

Two different model active ingredients (model actives) were used in this example, i.e. a hydrophilic and a lipophilic model active. The lipophilic model active is acridine orange 10-nonyl bromide (AO). The hydrophilic model active is

5(6)-carboxyfluorescein (CF). The penetration of these model actives correspond to the penetration that would be obtained for typical hydrophilic and lipophilic drugs. The structures of these model actives are shown below.



Acridine orange 10-nonyl bromide

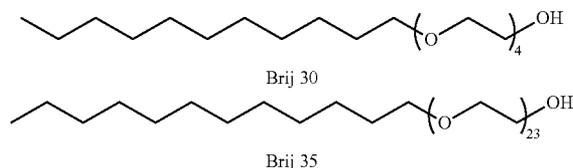


5(6)-Carboxyfluorescein

The non-ionic adjuvants used were tetraethylene glycol monododecyl ether (Brij® 30) and polyoxyethylene 23 dode-

19

cyl ether (Brij® 35), and were obtained from Sigma-Aldrich (St. Louis, Mo.). Their structures are shown below.



Three different variations of the formulations were studied for each model active. These formulation variations are defined as Formulation A, B and C as follows:

A) Formulation with 50% of the model active in the vesicle phase and 50% in the foam phase;

B) Formulation with all of the model active in vesicle phase; and

C) Formulation containing Brij® 30 and Brij® 35, with 50% of the model active in vesicle phase and 50% in the foam phase. The non-ionic adjuvants were added to the vesicle fraction and the foam fraction, and constituted 1.0 wt % of the total formulation.

Of the model actives, 0.028 wt % ($5.9 \cdot 10^{-4}M$) of AO was used; and 0.011 wt % ($3.0 \cdot 10^{-4}M$) of CF was used.

Characterization of Vesicle Phase

A comparison of the particle size, polydispersity index and zeta potential of the vesicles of Formulations A, B and C was conducted.

An autosizer (Malvern Zetasizer 1000HS, Malvern Instruments Ltd, Malvern, UK) was used to measure the size distribution of the vesicles. A zetasizer (Malvern Zetasizer 2000, Malvern Instruments Ltd, Malvern, UK) was used to measure the zeta potential. The zeta-potential is defined as the potential across the diffuse layer of ions surrounding the vesicles. The zeta-potential is related to the stability of the vesicles in such a way that a high magnitude of the zeta-potential implies vesicles with a higher surface charge. This higher surface charge in turn increases the repulsion between the vesicles and accordingly the stability of the formulation.

Preferably, the samples were diluted before measurements were taken. For example, before measuring the size distribution, water was used to dilute the sample. Before measuring the zeta-potential, 10 mM NaCl was used to dilute the sample.

A comparison of Formulations A, B and C with respect to the parameters of particle size, polydispersity index and zeta potential are shown in Table 1.

TABLE 1

Formulation	Parameters of the Vesicle Phase for Formulations A, B and C.					
	CF			AO		
	A	B	C	A	B	C
Particle diameter (nm)	276	494	975	345	1730	1395
Polydispersity index	0.4	0.7	0.9	0.5	1.0	1.0
Zeta-potential (mV)	-39	-41	-33	-36	-35	-30
pH	7.5	7.4	7.4	7.3	7.3	7.3

As described above, the A and C formulations (CF-A, AO-A, CF-C and AO-C) have 50% of the model active in the vesicle phase and 50% in the foam phase. Only the C formulations (CF-C and AO-C) include the non-ionic adjuvants. A comparison of the A and C formulations shows that the pres-

20

ence of the non-ionic adjuvants significantly increase vesicle size and decreases the magnitude of zeta-potential. See Table 2.

The inclusion of the non-ionic adjuvants into the vesicle membrane results in ethylene oxide coils reaching out from the vesicle surfaces. Without wanting to be bound to a theory, it is believed that a reason for the increase in vesicle size is that a lateral pressure between ethylene oxide coils in the membrane counteracts the creation of very small vesicles. It is also believed that these coils bind water thereby increasing the mass of the vesicles and reducing their mobility which results in a decrease in the zeta-potential (Silvander et al. *Langmuir* 16:3696-3702 (2000)).

As described above, the A formulations (CF-A and AO-A) have 50% of the model active in the vesicle phase and 50% in the foam phase. The B formulations (CF-B and AO-B) have 100% of the model active in the vesicle phase. A comparison of the A and B formulations shows that the vesicle size increases when all the active is added to the vesicle phase. See Table 1.

This increase in vesicle size is much more dramatic for the formulations containing AO than those containing CF. Without wanting to be bound to a theory, it is believed that this increase results from the interaction of the lipophilic active with the membranes of the vesicles in destabilizing manner. Even though there is a small increase in the vesicle size when all the CF is added to the vesicle phase (Formulation CF-B), it is not believed that CF interacts with the membranes to any large extent. Instead, the difference is likely due to a normal variance in the preparation process.

Characterization of the Foam Phase

The foam phase was investigated by means of light microscopy. As can be seen in FIG. 5, the distribution of the gas spheres of the foam phase is broad. No differences in the parameters of particle size, polydispersity index and zeta potential were found between Formulations A, B and C for each model active. The phase volume of air directly after production was estimated to 7% directly after production (Master size measurements) and was the same after five days storage at room temperature.

Stability of the Formulations

A change in color of the formulations would indicate oxidation of phospholipids or physical separation. No color change was observed even after 12 months storage both at about 25° C. and at about 40° C. It is believed that the physical stability is ensured due to the negative potential of the small particles together with the gel-like character of the total formulation.

Example 7

Skin Penetration Model

Diffusion Cell

Pig skin was chosen to investigate skin penetration since its stratum corneum structure resembles human stratum corneum more than does mouse skin (Bouwstra et al. *J. Lipid Res.* 36(4): 685-95 (1995)).

Ears of seven to eight month old pigham pigs were obtained from Swedish Meat (Uppsala, Sweden) approximately two hours after slaughter and used the same day. Patches of ear skin were removed with a scalpel. The appropriate thickness (640 μ m) was obtained by use of a manual dermatome (Padgett Dermatome, Padgett Instruments Inc., Kansas City). The skin was mounted on diffusion cells of a skin permeation system (Laboratory Glass Apparatus Inc., CA, USA). The receiver capacity of the system was 3 ml. The

skin was mounted with the stratum corneum facing upwards. The surface area of the skin patches was 0.67 cm².

An amount of 100 µl of each formulation being tested was applied to the skin and carefully spread to cover the entire surface area. The formulations tested were Formulations AO-A, AO-B, AO-C, CF-A, CF-B, CF-C from Example 6, and two reference formulations. For the AO formulations, Vaseline® containing 0.028 wt % AO was used as a reference. For the CF formulations, xanthan gum gel containing 0.011 wt % CF was used as a reference. Because of the high viscosity of the formulations, the exact amount was determined by weighing after application. For each formulation, three experiments were performed using skin patches from different pigs. The receiver compartment was continuously rinsed with 25 mM HEPES buffer containing 133 mM NaCl (isotonic conditions). The pH of the buffer was set to 7.4 by addition of 1 M NaOH. Before use, the buffer was placed in an ultrasound bath for a few minutes to remove air bubbles. When connecting the buffer solution to the receiver compartment, care was exercised to ensure that no air bubbles appeared on the dermal side of the skin or elsewhere in the receiver compartment. The receiver solution was continuously stirred using a small magnet and the temperature was maintained at 37° C. throughout the experiment by coupling a water bath (HETO, Denmark) to the cells. The experiments were carried out for 24 hours under non-occluded conditions and fractions were collected from the receiver. The flow rate of the receiver solution was set to 1-2 ml/h and fractions were collected every 90 minutes throughout the experiment. After 24 hours, the flow through the receiver compartment was stopped and the donor compartment was rinsed. The first rinsing was performed with 10 ml HEPES buffer followed by two rinses of 10 ml methanol. In cases where the formulation contained 10-nonyl bromide acridine orange, the first rinsing step was excluded since the probe is not soluble in HEPES buffer.

Tape Stripping Procedure

The skin patches were placed on a board. The remaining dried formulations were removed and placed in HEPES buffer. Then the skin patches were stripped. The stripping was carried out using adhesive tape (Scotch magic tape, 3M) by covering the area of the skin that had been in contact with the formulation with a piece of tape, 1.9 cm wide and 4 cm long. Fifteen strippings were performed to ensure that the stratum corneum was removed (Plessis et al. *Int. J. Pharm.* 103:R1-R5 (1994)). The first two tape strips (Strips 1 and 2) were used to get rid of excess formulation on the skin. Strips 1 and 2 were used to get rid of excess formulation on the skin. Strips 3-5 represent the upper stratum corneum. Strips 6-10 represent the middle stratum corneum. Strips 11-15 represent the lower stratum corneum. The strips were placed into 5 ml HEPES buffer or ml methanol depending on the solubility of the probe. The remaining skin was placed in HEPES buffer for at least 48 hours and after that in methanol for at least 24 hours. These solutions are referred to as the extraction fractions. In cases where the formulation contained acridine orange 10-nonyl bromide, the skin was only placed in methanol for at least 24 hours.

In summary, after stopping the flow through the receiver compartment, the skin was rinsed and tape stripped giving rise to the following fractions:

1. 10 ml HEPES buffer
2. 10 ml methanol
3. 10 ml methanol
4. Remaining dried formulation
5. Tape strips 1-2, excess formulation
6. Tape strips 3-5, surface stratum corneum

7. Tape strips 6-10, middle stratum corneum
8. Tape strips 11-15, deeper stratum corneum
9. Extraction fractions

Fraction Analysis

The collected fractions were analysed by use of a spectrofluorimeter (FluoroMax-2, Instruments S. A., Inc.). The wave lengths found were 490 nm (excitation) and 513 nm (emission) for CF in HEPES, and 490 nm (excitation) and 517 nm (emission) for AO in methanol. Special care was taken in order for the fractions containing CF to be in a linear concentration to intensity region (Weinstein et al. *Liposome Technology* Gregoriadis, G., ed. Vol. 3, pp. 183, CRC Press, Boca Raton).

Example 8

Skin Penetration Results of the Formulations of Example 7

This example shows the performance results of the penetration of Formulations AO-A, AO-B, AO-C, CF-A, CF-B, CF-C, and the references Vaseline® and xanthan gum gel, as tested by the model described in Example 7. These results demonstrate that the non-ionic adjuvants work well both for hydrophilic and lipophilic actives.

Results for the CF Formulations

The penetration behaviours of the hydrophilic active for the different CF formulations (CF-A, CF-B, CF-C), and for the reference xanthan gum gel formulation, are shown in FIG. 6.

The amount detected in stratum corneum was similar for CF-A, CF-B and the reference xanthan gum gel. A larger amount of CF was found in the stratum corneum for the CF-C formulation, thus demonstrating that the adjuvants increase penetration.

Concerning the total amount detected in skin, both the CF-B and CF-C formulations penetrate better than does the reference xanthan gum gel. These results show that it is beneficial to distribute more of a hydrophilic active in the vesicle phase when a larger uptake is desired; and that it is beneficial to add non-ionic adjuvants to a formulation when a larger uptake is desired.

These results also show that in addition to the size of the vesicles influencing penetration, there is an effect of the vesicle carrier per se. That is, although the vesicles are smaller in the CF-B formulation vis-à-vis the CF-C formulation, the total amount of the active ingredient detected in the skin is similar. Without wanting to be bound by a mechanism, it is believed that the effect is probably due to an ability of small vesicles to function as carriers down to a lower depth of the skin.

The largest amount of actives found in the receiver was for the reference xanthan gum gel formulation. That is, an active in the gel is more easily transferred to the receiver than is an active incorporated into the lipid matrices of the formulations of the present invention. Thus an active incorporated into the xanthan gum gel is not retained. Without wanting to be bound by a mechanism, it is believed that this occurs because the amount of free water in the xanthan gum is larger than in the other formulations. Water is known to work as a penetration enhancer (Williams et al. *Crit. Rev. Ther. Drug Carrier Syst.* 9(3-4):305-53 (1992)). Moreover, the conditions with a large amount of free water in a gel layer of non-negligible height is close to occluded conditions. Such conditions have been reported beneficial for uptake of drugs (Honeywell et al. *J. Controlled Release* 90:243-55 (2003), Bodde et al. *Crit. Rev. Ther. Drug Carrier Syst.* 61:87-115). However, the slow

23

release from the formulations of the present invention to the receiver indicate a slow release mechanism that is beneficial for many topical treatments since systemic toxicity is more easily avoided.

Results for the AO Formulations

The penetration behaviours of the lipophilic active for the different AO formulations (AO-A, AO-B, AO-C) and the reference Vaseline®, are shown in Table 2 and FIG. 7.

The amount of AO in the total skin is highest for the formulation containing the non-ionic adjuvants, i.e. AO-C. The incorporation of all of the AO into the vesicle phase (AO-B) did not have any beneficial effect on the total skin penetration. Without wanting to be bound to a mechanism, it is believed that this is due in part to that the homogenization was less efficient with all of the AO placed into the vesicle phase. This mechanism is supported by the observation that the vesicle size distribution was large. (See Table 2).

The deeper layers of the stratum corneum contain much less AO when Vaseline® is used than when the other formulations are used. See Table 2 and FIG. 8. Notably, the formulation containing the adjuvants (AO-C) delivered more than twice the total amount of AO to the deeper layer of the stratum corneum than that delivered by the reference. This is a dramatic improvement. Also, when evaluating the deeper parts of the skin (i.e. below SC), delivery is increased by over four times.

TABLE 2

Penetration of AO and Vaseline into the Stratum Corneum				
	AO-A	AO-B	AO-C	Vaseline ®
Surface SC	0.56	0.93	1.03	1.25
Middle SC	0.70	0.55	0.68	0.45
Deeper SC	0.44	0.34	0.40	0.17
Total SC	1.70	1.82	2.11	1.87

Note that no amount of AO could be detected in the receiver since its water solubility is low.

Example 9

Variation of the Vesicle Fraction of the Formulation

The object of this example was to evaluate how the physical properties of the vesicle fraction change when its formulation is varied. The vesicle fraction of the formulation of Example 2 was varied with respect to pH, amount of cholesterol, type of phospholipids and addition of surface active agents. The parameters which were varied are presented in Table 3. In particular, fraction L1 is the standard formulation of Example 2. Fraction L3 is the same as fraction L1 except that the Epikuron 200SH phospholipid mixture is replaced with Epikuron 170. Fraction L7 is the same as fraction L1 except that Epikuron 200SH is replaced with Epikuron 200. Fractions L8, L9 and L10 are the same as fraction L7 except that the amount of cholesterol is varied. Fraction L11 is the same as fraction L1 except that surface active agents are included (i.e. Brij 30 and Brij 35). Fractions L2, L5 and L6 are the same as fraction L1 except that the pH is varied. Fraction L4 is the same as fraction L1 except that the amount of cholesterol is reduced.

All fractions were prepared as described in Example 2 except for the varied characteristic. Additionally, unlike in Example 2, the sonication time was prolonged up to 120 minutes in order to study the effect of this on the vesicle

24

properties. Samples were collected after 30, 60 and 120 minutes of sonication for most of the fractions.

TABLE 3

Variation of the composition of the vesicle fraction.	
Fraction Name	Varied Characteristic
L1	Example 2 Formulation (i.e. no variation)
L2	2.0 ml 5M NaOH per 1000 g water
L3	Epikuron 170
L4	17% cholesterol (of total amount)
L5	4.0 ml 5M NaOH per 1000 g water
L6	7.0 ml 5M NaOH per 1000 g water
L7	Epikuron 200, 50% cholesterol
L8	Epikuron 200, 20% cholesterol
L9	Epikuron 200, without cholesterol
L10	Epikuron 200, 10% cholesterol
L11	Addition of 0.5% Brij 30 and 0.5% Brij 35

The particle sizes in the vesicle fractions after different sonication times are summarized in Table 4. The diameter given is the Z-average that has been calculated directly from Stoke-Einsteins equation. PI is the polydispersity index. For L3-L6, the particle size was only studied after 30 and 120 minutes sonication.

TABLE 4

Vesicle size and polydispersity index (PI) after 30, 60 and 120 min sonication.							
Fraction	Zeta Potential (mv)	30 min		60 min		120 min	
		Diam-eter (nm)	PI	Diam-eter (nm)	PI	Diameter (nm)	PI
L1	-44 ± 1.6	130	0.43	130	0.42	131	0.42
L2	-50 ± 0.9	140	0.34	130	0.36	140	0.36
L3	-47 ± 2.9	200	0.27	—	—	370	0.51
L4	-41 ± 0.8	1100	1.00	—	—	2300	1.00
L5	-50 ± 3.6	170	0.23	—	—	190	0.23
L6	-38 ± 1.2	210	0.27	—	—	190	0.24
L7	-51 ± 2.9	860	1.00	—	1.00	130	0.45
L8	-29 ± 3.6	530	0.66	170	0.28	180	0.39
L9	-31 ± 4.7	150	0.50	—	1.00	130	0.78
L10	-32 ± 3.8	160	0.62	170	0.56	220	0.58
L11	-30 ± 0.4	780	1.00	1600	1.00	1500	1.00

The choice of phospholipid is shown to be important for the properties of the vesicle fraction. Epikuron 200SH, 200 and 170 all are mixtures of phospholipids but differ in the saturation and chain length of the phospholipids and also in their amounts of soya phosphatidylcholines (PC).

From the results presented in Table 4, it is clear that use of Epikuron 170 (fraction L3) gives rise to larger vesicles vis-à-vis Epikuron 200SH (fraction L1). The phospholipids of Epikuron 170 are less saturated than the phospholipids in Epikuron 200SH.

The phospholipids in Epikuron 200 (fraction L7) are also less saturated than Epikuron 200SH. However, the difference in vesicle size between fraction L1 (Epikuron 200SH) and fraction L7 (Epikuron 200) is small after 120 minutes sonication.

Thus, after 120 minutes of sonication, when compared to the standard formulation containing Epikuron 200SH, Epikuron 170 yields larger vesicles while Epikuron 200 does not. Without wanting to be bound by a mechanism, it is believed that this result is because Epikuron 170 contains approximately 8% phosphatidylethanolamine (PE), while Epikuron

200 does not. PE has much smaller head groups than PC and so forms inverted structures that can make the formation of membranes more difficult.

The amount of cholesterol also influences the vesicle size, and particle stability. For example, when the amount of cholesterol in the formulation is lowered to 17% (fraction L4) vis-à-vis the standard formulation wherein cholesterol is 50% (fraction L1), the vesicle size is dramatically increased, and the zeta potential is decreased.

Additionally, comparison between fractions L7, L8, L9 and L10 also indicates that the amount of cholesterol affects the stability of the vesicles in such a way that a higher amounts of cholesterol give rise to more stable vesicles (higher magnitude of the zeta potential). Fractions L7, L8, L9 and L10 contain 50%, 20%, 0% and 10% cholesterol, respectively. Fractions L8, L9 and L10 have much lower zeta potentials than L7. additionally, the level of cholesterol is also seen to affect the stability of vesicles more when saturated phospholipids are used vis-à-vis when unsaturated phospholipids are used.

For fractions L7 and L8, the sonication time is of importance to obtain vesicles of the desirable size and size distribution. There is a distinct decrease in vesicle size between 30 and 120 minutes of sonication for these fractions. However, for the other fractions sonication for more than 30 minutes seem to be unnecessary since there is no particular change in vesicle size with increased time of sonication. In some cases, for example fraction L4, it even appears that the particle size is increased with increased sonication time. Without wanting to be bound by a mechanism, a possible explanation for this increase is that oxidation occurs in the sample during the sonication.

The addition of the surfactants Brij 30 and Brij 35 (fraction 11) increases the vesicle size considerably. Without wanting to be bound by a mechanism, an explanation for this is that the addition of surfactants increases the fluidity of the vesicle membranes. It is also possible that additional surface active agents decrease the stability of the vesicles by increasing the steric repulsions between the head groups on the inside of the vesicles. What is usually an advantage for the outer part of the membrane has in general a negative effect on the inside of the vesicles.

I claim:

1. A method of delivering an active substance through the stratum corneum, the method comprising applying to skin a delivery composition comprising:

an aqueous carrier, wherein water comprises 65% or more of the delivery composition by weight;

a lipid component suspended in the aqueous carrier comprising lipids consisting essentially of

(a) fatty acid, which comprises 0.5-10% by weight of the delivery composition, which fatty acid is fatty acid of 10 to 24 carbons,

(b) cholesterol, which comprises 0.5-7% by weight of the delivery composition, and

(c) phospholipid and/or ceramide which component is 0.5-20% by weight of the delivery composition, wherein the phospholipid and/or ceramide component comprises 5% or more by weight phospholipid, and wherein the weight ratio of phospholipid/ceramide to cholesterol is 2:1 to 5.9:1, and

(d) optionally, skin lipid precursors, wherein a combination of said lipids comprises 2 to 20% by weight of the delivery composition;

said lipid component comprises:

(i) a lipid particle component comprising particles formed from said lipids, said particles being sur-

rounded by a lipid monolayer, the particles ranging from approximately 1 μm to approximately 150 μm in diameter, and

(ii) a vesicle component comprising vesicles of formed from said lipids enclosed by a lipid bilayer, the vesicles ranging from approximately 0.02 μm to approximately 0.5 μm in diameter; and

a bioactive agent suitable for delivery to or through skin.

2. The method of claim 1, wherein the phospholipid and/or ceramide component comprises 10% or more by weight phospholipid.

3. The method of claim 1, wherein the phospholipid and/or ceramide component comprises 15% or more by weight phospholipid.

4. The method of claim 1, wherein the phospholipid and/or ceramide component comprises 20% or more by weight phospholipid.

5. The method of claim 1, wherein a predominant portion of the fatty acid component is C16 or C18 fatty acid.

6. The method of claim 1, wherein the weight ratio of phospholipid/ceramide to fatty acid is 2:1.5 to 2.95:0.5.

7. The method of claim 6, wherein phospholipid and/or ceramide component comprises 20% or more by weight phospholipid.

8. The method of claim 6, wherein the combination of said lipids comprises 3 to 18% by weight of the delivery composition.

9. The method of claim 6, wherein the combination of said lipids comprises 4 to 16% by weight of the delivery composition.

10. The method of claim 6, wherein the combination of said lipids comprises 5 to 13% by weight of the delivery composition.

11. The method of claim 6, wherein a predominant portion of the fatty acid component is C16 or C18 fatty acid.

12. The method of claim 6, wherein the bioactive agent is a peptide, protein, sunscreen, tanning agent, skin anti-wrinkling agent, anti-dandruff agent, anti-acne agent, hair growth stimulant, hormone, nicotine, interferon, pain killer, vitamin, antifungal, anti-acne, anti-lice agent, anti-skin cancer agent or a substance to treat eczema, dry skin, itchy skin, hair loss, psoriasis or skin lesions.

13. The method of claim 6, wherein the bioactive agent is a steroid hormone.

14. The method of claim 6, wherein the lipid component comprises 25-hydroxycholecalciferol, mevalonic acid, mevalonic acid lactone or mixtures thereof as skin lipid precursor.

15. The method of claim 1, wherein the combination of said lipids comprises 3 to 18% by weight of the delivery composition.

16. The method of claim 1, wherein the combination of said lipids comprises 4 to 16% by weight of the delivery composition.

17. The method of claim 1, wherein the combination of said lipids comprises 5 to 13% by weight of the delivery composition.

18. The method of claim 1, wherein the bioactive agent is a peptide, protein, sunscreen, tanning agent, skin anti-wrinkling agent, anti-dandruff agent, anti-acne agent, hair growth stimulant, hormone, nicotine, interferon, pain killer, vitamin, antifungal, anti-acne, anti-lice agent, anti-skin cancer agent or a substance to treat eczema, dry skin, itchy skin, hair loss, psoriasis or skin lesions.

19. The method of claim 1, wherein the bioactive agent is a steroid hormone.

27

20. The method of claim 1, wherein the lipid component comprises 25-hydroxycholecalciferol, mevalonic acid, mevalonic acid lactone or mixtures thereof as skin lipid precursor.

21. The method of claim 1, wherein water comprises 70% or more of the delivery composition by weight.

22. The method of claim 21, wherein the phospholipid and/or ceramide component comprises 10% or more by weight phospholipid.

23. The method of claim 21, wherein the phospholipid and/or ceramide component comprises 15% or more by weight phospholipid.

24. The method of claim 21, wherein the phospholipid and/or ceramide component comprises 20% or more by weight phospholipid.

25. The method of claim 21, wherein a predominant portion of the fatty acid component is C16 or C18 fatty acid.

26. The method of claim 21, wherein the weight ratio of phospholipid/ceramide to fatty acid is 2:1.5 to 2.95:0.5.

27. The method of claim 26, wherein the phospholipid and/or ceramide component comprises 10% or more by weight phospholipid.

28. The method of claim 26, wherein the phospholipid and/or ceramide component comprises 15% or more by weight phospholipid.

29. The method of claim 26, wherein the phospholipid and/or ceramide component comprises 20% or more by weight phospholipid.

30. The method of claim 26, wherein the combination of said lipids comprises 3 to 18% by weight of the delivery composition.

31. The method of claim 26, wherein the combination of said lipids comprises 4 to 16% by weight of the delivery composition.

32. The method of claim 26, wherein the combination of said lipids comprises 5 to 13% by weight of the delivery composition.

33. The method of claim 26, wherein a predominant portion of the fatty acid component is C16 or C18 fatty acid.

34. The method of claim 26, wherein the bioactive agent is a peptide, protein, sunscreen, tanning agent, skin anti-wrinkling agent, anti-dandruff agent, anti-acne agent, hair growth stimulant, hormone, nicotine, interferon, pain killer, vitamin, antifungal, anti-acne, anti-louse agent, anti-skin cancer agent or a substance to treat eczema, dry skin, itchy skin, hair loss, psoriasis or skin lesions.

35. The method of claim 26, wherein the bioactive agent is a steroid hormone.

36. The method of claim 26, wherein the lipid component comprises 25-hydroxycholecalciferol, mevalonic acid, mevalonic acid lactone or mixtures thereof as skin lipid precursor.

37. The method of claim 21, wherein the combination of said lipids comprises 3 to 18% by weight of the delivery composition.

38. The method of claim 21, wherein the combination of said lipids comprises 4 to 16% by weight of the delivery composition.

39. The method of claim 21, wherein the combination of said lipids comprises 5 to 13% by weight of the delivery composition.

40. The method of claim 21, wherein the bioactive agent is a peptide, protein, sunscreen, tanning agent, skin anti-wrinkling agent, anti-dandruff agent, anti-acne agent, hair growth stimulant, hormone, nicotine, interferon, pain killer, vitamin, antifungal, anti-acne, anti-louse agent, anti-skin cancer agent or a substance to treat eczema, dry skin, itchy skin, hair loss, psoriasis or skin lesions.

28

41. The method of claim 21, wherein the bioactive agent is a steroid hormone.

42. The method of claim 21, wherein the lipid component comprises 25-hydroxycholecalciferol, mevalonic acid, mevalonic acid lactone or mixtures thereof as skin lipid precursor.

43. The method of claim 1, wherein the composition is delivered to the skin as a foam and water comprises 75% or more of the delivery composition by weight.

44. The method of claim 43, wherein the phospholipid and/or ceramide component comprises 10% or more by weight phospholipid.

45. The method of claim 43, wherein the phospholipid and/or ceramide component comprises 15% or more by weight phospholipid.

46. The method of claim 43, wherein the phospholipid and/or ceramide component comprises 20% or more by weight phospholipid.

47. The method of claim 43, wherein a predominant portion of the fatty acid component is C16 or C18 fatty acid.

48. The method of claim 43, wherein the weight ratio of phospholipid/ceramide to fatty acid is 2:1.5 to 2.95:0.5.

49. The method of claim 48, wherein the phospholipid and/or ceramide component comprises 10% or more by weight phospholipid.

50. The method of claim 48, wherein the phospholipid and/or ceramide component comprises 15% or more by weight phospholipid.

51. The method of claim 48, wherein the phospholipid and/or ceramide component comprises 20% or more by weight phospholipid.

52. The method of claim 48, wherein the combination of said lipids comprises 3 to 18% by weight of the delivery composition.

53. The method of claim 48, wherein the combination of said lipids comprises 4 to 16% by weight of the delivery composition.

54. The method of claim 48, wherein the combination of said lipids comprises 5 to 13% by weight of the delivery composition.

55. The method of claim 48, wherein a predominant portion of the fatty acid component is C16 or C18 fatty acid.

56. The method of claim 48, wherein the bioactive agent is a peptide, protein, sunscreen, tanning agent, skin anti-wrinkling agent, anti-dandruff agent, anti-acne agent, hair growth stimulant, hormone, nicotine, interferon, pain killer, vitamin, antifungal, anti-acne, anti-louse agent, anti-skin cancer agent or a substance to treat eczema, dry skin, itchy skin, hair loss, psoriasis or skin lesions.

57. The method of claim 48, wherein the bioactive agent is a steroid hormone.

58. The method of claim 48, wherein the lipid component comprises 25-hydroxycholecalciferol, mevalonic acid, mevalonic acid lactone or mixtures thereof as skin lipid precursor.

59. The method of claim 43, wherein the combination of said lipids comprises 3 to 18% by weight of the delivery composition.

60. The method of claim 43, wherein the combination of said lipids comprises 4 to 16% by weight of the delivery composition.

61. The method of claim 43, wherein the combination of said lipids comprises 5 to 13% by weight of the delivery composition.

62. The method of claim 43, wherein the bioactive agent is a peptide, protein, sunscreen, tanning agent, skin anti-wrinkling agent, anti-dandruff agent, anti-acne agent, hair growth stimulant, hormones, nicotine, interferon, pain killer, vita-

29

min, antifungal, anti-acne, anti-louse agent, anti-skin cancer agent or a substance to treat eczema, dry skin, itchy skin, hair loss, psoriasis or skin lesions.

63. The method of claim 43, wherein the bioactive agent is a steroid hormone.

64. The method of claim 43, wherein the lipid component comprises 25-hydroxycholecalciferol, mevalonic acid, mevalonic acid lactone or mixtures thereof as skin lipid precursor.

65. The method according to claim 1, wherein the delivery composition comprises: fatty acid at between 0.5-10%; the cholesterol at between 0.5-10%; the lipid precursors at between 0.000001-10%; and the ceramide/phospholipid portion at between 0.005-20%.

66. The method according to claim 1, wherein the delivery composition comprises: fatty acid comprising ten to twenty-four carbon atoms.

67. The method according to claim 1, wherein the water content in the delivery composition exceeds 79%.

68. The method according to claim 1, wherein the water content in the delivery composition exceeds 90%.

69. The method according to claim 1, wherein the delivery composition comprises a combination of:

30

Fatty Acid 0.5-10%

Phospholipid 0.5-10%

Cholesterol 0.5-7%

Lipid precursor 0.000001-10%

Ceramide 0.005%-7%.

70. The method according to claim 69, wherein the lipid precursor in the delivery composition is mevalonic acid.

71. The method according to claim 69, wherein the delivery composition further comprises

Glycerine 0-5%

Propylene glycol 0-48%

PVP (M weight 40.000) 0-5%

triethanolamine (TEA) 0-3%.

72. The method according to claim 69, wherein the delivery composition further comprises

25-Hydroxycholecalciferol 0.015%

Acylceramides 0.025%.

73. The method according to claim 69, wherein the lipid precursor comprises 0.01% of Mevalonic acid, 0.0015% 25-Hydroxycholecalciferol, or a combination of Mevalonic acid, and 25-Hydroxycholecalciferol.

* * * * *

- **Source :** Press Release
- **Date :** 2002-02-12
- **Companies :** CollaGenex Pharmaceuticals Inc.

CollaGenex Licenses Novel Dermal Drug Delivery Platform

NEWTOWN, Pa., Feb 12, 2002 (BUSINESS WIRE) -- CollaGenex Pharmaceuticals, Inc. (NASDAQ:CGPI) today announced that it has licensed a novel dermal and transdermal drug delivery technology from its inventor.

The technology, named Restoraderm(TM), is designed to enhance the dermal delivery of a variety of active ingredients and will form the basis for a novel, proprietary and differentiated portfolio of topical dermatological pharmaceuticals.

The technology is based on the ability of certain lipid compositions to enhance the natural skin barrier and facilitate the dermal and transdermal delivery of known active ingredients. The Restoraderm technology is currently still under development, and CollaGenex anticipates that the first products to be developed using the technology will be available in late 2002.

In exchange for the rights to the technology, CollaGenex will pay the inventor milestone fees upon the achievement of certain objectives as well as royalties on future sales of products based on the technology.

"The licensing of the Restoraderm drug delivery technology is an important element of our strategy to build a diversified portfolio of products for the dermatology market," noted Brian M. Gallagher, PhD, chairman, president and chief executive officer of CollaGenex. "We anticipate that our future business in dermatology will include three key elements. Our first sales in this area will come from established, under-promoted products that we in-license, and we expect to complete the first of these agreements in the near future. The second key business element will be composed of dermatology products based on the Restoraderm technology, the first of which we hope to launch later this year. Finally, and perhaps most importantly, will be the development of the clinical use of Periostat to treat acne and rosacea, for which we plan a series of clinical trials during 2002 and 2003."

CollaGenex Pharmaceuticals, Inc. is a specialty pharmaceutical company currently focused on providing innovative medical therapies to the dental and dermatology market. The Company's lead product, Periostat, is the first and only pharmaceutical to treat periodontal disease by inhibiting the enzymes that destroy periodontal support tissues.

Periostat is marketed to the dental community through a professional pharmaceutical sales force composed of approximately 120 sales representatives and managers.

Currently, the Company's dental sales force is also marketing Vioxx(R), a Merck & Co. drug that CollaGenex co-promotes for the treatment of acute dental pain, and Atridox(R), Atrisorb(R) and Atrisorb-D(R), Atrix Laboratories Inc.'s products for the treatment of adult periodontitis.

Research has shown that the enzyme suppression technology underlying Periostat may also be applicable to other diseases involving destruction of the body's connective tissues, including cancer metastases (Metastat) and a broad range of inflammatory diseases.

CollaGenex is developing a series of novel, proprietary compounds known as IMPACS (Inhibitors of Multiple Proteases and CytokineS) to address these applications. The Company intends to pursue further research and development of these technologies primarily through partnerships with third parties.

To receive additional information on the Company, please visit our Web site at www.collagenex.com, which is not a part of this press release.

This news release contains forward-looking statements within the meaning of Section 21E of the Securities and Exchange Act of 1934, as amended. Investors are cautioned that forward-looking statements involve risks and uncertainties, which may affect the Company's business and prospects.

The Company's business of selling, marketing and developing pharmaceutical products is subject to a number of significant risks, including risks relating to the implementation of the Company's sales and marketing plans for Periostat; risks inherent in research and development activities; risks associated with conducting business in a highly regulated environment and uncertainty relating to clinical trials of products under development, all as discussed in the Company's periodic filings with the US Securities and Exchange Commission.

Periostat(R), Metastat(R) and IMPACS(R) are trademarks of CollaGenex Pharmaceuticals, Inc.

VIOXX(R) is a trademark of Merck & Co., Inc.

Atridox(R), Atrisorb(R) and Atrisorb-D(R) are trademarks of Atrix Laboratories, Inc.

Periostat(R) and CollaGenex(R) are trademarks of CollaGenex International Limited.

CONTACT: CollaGenex Pharmaceuticals, Inc.
Robert A. Ashley, 215/579-7388

URL: <http://www.businesswire.com>
Today's News On The Net - Business Wire's full file on the Internet with Hyperlinks to your home page.

Copyright (C) 2002 Business Wire. All rights reserved.

American Contact Dermatitis Society

Exhibit **T 144**
Skold v. Galderma
Cancellation No. 92052897

Excellence in Occupational & Contact Dermatitis Research,
Practice & Education

ABSTRACTS

American Contact Dermatitis Society

16th Annual Meeting
February 17, 2005

Hilton New Orleans Riverside
New Orleans, LA

Visit ACDS at www.contactderm.org



2005 Sponsors

The American Contact Dermatitis Society wishes to thank those organizations listed below for their support of the society's educational programs in 2005.

Platinum Level

- Connetics Corporation
- Cosmetic, Toiletry & Fragrance Association

Gold Level

- Allerderm Laboratories
- CollaGenex
- Ferndale
- Fujisawa Health Care, Inc.
- Novartis
- Procter & Gamble

Silver Level

- Dormer/Chemotechniques
- Mary Kay
- Pharmaceutical Specialties

Patrons

- Biersdorf
- Galderma
- Neutrogena
- Summer Labs

Table of Contents



**American Contact Dermatitis Society
16th Annual Meeting
Hilton New Orleans Riverside
Ballroom B
New Orleans, LA
February 17, 2005**

Schedule of Events	5
Exhibitor Listing	7
Abstracts Summary	9
Abstracts	11

Schedule of Events

7:00 AM	Registration Open	Grand Ballroom B
7:30 AM	<u>ACDS Breakfast Symposium</u> David Cohen, MD: Therapies for Facial Dermatitis <i>Sponsored by CollaGenex</i>	Grand Salon 15/18
8:30 AM	<u>Welcome to the 16th ACDS Annual Meeting</u> Anthony Gaspari, MD, ACDS President Bruce Brod, MD, ACDS Annual Meeting Committee Chair	Grand Ballroom B
8:35 AM	<u>General Session</u> Linda Moreau, MD, FRCP: Allergic Contact Dermatitis Associated with Reactive Dyes in a Dark Garment: A Case Report*	
8:45 AM	Kim Eickhorst, MD: Rue the Herb: Ruta Graveolens Associated Phytophototoxicity*	
8:55 AM	Denise Aaron, MD: Burden and Bother of Dermatitis in Patients Referred to a NACDG Center for Patch Testing*	
9:05 AM	Giuseppe Militello, MD: The Utility of the TRUE Test in a Private Practice Setting*	
9:15 AM	Anna A. Bar, MD: Antigenicity of Patch Test Allergens Over Time*	
9:25 AM	Krista Shackelford, MD: Adverse Events from Patch Testing: A Case Report of Pemphigus Foliaceus and Epidermal Detachment*	
9:35 AM	Divya Srivastava, MD: Identification of the Constituents of Balsam of Peru in Tomatoes*	
9:45 AM	Mary Sheu, MD: Allergic Contact Dermatitis from Tom's of Maine Natural Deodorant: A Report of 4 Cases Associated with Lichen Acid Mix Allergy*	
9:55 AM	Golara Honari, MD: The Utility of Patch Testing with Topical Medicaments as an Adjunct to Standard Screening Panels*	
10:05 AM	Dan Slodownik, MD: Allergic Contact Cheilitis and Stomatitis to Toothpastes in Israeli Patients* **	
10:15 AM	Peter C. Schalock, MD: Efficacy and Patient Perception of Grenz Ray Therapy in the Treatment of Dermatoses Refractory to Other Medical Therapy*	
10:25 AM	Samara Mimesh, MD: ACD to Corticosteroids: Reproducibility of Patch Testing and Correlation with Intradermal Testing*	
10:35 AM	Break/Exhibits/Posters Posters in Grand Salon 10/7	Grand Salon 10/7
11:00 AM	James Yiannias, MD: Update on ACDS Databases.	

* Candidates for the Alexander A. Fisher Resident Award.

** Howard I. Maibach International Travel Award recipient.

- 11:05 AM **Occupational Dermatology Symposium:**
The Donald J. Birmingham Occupational Skin Diseases Symposium is supported by the National Occupation Research Agenda (NORA).
Moderated by Boris Lushniak, MD
- 11:05 AM **D Linn Holness, MD:** Dermatologist Occupational Disease Practice Survey
- 11:15 AM **Linda Moreau, MD, FRCP:** Occupational Allergic Contact Dermatitis
From Triphenyl Phosphite*
- 11:25 AM **Curtis P. Hamann, MD:** Prevalence of Latex Allergy in Dental Professionals in Japan and the United States
- 11:35:00 AM **Albert Wolkerstorfer, MD:** Unexpected Exposure to Nickel in Electroplating
- 11:45:00 AM **Malin Frick, MD:** Poor Correlation Between Stated and Found Concentrations of Isocyanates in Patch-Test Preparations
- 11:55:00 AM **Alexander Zemtsov, M.D., MSc:** Occupational Allergic Contact Dermatitis from Sodium Lauroyl Sarcosinate in the Liquid Soap
- 12:05 PM **ACDS Roundtable Lunch** **Grand Salon 15/18**
Sponsored by Allerderm
- 1:30 AM **General Session**
Ronald Brancaccio, MD and David Cohen, MD: Remembering Alexander Fisher
- 1:40 AM **Alexander Fisher Lecture**
Melanie Pratt, MD: The Role of Mentoring in the Field of Contact Dermatitis
- 2:30 AM **ACDS Awards**
- 2:45 PM **Douglas L. Powell, MD:** Cutaneous Reactions to Silicone
- 2:55 PM **Klaus-Peter Wilhelm, MD:** Proclivity to Cumulative Skin Irritation: Dependence Upon Age and Sex
- 3:05 PM **Break/Posters/Exhibits**
Posters in Grand Salon 10/7
- 3:35 PM **Mark Davis, MD:** Back to Basics: In Calculating Patch Test Reactions, Should Macular Erythema and Lesser Reactions be Included?
- 3:45 PM **Vinod Kumar Sharma, MD:** Evolution of Clinical Pattern of Parthenium Dermatitis: A Study of 74 Cases**
- 3:55 PM **Susanne Astner, MD:** In-vivo confocal microscopy of contact dermatitis
- 4:05 PM **Cecilia Svedman, MD:** Contact Allergy to Metals After Percutaneous Transluminal Coronary Angioplasty (PTCA) and Stenting**
- 4:15 PM **Mark Davis, MD:** Patch Testing to the Dust Mite (Dermatophagoides Mix 0.1%): High Rate of Reaction in Both Atopic and Nonatopic Patients
- 4:25 PM **Rochelle R. Torgerson, MD, PhD:** Contact Sensitivities in Oral Disease
- 4:35 PM **ACDS Business Meeting**
- 5:00 PM **Cocktail Reception** **Jasperwood**
Sponsored by Ferndale Laboratories

* Candidates for the Alexander A. Fisher Resident Award.

** Howard I. Maibach International Travel Award recipient.

37	Mark Davis, MD	Patch Testing to the Dust Mite (<i>Dermatophagoides Mix</i> 0.1%): High Rate of Reaction in Both Atopic and Nonatopic Patients
38	Rochelle Torgerson, MD, PhD	Contact Sensitivities in Oral Disease

Abstracts: Posters

39	Tove Agner, MD	Short-term effects of alcohol-based disinfectant and detergent on skin irritation
40	Susun An	Influence of vehicles on the induction of skin irritation
41	Sachin Bhardwaj, MD	A Double-blind, Randomized, Placebo-Controlled Trial Comparing Topical Immunomodulating Agents and Corticosteroids for Treatment of Experimentally Induced
42	Normita Chua-Vivar, MD	Moringa Oleifera Leaf Extract as Active Antibacterial Property in a Bar Soap: A Randomized, Double-Blind, Paceybo-Controlled Trial
43	Mark Davis, MD	Delayed Readings of Patch Test Reactions to Topical Corticosteroids: Low Yield
44	Joseph Fowler MD	A Comparator Study of an Adjunctive Dermal Lipid Replacement Foam (Restoraderm®) in the Management of Refractory Hand Contact Dermatitis
45	Marcos Hervella, MD	Paraben "Para-" Doxes
46	Soogan Celeste Lalla, MD	Patch Testing in Children with Dermatitis
47	Eunyoung Lee	A Study of Influencing Factors for Sensory Irritation Due to Preservatives of Cosmetics
48	Meltem Onder, MD	Common Contact Sensitizers in Ankara, Turkey: A Study of 1585 Patients with the European Standard Series
49	Mario C. Pires, MD	Contact Dermatitis to Latanoprost
50	Mario C. Pires, MD	Contact Dermatitis in Children
51	Erik Zimerson, MD	Photoallergic Contact Dermatitis from Ketoprofen in Southern Sweden

A COMPARATOR STUDY OF AN ADJUNCTIVE DERMAL LIPID REPLACEMENT FOAM (RESTORADERM®) IN THE MANAGEMENT OF REFRACTORY HAND CONTACT DERMATITIS

Fowler JF, Perryman JH; U. of Louisville, Louisville, KY.

Background: Dermatitis (irritant, allergic, or both) is the most common occupational skin disease. Although many “barrier creams” with high concentrations of petrolatum are sold, none have shown consistent effectiveness.

Restoraderm is composed of an exclusive non-alcohol, water-based formulation of lipids that mimics the body’s own natural skin barrier system. It contains ceramides, cholesterol, palmitic acid and two biologic precursors, mevalonic acid and hydroxycholecalciferol. It does not contain petrolatum, and is a non-greasy formulation. Many occupational hand dermatitis patients, find it difficult to work when using a product with petrolatum as it’s greasy residue can negatively affect grip and impair the protection of latex gloves.

Objective: To measure the effectiveness of Restoraderm in reducing or eliminating chronic hand contact dermatitis. The primary endpoints were mean percent change from baseline in the Clinician’s Global Assessment Score and mean change in frequency of topical steroid use.

Methods: Thirty-one patients were randomized to receive either Restoraderm or a comparator (ointment or lotion) at the baseline visit. Each patient received Restoraderm for a 3 week period followed by comparator or vice versa. There was a two week wash out between study phases.

Results: Restoraderm proved to be effective in reducing or eliminating chronic hand contact dermatitis caused by occupational exposures. It was preferred by patients over the comparators. The non-greasy foam formulation of Restoraderm may contribute to compliance, ease of use, and patient satisfaction in patients with chronic hand dermatitis.

This study was supported by an unrestricted grant from CollaGenex Inc.

Notes: _____

Industries [Company profiles](#)[Industry reports](#)[Business articles](#)[Research Center](#)[Business information](#) > [Industry reports](#) > [Manufacturing: Equipment, Computers, and Controlling and Measuring Devices](#)

Electron Tubes

SIC 3671

[Share](#) [Like](#) 0 [Tweet](#) 0 0

Companies in this industry

[NAICS 334411: Electron Tube Manufacturing](#)

Industry report:

This category covers establishments primarily engaged in manufacturing electron tubes and tube parts. Establishments primarily engaged in manufacturing X-ray tubes and parts are classified in SIC 3844: X-Ray Apparatus and Tubes and Related Irradiation Apparatus, those manufacturing liquid crystal displays (LCDs) are classified in SIC 3679: Electronic Components, Not Elsewhere Classified, and those manufacturing computer terminals are classified in SIC 3575: Computer Terminals.

Industry Snapshot

Approximately 85 companies operated in this industry in 2007, down about 40 percent from the number of firms in the early years of the twenty-first century's first decade. After a period of growth during the late 1990s, the industry was affected by an economic recession, price erosion, and shifting consumer demands. Shipment values in 2008 were \$1 billion while \$345 million was spent on materials. The industry employed 5,241 in 2007 with 3,145 as production workers who earned \$222 million in wages.

In the middle of the first decade of the 2000s, production of new and rebuilt receiving-type electron tubes, including cathode ray tubes (CRT), accounted for just under 75 percent of industry revenue. The other major product group, which accounted for approximately 20 percent of shipment values, consisted of transmittal, industrial, and special-purpose electron tubes (except X-ray tubes). The remainder of shipments consisted of electron tube parts.

According to U.S. Census data, the industry shipped \$1.05 billion in electron tubes and tube parts in 2009 followed by \$1.2 billion in 2010. Although shipments continued to fall, the total cost of materials increased. In addition, the total cost of materials grew from nearly \$485 million in 2009 to over \$558 million in 2010. As demand for electron tubes dwindled, so did the industry's workforce, to 4,849 workers in 2009 who earned \$261 million in wages. For 2010, the industry employed 4,997 workers, of which 3,913 worked in production with wages that totaled more than \$198 million.

According to Paul Gagnon, director of DisplaySearch, "Digital broadcast transitions and more affordable flat panel TVs have caused consumers to replace their TVs, especially CRT models, in record numbers" in April 2011. That trend was going to continue, especially as core components for CRTs were becoming scarce.

Organization and Structure

The two most recognizable types of electron tubes were the ordinary television and computer tube and the once common vacuum tube traditionally used in radios and other electronic equipment. Generally speaking, electron tubes were sealed glass, enamel, or metallic tubes of varying sizes into which electrons were fired for the purpose of displaying images or conducting, transmitting, or multiplying light for non-display purposes. Although television tubes and computer displays were the most common products, industry firms also manufactured camera tubes, microwave tubes, Geiger counters, radar screens, and specialized devices such as electron beam (beta ray) generator tubes, klystron tubes, magnetron tubes, planar triode tubes, and tubes for operating above the X-ray spectrum.

Electron tubes varied according to the extent to which they were "evacuated," or emptied of gases and vapors; by the capability and type of the electron source; and by the number and configuration of electrodes they contained. The amount of power used in electron tubes ranged from milliwatts to hundreds of megawatts, and the frequency of operation ranged between zero and ten-to-the-eleventh-power Hertz depending on the type of tube. In general, CRTs operated by playing a beam of electrons of varying intensities over a display surface such as a phosphor screen, which formed patterns of light that took the form of characters or images. The three basic components of a CRT were the envelope, the electron gun, and the phosphor screen. The electrons were fired through a funnel-shaped element toward the faceplate on the broad end of the envelope that usually was made of glass. The electrons were heated and formed into a beam before being directed through the electron gun to different parts of the screen by the magnetic fields that surrounded the envelope. The phosphor screen consisted of a layer of phosphor dots that coated the inner surface of the CRT's faceplate. Color CRTs used a screen made up of red, green, and blue phosphors, with an electron gun for each color, while monochrome CRT screens employed one electron gun.

[Online Marketing Strategy](#)

[PRWeb.com](#)

Press Releases Are Effective For Marketing - Register Free, Now!



[Veterinary Ultrasound](#)

[www.sonosite.com](#)

Helps Guide Healthcare Providers to Improve Care and Efficiency.



[Ditch The Sales Pitch](#)

[SalesEngineIntl.com/Why-Automate](#)

Free Report: How To Use Marketing Automation To Drive Conversions.



[X-Ray Repair & Sales](#)

[www.jcxray.com/BestPrices](#)

DR at CR Prices, Medical, Chiro Vet Digital & Older (all X-Ray Systems)

AdChoices 

Exhibit	T151
Skold v. Galderma	
Cancellation No. 92052897	

PUBLIC

In the everyday family "direct view" TV, the face of the picture tube on which the electrons are projected is the same as the screen the viewer sees. In the rear-projection televisions that became increasingly common in the 1980s, images were projected indirectly from three small CRTs (one each for red, green, and blue) through a series of mirrors to a translucent screen. In the mid-1990s, projection TV tube manufacturers used compact CRTs and lenses with shorter focal lengths to reduce the amount of space taken up by the television box, reducing the size of the once bulky rear projection sets by one-third. In contrast to the 4:3 aspect ratio of the standard television tube, wide-screen TVs used a 16:9 ratio that resembled the wide ratio of movie theater screens and that allowed them to be marketed as the precursor to the so-called high-definition television (HDTV) technology trumpeted by Japanese TV makers in the 1990s. Computer CRTs increasingly took advantage of advanced data streaming technology to display downloaded and/or digital video disk (DVD) movies and multimedia entertainment.

Despite its continued popularity in the 1990s, the CRT was by no means a perfect piece of technology. The CRT remained the last holdover of the analog glass vacuum tube in a world increasingly permeated by digital solid state electronics technology. It was bulky, hot, and heavy, used large amounts of power, and was prone to disruptions of glare and magnetic and electrical fields. By the mid-1990s, few experts doubted the days of the CRT were numbered for mainstream computer and TV uses. High definition liquid crystal display (LCD) screens, which used an active matrix view panel, replaced them for computers. Display resolution often surpassed the capabilities of traditional CRT displays. While such technology was often far more expensive, the promise of continually decreasing manufacturing costs and higher consumer demand marked LCD technology as the heir-apparent to traditional CRT use for computer displays.

The second largest industry product group, transmittal, industrial, and special purpose electron tubes, included electro-optical tubes and miscellaneous special-purpose tubes. The electro-optical tube segment included everything from camera tubes and photo cells to other photo-conductive and photo-emissive tubes, most notably the airport bomb detector picture tube, the largest market of the electro-optical tube segment.

Microwave tubes were primarily used in high and ultra-high frequency applications such as radar, telecommunications equipment, military communication and control systems, high-frequency microwave ovens, scientific research equipment, FM radio transmitters, and industrial heating equipment. Traveling wave tubes, which were divided into forward and backward wave electron tubes, accounted for a majority of the microwave electron tubes produced. Microwave tubes comprised a majority of the power and special-purpose tube market. Gas tubes were used primarily in industrial applications because of their efficiency as well as their ability to handle high levels of power or current at generally low frequency levels. Product types included diodes, rectifiers, control-type industrial triodes, hydrogen and non-hydrogen thyratons, and other gas and vapor tubes. High-power tubes were also used in broadcasting transmitters. Vacuum tubes, once the primary element in electrical circuits, were mainly used in applications where low noise and high frequency were involved.

Background and Development

Electron tubes were the principal components of almost all electronic circuits and equipment until semiconductors were developed and began to replace them in the late 1940s and 1950s. The first application of CRT technology was for an oscilloscope in 1897, and the first television using a CRT was developed in the late 1920s. Commercial production of monochrome television picture tubes began in the late 1940s. After World War II, U.S. electron tube manufacturers found a diverse and lucrative market in defense applications, ranging from radar to communication and control equipment.

By the mid-1990s, the fastest-growing segment of the TV picture tube market was big-screen TVs that provided from 31 to 58 inches of viewable screen image. Despite the fact that by the mid-1990s nearly every U.S. home had at least one TV, there were 22.9 million direct-view TVs sold in 1999. In 1994 more than 26 million color TVs were sold in the United States. Spurred on by demand that was projected to reach \$20 billion by the turn of the century, industry firms made significant strides in improving the CRT's resolution, brilliance, size, energy usage, and cost. Television tubes and computer monitors became flatter and bigger as the standard 14-inch PC monitor, for example, gave way to 17- and even 20-inch models; digital circuits were used to enhance picture quality; and advances in non-electron tube technology were developed so quickly that the CRT itself seemed destined for only niche uses in specialized applications.

In the 1990s the CRT sector of the electron tube industry continued to establish itself as the sector's primary revenue machine. Despite a drop in government spending for military-related CRT display technologies, the consumer computer CRT and television tube markets provided more than enough demand to fuel the industry's continued growth. Between 1994 and 1999, the value of PC system sales, which included a CRT monitor, grew almost 77 percent. Concurrent expansion occurred in the number of systems sold, which increased over the same period by 121 percent. A total of 90.5 million CRTs were sold in 1998, generating a \$17.2 billion market share of the electron tube industry.

In the late 1990s, the battle between the computer CRT and the flat panel display (FPD) intensified. Developed in the United States, but later co-opted by Japanese firms, the FPD encompassed several display technologies, from active and passive matrix LCDs to field emission, micromirror, diamond emission, and neon- or xenon-based gas plasma displays. By the late 1990s, FPD manufacturers had overcome hurdles in FPD design complexity and subsequent high cost and the technology's high power requirements. At one time, the only CRT markets immediately threatened by FPDs were point-of-sale terminals, medical imaging applications, and displays for instrumentation and factory automation. However, at the end of the twentieth century, manufacturers had broken out of the laptop and avionics display markets into the television tube and PC monitor markets that comprised the electron tube's home turf.

FPD technology began to be applied in a wide variety of ways at the end of the 1990s. According to the U.S. Display Consortium, innovative uses included analytical equipment, conference room

PUBLIC

equipment, marine instruments, hand-held devices, electronic books, passenger entertainment systems, and home appliances. Cutting-edge technology also included field emission displays (FEDs). According to Electronic Business, revenues from flat panel display sales at the end of 1999 were estimated at \$11 billion.

Throughout the 1990s, high resolution HDTV was marketed as the next great advance in television technology. Because its superiority was only noticeable in 40-inch screens, the resulting increases in TV tube size spelled more trouble for the electron CRT's future. As the resolution of television screens increased, the brightness of the traditional CRT fell, and the FPD became no more expensive than a comparably sized CRT, but was 75 percent thinner. In addition, the distinction between the television tube and the computer monitor threatened to vanish as technologies like Zenith's "NetVision" allowed consumers to watch TV or surf the World Wide Web from the same screen.

Industry shipments declined from \$3.82 billion in 1999 to \$3.56 billion in 2000, while the cost of materials increased from \$2.08 billion to \$2.21 billion. Industry employment declined steadily through the late 1990s and 2000, falling from 21,656 in 1997 to 16,187 in 2000. The number of production workers over this period dropped from 16,774 to 12,718.

The electron tube industry continued to decline during the early years of the first decade of the 2000s in response to the economic recession, price erosion, and shifting consumer demands. Shipment values in 2002 were \$2.45 billion, down 24 percent from 2001 and 36 percent from 1998. To limit losses, the industry reduced capital expenditures 75 percent during 2002, from \$162 million in 2001 to just \$40.1 million in 2002.

By the late 2000s, the future of CRTs was uncertain. The sales of CRT-based computer monitors were slipping. In 2003, U.S. sales of LCD models outpaced CRTs for the first time. Consumer demand, falling prices of LCD models, and computer packaging deals spurred the increased LCD sales. According to research firm iSuppli/Sanford Resources, the average selling price of a 17-inch LCD monitor fell from \$915 in 2001 to \$271 in 2005. On the other hand, a 17-inch CRT monitor that cost an average of \$213 in 2001 sold for approximately \$100 in 2005. Responding to consumer demand, computer suppliers like Dell offered aggressive packaging deals that included an LCD monitor.

In 2004, global shipments of LCD monitors overtook CRTs for the first time. According to the Japan Electronics and Information Technology Industries Association, sales of LCD monitors grew 36 percent during 2004, to 67.64 million units, while CRT monitor sales fell 11 percent to 59.64 million units. By the late years of the first decade of the 2000s, LCD monitors claimed as much as 75 percent of the market.

While LCD monitors are quickly outpacing CRT monitors, CRTs continue to hold their own in the television market and are expected to continue to do so until the price for flat panel models falls below \$500. In the early years of the first decade of the 2000s, CRT-based television sets accounted for nearly 98 percent of all sales, and in 2005 CRTs continued to hold approximately 85 percent of the market.

Despite the continued strong performance of CRTs in the television sector, the future seems to point toward flat panels. In a December 1, 2003 article in Popular Science entitled "CRT, R.I.P.," author Mark Anders noted, "CRTs will probably be around for another decade, but even today the larger a TV is, the less likely it is to be powered by one. Tubes are just too big and heavy. . . . Of course, the CRT won't be completely supplanted until small-scale flat panels (under 19 inches) can compete on price." However, prices were coming down on flat panels as sets that once cost \$10,000 cost \$2,500 by the mid-years of the first decade of the 2000s and dropped further in the decade's late years to where some could be purchased for less than \$1,000.

Nonetheless, CRTs, which can be purchased in comparable size to flat panels for \$300, continued to lead in the price wars in the early years of the first decade of the 2000s. In addition, CRT makers were not ready to concede the market to LCDs. Several manufacturers were working on new technology to decrease the size and weight of CRT models, and CRT flat panel technology also is being advanced.

Current Conditions

According to Austin-based market research and consulting firm DisplaySearch, LCD TV shipments totaled 105 million units in 2008, up 33 percent compared to the previous year. More importantly, this marked the first time LCD TV sales surpassed CRT TV sales. One reason demand for LCD TVs was outpacing CRT TVs was consumers were preparing for the upcoming switch from analog to digital television scheduled for June 2009, at which time television broadcasting was going digital. Another reason for the popularity of the LCD TV was that prices were falling 20 to 30 percent or more annually. In fact, The Information Network projected panels for LCD TVs would grow 26.6 percent in 2009. Global CRT TV shipments were projected to decline to 32 million units as demand continued to fade in 2010.

In 2009 global shipments for monitor LCD panels were expected to decline by 17 percent to 144.9 million units, while panels for notebooks were projected to increase by 26.6 percent to 177 million units. According to research firm IDC, the LCD market commanded nearly 97 percent of the total PC monitor market by the second quarter of 2010, which left about three percent market share for the CRT market mainly in the "lower education segment," but was increasingly leaning toward the LCD market. "With just close to 3 percent market share, the CRT is almost dead," Varun Aggarwal noted in CRN, in November 2010.

A report released by the Consumer Electronics Association (CEA) titled "Materials Footprint Reduction of Televisions and Computer Monitors: 2004-2010" claimed that flat screen TVs were 75 percent smaller and 82 percent lighter than preceding CRT TVs. As of 2011, there were millions of CRT TVs and monitors in use globally, which means that over the coming years the majority of

PUBLIC

recycling will involve these bulkier products. Once CRT-based displays are no longer produced, and most reach the end of their lives to be recycled and disposed of, electronic waste levels should witness a noticeable decline.

Industry Leaders

In the late years of the first decade of the 2000s, LG Display Co. (formerly LG Philips LCD Co.), based in Seoul, South Korea, was the world's leading manufacturer of CRTs. LG Phillips shipped \$12.8 billion in products in 2008 to claim approximately one third of the market share. Among the electron tube industry's leading firms during the late years of the first decade of the 2000s was Zenith Electronics Corporation, which had sales of approximately \$109 million in 2008. The company was purchased by LG and shifted its focus to research and development. Other major industry players included Hitachi Electronic Devices; Toshiba Westinghouse Electronic; GM Hughes Electronics Corporation; Hewlett-Packard Co.; ITT Corporation; Litton Industries Inc., Electron Devices Division; Philips Electronics North America; and Raytheon Electronic Components.

Research and Technology

The growing demand for computer monitors for use in homes and offices starting in the 1980s forced industry firms to develop more user-friendly monitor designs, such as the "flatsquare CRT," in which the curvature of the CRT's screen was greatly reduced. CRT display technology also continued to evolve in the areas of unit price and color display capabilities.

The application of multifunctional CRT displays in the instrument panels of military aircraft, and, to a lesser degree, commercial aircraft, continued in the 2000s. However, the inherent disadvantages of CRTs, including limited screen size, unwieldy shape, high power requirements, and fragility, led manufacturers to investigate alternatives to CRT technology, such as light-emitting diodes, FPDs, and LCDs. Improvements in LCDs, which were thinner and lighter than CRTs, enabled them to compete in price with CRT-based, large screen video data projectors while offering roughly two to four times their brightness.

Flat panel displays increasingly emerged as the favored display technology, especially in aircraft cockpit applications where limited space and high levels of glare diminished the usefulness of CRTs. Field emission display, another emergent technology that further threatened to unseat the electron CRT, was structurally less complex and thinner in size than LCDs. Field emission displays were based on vacuum microelectronics and combined the advantages of vacuum tube technology with the benefits of digital computer chips. Advances in research and technology also continued in non-CRT product categories in the first decade of the 2000s. Direct broadcast satellites that used electron tubes, such as traveling wave tubes, for non-cable HDTV transmissions, as well as for other uses, were developed for satellite tubes and uplink stations with tube lifetimes of up to 15 years.

To combat the onslaught of the flat panel television industry, some CRT manufacturers were pushing new technology to make CRTs flatter and lighter than their predecessors. A 36-inch CRT television can weigh as much as 200 pounds and is 20 to 24 inches deep. In 2005, LG Phillips Displays and Samsung used new CRT technology to introduce CRT models that were much smaller than their predecessors. Although the models, which were 14 inches deep, were still much bigger than their LCD counterparts, the manufacturers argued that most DVD players are 12 to 14 inches deep, so the consumer had already allotted that much space. Pure flat screen CRT technology also was being advanced. The prototypes of the new flat CRT technology cost about 30 percent more than a traditional CRT model but were still 50 percent less expensive than a comparable LCD set.

© COPYRIGHT 2013 The Gale Group, Inc. This material is published under license from the publisher through the Gale Group, Farmington Hills, Michigan. All inquiries regarding rights should be directed to the Gale Group. For permission to reuse this article, contact the [Copyright Clearance Center](#).

Share

Like

0

Tweet

0

0

News and information about Electron Tubes



News Wire

[Wipo Publishes Patent of Toshiba Electron Tubes & Devices. Kabushiki Kaisha Toshiba, Hidero Anno, Tomonari Ishihara, Tetsuya Yonezawa, Harunobu Fukushima, Chiharu Tadokoro and Hitoshi Hattori for "Coolant Device, X-Ray Computer Tomography Device and X-Ray Computer Tomography Device Maintenance Method" \(Japanese Inventors\)](#)

US Fed News Service, Including US State News; February 18, 2013; 432 words ...RAY COMPUTER TOMOGRAPHY DEVICE, AND X-RAY COMPUTER TOMOGRAPHY DEVICE MAINTENANCE METHOD."Applicants: Toshiba Electron Tubes & Devices Co. Ltd. (JP), KABUSHIKI KAISHA TOSHIBA (JP), Hidero Anno (JP), Tomonari Ishihara (JP), Tetsuya...



News Wire

[US Patent Issued to Kabushiki Kaisha Toshiba, Toshiba Electron Tubes & Devices on Feb. 5 for "Radiation Detection Apparatus and Radiographic Apparatus" \(Japanese Inventors\)](#)

US Fed News Service, Including US State News; February 9, 2013; 485 words ...States Patent no. 8,366,319, issued on Feb. 5, was assigned to Kabushiki Kaisha Toshiba (Tokyo) and Toshiba Electron Tubes & Devices Co. Ltd. (Tochigi-Ken, Japan)."Radiation Detection Apparatus and Radiographic Apparatus" was...



News Wire

[US Patent Issued to Kabushiki Kaisha Toshiba, Toshiba Electron Tubes & Devices on Dec. 18 for "Image Intensifier" \(Japanese Inventor\)](#)

US Fed News Service, Including US State News; December 24, 2012; 385

PUBLIC

words ...States Patent no. 8,335,295, issued on Dec. 18, was assigned to Kabushiki Kaisha Toshiba (Tokyo) and Toshiba Electron Tubes & Devices Co. Ltd. (Tochigi-Ken, Japan). "Image Intensifier" was invented by Ryuichi Uduka (Yaita, Japan...



News Wire

[Uspto Issues Trademark: Electron Tubes](#)

US Fed News Service, Including US State News; November 6, 2012; 700+ words ...Nov. 6 -- The trademark ELECTRON TUBES (Reg. No. 4231889; International...consists of the black wording "ELECTRON TUBES" with the word "TUBES" enclosed...light-detecting instruments, electron tubes, radiation detectors, radiation...



News Wire

[Wipo Publishes Patent of Kabushiki Kaisha Toshiba, Toshiba Electron Tubes & Devices, Homma Katsuhisa for "Radiation Detector" \(Japanese Inventor\)](#)

US Fed News Service, Including US State News; August 17, 2012; 445 words ...Aug. 9. Title of the invention: "RADIATION DETECTOR." Applicants: KABUSHIKI KAISHA TOSHIBA (JP), TOSHIBA ELECTRON TUBES & DEVICES CO. LTD. (JP) and HOMMA Katsuhisa (JP). Inventors: Katsuhisa Homma (JP). According to the abstract...



News Wire

[Contract Notice: Defense Logistics Agency \(Ohio\) Issues Solicitation for Electron Tubes](#)

US Fed News Service, Including US State News; May 18, 2012; 241 words WASHINGTON, May 28 -- Defense Logistics Agency, DLA Acquisition Locations has a requirement for electron tubes. The solicitation no. SPM7M512TC347 was posted on May 11. All responses are due by May 28. Notice Type: Combined Synopsis...



News Wire

[WIPO PUBLISHES PATENT OF TOSHIBA, TOSHIBA ELECTRON TUBES & DEVICES FOR "FLAT PANEL RADIATION IMAGER REFRESH OPERATION METHOD" \(JAPANESE INVENTOR\)](#)

US Fed News Service, Including US State News; December 10, 2011; 346 words ...FLAT PANEL RADIATION IMAGER REFRESH OPERATION METHOD." Applicants: KABUSHIKI KAISHA TOSHIBA (JP) and Toshiba Electron Tubes & Devices Co., Ltd. (JP). Inventors: Hiroshi Onihashi (JP). According to the abstract posted by the World...



News Wire

[US Patent Issued to Toshiba Electron Tubes & Devices on April 17 for "Radiation Detector and Method for Manufacturing the Same" \(Japanese Inventors\)](#)

US Fed News Service, Including US State News; April 25, 2012; 405 words ...ALEXANDRIA, Va., April 23 -- United States Patent no. 8,158,949, issued on April 17, was assigned to Toshiba Electron Tubes & Devices Co. Ltd. (Tochigi-Ken, Japan). "Radiation Detector and Method for Manufacturing the Same" was...

[Search all articles about Electron Tubes](#)

[Sign up for a FREE, 7-day trial](#) or call 1-888-928-9422 to request a demo.

HighBeam Business is operated by [Cengage Learning](#). © Copyright 2013. All rights reserved.

[About us](#) [Contact us](#) [Terms and conditions](#) [Privacy policy](#)

[Arrive Prepared](#) – our blog about business news and market research.

PUBLIC

Tube sound

From Wikipedia, the free encyclopedia

Tube sound (or valve sound) is the characteristic sound associated with a vacuum tube-based audio amplifier.^[1]

The audible significance of tube amplification on audio signals is a subject of continuing debate among audio enthusiasts.^[2]

Many electric guitar, electric bass, and keyboard players in a range of popular, rock, funk, blues, reggae and jazz genres also prefer the sound of tube instrument amplifiers or preamplifiers.



Vacuum tubes glowing inside the preamp section of a modern guitar amplifier.

Contents

- 1 History
- 2 Sound reproduction
- 3 Musical instrument amplification
- 4 Audible differences
- 5 Harmonic content and distortion
- 6 Design comparison
 - 6.1 Input impedance
 - 6.2 Output impedance
 - 6.3 Soft clipping
 - 6.4 Bandwidth
 - 6.5 Negative feedback
 - 6.6 Power supplies
 - 6.7 Class A
 - 6.8 Push-pull amplifiers
 - 6.9 Single-Ended Triode (SET) amplifiers
 - 6.10 Single-ended pentode and tetrode amplifiers
 - 6.11 Class AB
- 7 Intentional distortion
 - 7.1 Tube sound from transistor amplifiers
 - 7.2 Hybrid amplifiers
- 8 Tube sound enthusiasts
- 9 See also
- 10 Notes
- 11 References

Exhibit	T152
Skold v. Galderma	
Cancellation No. 92052897	

PUBLIC

History

Before the commercial introduction of transistors in the 1950s, electronic amplifiers used vacuum tubes (known in Great Britain as "valves"). By the 1960s, solid state (transistorized) amplification had become more common because of its smaller size, lighter weight, lower heat production, and improved reliability. Tube amplifiers have retained a loyal following amongst some audiophiles and musicians. Some tube designs command very high prices, and tube amplifiers have been going through a revival since Chinese and Russian markets have opened to global trade—tube production never went out of vogue in these countries.

Sound reproduction

Audiophiles may agree or disagree on the relative merits of tube vs solid state amplification. Some say they prefer the sound produced from tube amplifiers on the grounds that it is more natural and satisfying than the sound from transistor amplifiers. Otherwise this preference or difference is far too generalised or even vague without taking amplifier designs into consideration, and there are many. Certainly these audible differences are due to distortion types: harmonic, distribution, level and many other factors.

Those who subscribe to measurement and scientifically-based approaches to high fidelity note that in general, solid state designs can be manufactured without output transformers and are therefore immune to speaker-dependent impedance mismatches and other transformer effects which alter the system spectral response. On the other hand, ruler flat frequency response does not necessarily mean a good sounding amplifier. It should be noted that the loudspeaker itself (regardless of price) will likely produce more distortions (non-linearity and uneven frequency response) than any other part of the system. Typically, in sound reproduction systems, accurate reproduction of the sound of the original recording is the goal; distortion and uneven spectral response within the audible frequency band is something designers deliberately seek not to introduce.^[3]

Musical instrument amplification

Some musicians^[4] also prefer the distortion characteristics of tubes over transistors for electric guitar, bass, and other instrument amplifiers. In this case, generating deliberate (and sometimes considerable, in the case of electric guitars) audible distortion or overdrive is usually the goal. The term can also be used to describe the sound created by specially-designed transistor amplifiers or digital modeling devices that try to closely emulate the characteristics of the tube sound.

The tube sound is often subjectively described as having a "warmth" and "richness", but the source of this is by no means agreed on. It may be due to the non-linear clipping that occurs with tube amps, or due to the higher levels of second-order harmonic distortion, common in single-ended designs resulting from the characteristics of the tube interacting with the inductance of the output transformer.

See also: Distortion (guitar) and Guitar effects

Audible differences

The sound of a tube amplifier is partly a function of the circuit topologies typically used with tubes versus the topologies typically used with transistors, as much as the gain devices themselves. Beyond circuit design, there are other differences such as the electronic characteristics of a triode and MOSFET, or a tetrode and a bipolar

transistor.

The low frequency roll-off can be explained by many tube amplifiers having high output impedance compared to transistor designs, due to the combination of both higher device impedance itself and typically reduced feedback margins (more feedback results in a lower output impedance).

Harmonic content and distortion

Triodes (and MOSFETs) produce a monotonically decaying harmonic distortion spectrum. Even-order harmonics and odd-order harmonics are both natural number multiples of the input frequency.

Psychoacoustic phenomena include the effect that high-order harmonics are more offensive than low. Thus, in distortion measurements this should be taken into consideration to weight audible high-order harmonics more than low. The importance of high-order harmonics suggests that distortion should be regarded in terms of the complete series or of the composite wave-form that this series represents. It has been shown that weighting the harmonics by the square of the order correlates well with subjective listening tests. Weighting the distortion wave-form proportionally to the square of the frequency gives a measure of the reciprocal of the radius of curvature of the wave-form, and is therefore related to the sharpness of any corners on it.^[5] Based on said discovery, highly sophisticated methods of weighting of distortion harmonics have been developed.^[6] Since they concentrate in the origins of the distortion, they are mostly useful for the engineers who develop and design audio amplifiers, but on the other hand they may be difficult to use for the reviewers who only measure the output.^[7]

Push-pull amplifiers use two nominally identical gain devices "back to back". One consequence of this is that all even-order harmonic products cancel, leaving odd order products to dominate.^[8] A push-pull amplifier is said to have a symmetric (odd symmetry) transfer characteristic, and accordingly produces only odd harmonics.

A single-ended amplifier has an asymmetric transfer characteristic, and produces both even and odd harmonics.^{[9][10][11]} As tubes are often run single-ended, and semiconductor amplifiers are often push-pull, the types of distortion are incorrectly attributed to the devices (or even the amplifier class) instead of the topology. Push-pull tube amplifiers can be run in class A, AB, or B. Also, a class B amplifier may have crossover distortion that will be typically high order and thus sonically very undesirable indeed.^[12]

Another factor is that the distortion content of class A circuits (SE or PP) typically monotonically reduces as the signal level is reduced, asymptotic to zero during quiet passages of music. For this reason class A amplifiers are especially desired for classical and acoustic music etc. cf. class B and AB amplifiers, for which the amplitude of the crossover distortion is more or less constant, and thus the distortion relative to signal in fact increases as the music gets quieter. Class A amplifiers measure best at low power, class AB and B amplifiers measure best just below max rated power.

Loudspeakers present a reactive load to an amplifier (capacitance, inductance and resistance). This impedance may vary in value with signal frequency and amplitude. This variable loading affects the amplifier's performance both because the amplifier has finite output impedance (it cannot keep its output voltage perfectly constant when the speaker load varies) and because the phase of the speaker load can change the stability margin of the amplifier. The influence of the speaker impedance is different between tube amplifiers and transistor amplifiers, principally because tube amplifiers normally use output transformers, and cannot use as much negative feedback due to phase problems in transformer circuits. A notable exception is Berning's unique tube-transformerless "ZOTL" circuit.

PUBLIC

The design of speaker crossover networks and other electro-mechanical properties may result in a speaker with a very uneven impedance curve, for a nominal 8 Ω speaker, being as low as 6 Ω at some places and as high as 30–50 Ω elsewhere in the curve. An amplifier with little or no negative feedback will always perform poorly when faced with a speaker where little attention was paid to the impedance curve.

Design comparison

There has been considerable debate over the characteristics of tubes versus bipolar junction transistors. Triodes and MOSFETs have certain similarities in their transfer characteristics, whereas later forms of the tube, the tetrode and pentode, have quite different characteristics that are in some ways similar to the bipolar transistor. Despite this, e.g. MOSFET amplifier circuits typically do not reproduce tube sound any more than typical bipolar designs, due to the circuit topology differences between a typical tube design and a typical MOSFET design. But there are exceptions, for example designs such as the Zen series by Nelson Pass.

Input impedance

A characteristic feature of most tube amplifier designs is the high input impedance (typically 100 k Ω or more) in modern designs and as much as 1 M Ω in classic designs.^[13] The input impedance of the amplifier is a load for the source device. Even for some modern music reproduction devices the recommended load impedance is over 50 k Ω .^{[14][15]} This implies that the input of an average tube amplifier is a problem-free load for music signal sources. By contrast, some transistor amplifiers for home use have lower input impedances, as low as 15 k Ω .^[16] Since it is possible to use high output impedance devices due to the high input impedance, other factors may need to be accounted for, such as cable capacitance and microphonics in such cases.

Output impedance

Audio amplifiers are usually loaded by loudspeakers and in the history nearly all loudspeakers have been electrodynamic loudspeakers, while there exists also minority of electrostatic loudspeakers and some other even more exotic loudspeakers. Electrodynamic loudspeakers transform electric current to force and force to acceleration of the diaphragm which causes sound pressure. Due to the principle of an electrodynamic speaker, most loudspeaker drivers ought to be driven by an electric current signal. In an ideal current or transconductance amplifier the output impedance approaches infinity, while practically all commercial audio amplifiers are voltage amplifiers, and their output impedances have been intentionally developed to approach zero. Due to the nature of vacuum tubes and audio transformers, the output impedance of an average tube amplifier is usually considerably higher than of the modern audio amplifiers produced completely without vacuum tubes or audio transformers. Thus, most tube amplifiers with their higher output impedance are closer to the idea of a transconductance amplifier than the solid state voltage amplifiers. The current signal drives the electrodynamic speaker more accurately, causing less distortion than a voltage signal.^{[17][18][19]}

Soft clipping

Soft clipping is a very important aspect of tube sound especially for guitar amplifiers, although a Hi-fi amplifier should not normally ever be driven into clipping. The harmonics added to the signal are of lower energy with soft clipping than hard clipping. However, soft clipping is not exclusive to tubes, it can be simulated in transistor circuits (below the point that real hard clipping would occur). (See "Intentional distortion" section).

PUBLIC

Large amounts of negative feedback are not available in tube circuits, due to phase shift in the output transformer, and lack of sufficient gain without large numbers of tubes. With lower feedback, distortion is higher and predominantly of low order. The onset of clipping is gradual. Large amounts of feedback, allowed by transformerless circuits with many active devices, leads to numerically lower distortion but with more high harmonics, and harder clipping—as input increases, the feedback uses the extra gain to ensure that the output follows it accurately until the amplifier has no more gain to give and the output saturates.

In the recording industry and especially with microphone amplifiers it has been shown that amplifiers are often overloaded by signal transients. There is a major difference in the harmonic distortion components of the amplified signal, with tubes, transistors, and operational amplifiers separating into distinct groups.^{[20][21]}

Bandwidth

Early tube amplifiers often had limited response bandwidth, in part due to the characteristics of the inexpensive passive components then available. In power amplifiers most limitations come from the output transformer; low frequencies are limited by primary inductance and high frequencies by leakage inductance and capacitance. Another limitation is in the combination of high output impedance, decoupling capacitor and grid resistor, which acts as a high-pass filter. If interconnections are made from long cables (for example guitar to amp input), a high source impedance with high cable capacitance will act as a low-pass filter.

Modern premium components make it easy to produce amplifiers that are essentially flat over the audio band, with less than 3 dB attenuation at 6 Hz and 70 kHz, well outside the audible range.

Negative feedback

Tube amplifiers could not use as much negative feedback (NFB) as transistor amplifiers due to the large phase shifts caused by the output transformers and their lower stage gains. While the absence of NFB greatly increases harmonic distortion, it avoids instability, as well as slew rate and bandwidth limitations imposed by dominant-pole compensation in transistor amplifiers. Since transient intermodulation distortion was mainly caused by negative feedback,^{[22][23]} tube sound never suffered much of that kind of distortion.

Power supplies

Early tube amplifiers usually had unregulated power supplies. This was due to the high cost of a regulating element, and the relative insensitivity of the power output stage to voltage variations. The typical anode supply was a rectifier, perhaps half-wave, a choke (inductor) and a filter capacitor. When the tube amplifier was operated at high volume, the power supply voltage would dip as the amplifier draws more current (assuming class AB), reducing power output and causing signal modulation. This dipping effect is known as "sag", which may be desirable effect for some electric guitarists when compared with hard clipping. As the amplifier load or output increases this voltage drop will increase distortion of the output signal. Sometimes this sag effect is desirable for guitar amplification.

Some instrument tube amplifier designs use a vacuum tube rectifier instead of silicon diodes. A solid state rectifier arrangement could introduce audible noise (switching noise) into the amplifier, but only if poorly implemented, this may be audible as a buzzing sound at typically twice mains supply frequency.^[24] The voltage sag of a tube rectifier can be emulated with silicon rectifiers, by adding a resistance in series with the high voltage supply. This resistance can be switched in when required.

PUBLIC

Electric guitar amplifiers often use a class AB₁ amplifier. In a class A stage the average current drawn from the supply is constant with signal level, consequently it does not cause supply line sag until the clipping point is reached. Other audible effects due to using a tube rectifier with this amplifier class are unlikely.

One possible practical advantage of tube rectification is that the rectifier tube takes some time to warm up before it begins to conduct. This will allow a little time for the output tube heaters to warm up somewhat and allow them to start conducting before the high voltage (HT) reaches full potential allowing a soft start, possibly extending their lifespan. Some say that if the full high voltage supply (HT) is present during the warm up process, on output tubes, cathode damaged may result.

Some high end manufacturers, such as Welborne Labs in their premium kits, use silicon diodes on the basis that the cost and power required to operate a vacuum tube rectifier does not yield any measurable improvement in the sound.

Class A

The benefit of all Class A amplifiers is the absence of crossover distortion. This crossover distortion was found especially annoying after the first silicon-transistor Class B and Class AB transistor amplifiers arrived on the consumer market; earlier germanium-based designs with the much lower turn-on voltage of this technology and the non-linear response curves of the devices had not shown large amounts of cross-over distortion. Although crossover distortion is very fatiguing to the ear and perceptible in listening tests, it is also almost invisible (until looked for) in the traditional Total harmonic distortion (THD) measurements of that epoch.^[25]

Push-pull amplifiers

A Class A push-pull amplifier produces low distortion for any given level of applied feedback, and also cancels the flux in the transformer cores, so this topology is often seen by HIFI-audio enthusiasts and do-it-yourself builders as the ultimate engineering approach to the tube Hi-fi amplifier for use with normal speakers. Output power of as high as 15 watts can be achieved even with classic tubes such as the 2A3^[26] or 18 watts from the type 45. Classic pentodes such as the EL34 and KT88 can output as much as 60 and 100 watts respectively. Special types such as the V1505 can be used in designs rated at up to 1100 watts. See "An Approach to Audio Frequency Amplifier Design", a collection of reference designs originally published by G.E.C.

Single-Ended Triode (SET) amplifiers

SET amplifiers typically show poor measurements for distortion with a resistive load, have low output power, are inefficient, have poor damping factors and high measured harmonic distortion. But they perform somewhat better in dynamic and impulse response.

The triode, despite being the oldest signal amplification device, also can (depending on the device in question) have a more linear no-feedback transfer characteristic than more advanced devices such as beam tetrodes and pentodes.

Audiophiles who prefer SET-amplifiers state that measured sound performance is a poor indicator of real world sound performance and distortion level is not the only criterion for good sound reproduction. Their **PUBLIC** measurements not using resistive load but actual loudspeakers to back this up. In the 1970s, designers started



Blackheart 5 W single-ended class A guitar amplifier chassis, with additional GZ34 valve rectifier installed.

producing transistor amps with higher open loop gain to support a greater value of negative feedback. In the following years, amplifiers were built with modest gain but good open loop linearity, deployed with only minimal levels of NFB.

All amplifiers distort, so do SETs. This for the most part harmonic distortion is a distortion with a unique pattern of simple and monotonically decaying series of harmonics, dominated by modest levels of second harmonic. The result is like adding the same tone one octave higher. The added harmonic tone is lower, at about 1–5% or less in a no feedback amp at full power and rapidly decreasing at lower levels. It has been also claimed that a single-ended power amplifier's second harmonic distortion could reduce similar harmonic distortion in a single driver loudspeaker, if their harmonic distortions were equal and amplifier was connected to the speaker so that the distortions would neutralize each other.^{[27][28]}

SETs usually only produce about 2 watt (W) for a 2A3 tube amp to 8 W for a 300B up to the practical maximum of 40 W for a 805 tube amp. The resulting sound pressure level depends on the sensitivity of the loudspeaker and the size and acoustics of the room as well as amplifier power output. Their low power also makes them ideal for use as preamps. SET amps have a power consumption of a minimum of 8 times the stated stereo power. For example a 10 W stereo SET uses a minimum of 80 W, and typically 100 W.

Single-ended pentode and tetrode amplifiers

The special feature among tetrodes and pentodes is the possibility to obtain ultra-linear or distributed load operation with an appropriate output transformer. Ultra-linear connection is a negative feedback method, enabling less harmonic distortion.

Class AB

The majority of modern commercial Hi-fi amplifier designs have until recently used Class AB topology (with more or less pure low-level Class A capability depending on the standing bias current used), in order to deliver greater power and efficiency, typically 12–25 watts and higher. Modern designs normally include at least some negative feedback, although in the old times of High fidelity use of feedback was totally out of question. It should however be noted that Class D topology (which is vastly more efficient than Class B, and has garnered some respect from audiophiles) is more and more frequently applied where traditional design would use Class AB.

Class AB push-pull topology is nearly universally used in tube amps for electric guitar applications that produce power of more than about 10 watts. Whereas audiophile amps are primarily concerned with avoiding distortion, a guitar amp embraces it. When driven to their respective limits, tubes and transistors distort quite differently. Tubes clip more softly than transistors, allowing higher levels of distortion (which is sometimes desired by the guitarist) whilst still being able to distinguish the harmonies of a chord. This is because the soft profile of the tube amplifier's distortion means that the intermodulation products of the distortion are generally more closely related to the harmonies of the chord. All sides of the question are inclined to agree about valve guitar amplifiers offering a very useful sound, though there are also some well-respected solid-state designs.

Intentional distortion

Tube sound from transistor amplifiers

PUBLIC

Some individual characteristics of the tube sound, such as the waveshaping on overdrive, are straightforward to produce in a transistor circuit or digital filter. For more complete simulations, engineers have been successful in developing transistor amplifiers that produce a sound quality very similar to the tube sound. Usually this involves using a circuit topology similar to that used in tube amplifiers.

In 1982, Tom Scholz, a graduate of MIT and a member of Boston, introduced the Rockman, which used bipolar transistors, but achieved a distorted sound adopted by many well known musicians. Advanced digital signal processing offers the possibility to simulate tube sound. Computer algorithms are currently available that transform digital sound from a CD or other digital source into a distorted digital sound signal.

Using modern passive components, and modern sources, whether digital or analogue, and wide band loudspeakers, it is possible to have tube amplifiers with the characteristic wide bandwidth and "fast" sound of modern transistor amplifiers, including using push-pull circuits, class AB, and feedback. Some enthusiasts have built amplifiers using transistors and MOSFETs that operate in class A, including single ended, and these often have the "tube sound".^[29]

Hybrid amplifiers

Tubes are often used to impart characteristics that many people find audibly pleasant to solid state amplifiers, such as Musical Fidelity's use of Nuvistors, tiny triode tubes, to control large bi-polar transistors in their NuVista 300 power amp. In America, Moscode and Studio Electric use this method, but use MOSFET transistors for power, rather than bi-polar. Pathos, an Italian company, has developed an entire line of hybrid amplifiers.

To demonstrate one aspect of this effect, one may use a light bulb in the feedback loop of an infinite gain multiple feedback (IGMF) circuit. The slow response of the light bulb's resistance (which varies according to temperature) can thus be used to moderate the sound and attain a tube-like "soft limiting" of the output, though other aspects of the "tube sound" would not be duplicated in this exercise.

Tube sound enthusiasts

Different uses of tube amplifiers can be found due to the different personal preferences of the enthusiasts. From those who opt to restrict their use as active devices to those who opt to include them in the audio circuit, accepting the use of semiconductor gain devices in the power supply or as constant current sources. Others, still, will use tubes for the main amplification circuit but add semiconductors (such as solid-state diodes) for clipping purposes, particularly in the preamp section, which is often debated in advertised vintage instrument amplifiers such as the Marshall JCM900 or the Vintage Modern as to their integrity due to their utilization of solid-state devices in the tone-generation circuit. Other schisms concern the use of triodes vs. tetrodes and pentodes, and the use of directly heated tubes vs. indirectly heated tubes.

Many of the explanations relate to the circuit topologies pioneered using tubes, and traditionally associated with them ever since, regardless of whether they are built using tubes today, notably the directly heated single-ended triode amplifier circuit, which operates in class A and often has no external negative feedback; this topology is a classic source of the tube sound.



Directly heated triodes.

PUBLIC

Feedback paths coupled through the secondary of the output transformer reduce distortion because they compensate for the transformer's distortion to some extent. However only limited NFB can be used around the transformer, as there is phase lag caused by the transformer, and this causes instability if NFB is incorrectly (without any phase / frequency correction) used.

See also

- Audio system measurements
- British Valve Association
- European triode festival
- Virtual Valve Amplifier

Notes

1. [^] van der Veen, M. (2005). "Universal system and output transformer for valve amplifiers" (http://www.mennovanderveen.nl/nl/download/download_3.pdf). 118th AES Convention, Barcelona, Spain. http://www.mennovanderveen.nl/nl/download/download_3.pdf.
2. [^] Branch, John D. (2007-05-23). "Postmodern Consumption and the High-Fidelity Audio Microculture". In Russell Belk, Russell Belk Jr., John Sherry (eds.). *Consumer Culture Theory, Volume 11 (Research in Consumer Behavior)* (1 ed.). JAI Press. pp. 79–99. ISBN 0-7623-1446-X.
3. [^] The Noisy Audiophile. "Noisy' on Tubes vs. Solid State" (<http://www.soundstage.com/noisy04.htm>) in SoundStage!, March 1996.
4. [^] For example, Robert Walser *Running with the Devil: power, gender, and madness in heavy metal music*, Wesleyan University Press, 1993 ISBN 0-8195-6260-2 pages 43-44 discusses the "tube sound" sought by Eddie Van Halen
5. [^] Shorter, D. E. L. (April 1950). "The Influence of High-Order Products in Non-Linear Distortion". *Electronic Engineering (London, UK)* 22 (266): 152–153. "That high-order harmonics are more offensive than low has long been recognised..."
6. [^] Geddes, Earl R.; Lee, Lidia W. (October 2003). "Auditory Perception of Nonlinear Distortion" (http://hephaestusaudio.com/media/2008/11/distortion_aes_ii.pdf) (PDF). AES 115th Convention. AES 115th Convention (<http://www.aes.org/events/115/>). New York, New York: Audio Engineering Society. http://hephaestusaudio.com/media/2008/11/distortion_aes_ii.pdf.
7. [^] Howard, Keith (September 2005). "Weighting up" (http://www.gedlee.com/downloads/THD_.pdf) (PDF). *Multi Media Manufacturer (Peterborough, New Hampshire: Audio Amateur)*: 7–11.
8. [^] *A First Course in Electronics*, pg 414-416. Anwar A. Khan and Kanchan K. Dey
9. [^] Ask the Doctors: Tube vs. Solid-State Harmonics (<http://www.uaudio.com/webzine/2005/october/content/content2.html>)—Universal Audio Webzine
10. [^] Volume cranked up in amp debate (http://www.trueaudio.com/at_eetjlm.htm)—Electronic Engineering Times
11. [^] W. Bussey and R. Haigler (1981). "Tubes versus transistors in electric guitar amplifiers" (http://milbert.com/articles/tubes_vs_transistors_in_electric_guitar_amps). *IEEE International Conference on Acoustics, Speech, and Signal Processing*. pp. Volume 6 p. 800–803. http://milbert.com/articles/tubes_vs_transistors_in_electric_guitar_amps.
12. [^] Meusburger, Walter (October 1999). "4 Crossover Distortion in Class B" (http://www.moehrenbude.de/Moehre/images2/download/No_Crossoveramp_W.Meusberger.pdf) (PDF). *A Novel Power Amplifier Topology Without Crossover Distortion (D.Tech. thesis)*. Graz, Austria: Graz University of Technology. p. 27. Retrieved 2011-03-18. "Crossover distortion generates unpleasant high order harmonics with the potential to increase in percentage as signal level falls and is much more objectionable to the listener than distortion resulting from a smoothly curved characteristic, even if they have the same THD. Therefore it is desirable to reduce crossover distortion to a minimum amount." **PUBLIC**
13. [^] "Three-valve Stereophonic Amplifier". *Mullard Tube Circuits for Audio Amplifiers (2nd ed.)*. Peterborough,

- New Hampshire: Audio Amateur Press. 1959. p. 123. ISBN 1-882580-03-6.
14. ^ Sony Corporation 1999. Sony compact disc player CDP-XB930 Operating Instructions. (1). Specifications, p.20.
 15. ^ CDP-XB930/XB930E service manual (<http://www.qrz.ru/schemes/redirect.phtml?id=14227>) (PDF). Japan: Sony Corporation. 1999. p. 1.
 16. ^ Rotel stereo integrated amplifier RA-935BX owners manual. MN10002975-A. p.4
 17. ^ Mills, Paul G. L.; Hawksford, M. O. J. (March 1989). "Distortion Reduction in Moving-Coil Loudspeaker Systems Using Current-Drive Technology". *Journal of Audio Engineering Society* (University of Essex, Wivenhoe Park, Colchester, Essex, CO4 3SQ, UK) 37 (3): 129–148.
 18. ^ Meriläinen, Esa (February 2010). "5.7 The Secret of Tube Amplifiers". *Current-Driving of Loudspeakers*. Createspace. pp. 111–112. ISBN 1-4505-4400-2. "The most significant differences are, however, found in the output impedance. The output impedance of transistor amplifiers is typically less than $0.1\ \Omega$, which denotes pure voltage feed for the speaker. In tube amplifiers, instead, the output impedance varies rather widely; from tenths of an ohm to even more than five ohms (with $8\ \Omega$ loading). A source impedance of even a couple of ohms is able to weaken the speaker's EMF currents so that the effects are observable; and as the value exceeds $5\ \Omega$, the speaker may function at some frequencies even halfly current-driven."
 19. ^ "The Caged Frog -- A Pentode Based Transconductance Amplifier for Headphones" (<http://www.ecp.cc/CagedFrog.html>). ecp.cc. 22 August 2010. Retrieved 14 October 2012. "But, as I was about to disassemble it and put the parts away, I wondered what the circuit would sound like without any feedback. That is, just a pentode with a transformer load. I figured it was going to be awful, so I was not prepared for what I heard, which was near sonic bliss. From note one, this was something special. Turns out, I had built a transconductance amp more or less by accident."
 20. ^ Hamm, Russell O. (May 1973). "Tubes Versus Transistors –Is There an Audible Difference?". *J Audio Eng Soc* (New York: Audio Engineering Society) 21 (4): 267–273. Lay summary (<http://www.aes.org/e-lib/browse.cfm?elib=1980>) – AES. "This paper, however, points out that amplifiers are often severely overloaded by signal transients (THD 30%). Under this condition there is a major difference in the harmonic distortion components of the amplified signal, and operational amplifiers separating into distinct groups."
 21. ^ Hamm, Russell O. "Tubes Versus Transistors –Is There an Audible Difference?" (<http://www.milbert.com/tstxt.htm>). Milbert Amplifiers. Retrieved 19 July 2009.
 22. ^ Tapio M. Köykkä, "Katkoäänien rikkoutuminen äänentoistossa" (in Finnish), *ERT (Elektroniikka-Radio-TV)*, vol. 22, no. 1, pp. 27–32, 1969
 23. ^ Matti Ojala, "Transient Distortion in Transistorized Audio Power Amplifiers", *IEEE Transactions on Audio and Electroacoustics* vol. AU-18, No. 3 September 1970
 24. ^ S5 Electronics K-12M Tube Amp (http://www.siteswithstyle.com/VoltSecond/K-12M_AMP/K-12M_Push_Pull.html)
 25. ^ Langford-Smith, F. (1952). "14 Fidelity and distortion" (<http://www.pmillett.com/Books/RDH4.pdf>) (PDF). *Radiotron Designer's Handbook* (4th ed.). Sydney, Australia: Wireless Press. p. 610. "One interference which may reasonably be drawn is that any sharp kinks in the linearity curve, as usually occur in any Class AB_1 or AB_2 amplifier, have a far more serious subjective effect than is indicated by any of the standard methods of measuring distortion –whether total harmonic distortion, conventional weighted distortion factor or the standard form of intermodulation testing."
 26. ^ Pete Millett's DIY Audio pages. Tube data. RCA 2A3 Power Triode. (http://www.pmillett.com/tubedata/HB-3/Receiving_Tubes_Part_1/2A3.PDF)
 27. ^ About distortion behavior between SE amplifiers and speakers (http://www.audiopax.com/papers_part1.htm), Eduardo de Lima
 28. ^ System distortion (<http://gboers.xs4all.nl/daisy/home/g3/139/g1/loudspeakers/systemdistortion.html>), Gerrit Boers
 29. ^ Olsher, Dick (July 2001). "The Volksamp Aleph 30 SE Power Amplifier (product review)" (<http://www.enjoythemusic.com/magazine/equipment/0701/volksamp.htm>). Enjoy the Music.com. 5th paragraph. "It effectively bridges the gap between solid-state and tube sound, blending tube and transistor virtues into a musically satisfying whole."

PUBLIC

References

- Barbour, Eric. The Cool Sound of Tubes (<http://www.spectrum.ieee.org/print/1640>) in IEEE Spectrum Online.
- Hamm, Russell O. (September 14, 1972). "Tubes vs. Transistors: Is There An Audible Difference?" (<http://milbert.com/Files/articles/TvsT/tstxt.pdf>). Presented at the 43rd convention of the Audio Engineering Society, New York.
- Reisch, George. Scientists vs Audiophiles 1999 (<http://stereophile.com/thinkpieces/165/>) in Stereophile, March, 1999.
- Tube Data Archive (<http://tubedata.milbert.com>) - Massive collection (many gigabytes) of scanned original tube data sheets and technical information.

Retrieved from "http://en.wikipedia.org/w/index.php?title=Tube_sound&oldid=543108943"

Categories: [Valve amplifiers](#) | [Vacuum tubes](#) | [High-end audio](#) | [Audio amplifiers](#) | [Audio engineering](#)

- This page was last modified on 9 March 2013 at 23:49.
- Text is available under the Creative Commons Attribution-ShareAlike License; additional terms may apply. By using this site, you agree to the Terms of Use and Privacy Policy. Wikipedia® is a registered trademark of the Wikimedia Foundation, Inc., a non-profit organization.

PUBLIC



Electronics About.com Home Theater

Share

Vacuum Tube Rebels

Vacuum Tube Audio In The 21st Century (So Far)

By [Robert Silva](#), About.com Guide

Free Home Theater Newsletter!

Sign Up

[Discuss in my forum](#)

In the 21st century, we marvel at the wonders of the new technologies that have made our life easier and more enjoyable. In home electronics and home theater these days, "digital" rules. From the humble beginnings of the [transistor](#) we now have everything from microprocessors to such digital products as the [CD](#), [SACD](#), [DVD Video](#), [DVR/PVR](#), [HDTV](#), [Blu-ray Disc](#), [Network Media Players/Streamers](#), and of course, we can't overlook the extremely popular [iPod](#). But many of us still remember the analog world of the [Vacuum Tube](#), the trusted workhorse that started the whole home electronics boom in the first place.

The Eastern European Connection

Believe it or not, the vacuum tube is not only still with us (television CRTs are a type of vacuum tube), but as a side benefit of the fall of Eastern Europe and The Soviet Union, the traditional vacuum tube is becoming a more common site in Western high-end audio products. With U.S. and Asian companies firmly entrenched in production of digital solid state devices, countries that had previously been behind the digital curve such as [Russia, Eastern Europe, and even China](#) still have large tube manufacturing facilities and thus, have been producing and exporting vacuum tubes to the West more freely in the last decade or so. As a result, the high end audio market has tapped into this phenomenon like gangbusters.

Vacuum Tube HiFi Components

Many "true" audiophiles have never been completely satisfied with the sound quality and performance of transistors and integrated circuits, therefore, a niche market has opened up for vacuum tube audio equipment. Manufacturers, such as [Audio Research](#), [Cary Audio](#), [ECP Audio](#), [Granite Audio](#), [Manley Labs](#), [McIntosh](#), [Rogue Audio](#), and [others](#) are also quenching the thirst for vacuum tube products with their exceptional lineup of home audio equipment.

In fact, even the iPod hasn't escaped the vacuum tube treatment as [there are now an ever-growing assortment of iPod vacuum tube audio systems](#)

Home Theater Applications

The Vacuum Tube has also made its way into the home theater environment, with products, such as: The [Jolida Vacuum Tube CD Player](#), and the [Rockford Fosgate FAP-V1 5.1 Channel/Dolby Pro-Logic II Preamp](#). Add a multi-channel hybrid vacuum tube power amplifier, such as the [Butler Audio Model 5150](#), and you can have a vacuum tube based home theater audio system.

Vacuum tube audio for home theater hasn't gone unnoticed by big player Samsung, who has introduced a line of vacuum products, including an [Audio Dock and two Home Theater-in-a-Box Systems](#).

Vacuum Tubes In Your Ear and On The Road

In addition to home audio and home theater vacuum tube-based products, other innovative applications for vacuum tubes in audio also include the [Apex Audio](#) and [Vincent Audio](#) Vacuum Tube Headphone Amplifiers. Also, for those who can't leave their vacuum tubes at home, companies such as [Butler Audio \(Tube Driver\)](#) and [Milbert Amplifiers](#) produce a line of unique vacuum tube car audio products.

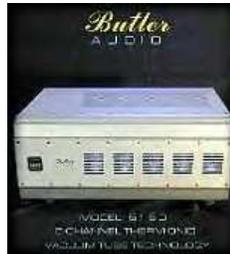
Sources For News and Information On Vacuum Tube Products

There are several print and online publications, including [Audiophilia](#), [The Absolute Sound](#), [Superior Audio](#), and [Stereophile Magazine](#) that regularly present and review vacuum tube audio products.

The Vacuum Tube Lives On

Even with all the emphasis on digital technology in the new century, the vacuum tube is making a big comeback with audio aficionados (or did it really ever leave?). Some say that the warm, glowing sound of a good vacuum tube amplifier has no equal.

I still have fond memories (early 70's) of owning a [Dynaco Stereo-70](#) tube power-amp which, today, is considered a true "classic" **PUBLIC** technology. Its design changed through the years and was discontinued for a time, but has now been revived with a new design, at a much higher price than I would have paid in my college years. [Check out a review of the Dynaco Stereo-70 by Stereophile Magazine](#).



Butler Audio 5150 5-channel Vacuum Tube Hybrid Power Amplifier

Image (c) Butler Audio

Exhibit **T153**
Skold v. Galderma
Cancellation No. 92052897

Supported by continuing loyalty from the audiophile community and audiophile press, in addition to increased profits for Russian, Eastern European, and Chinese suppliers, the vacuum tube's continued success might just be insured, despite the digital revolution.

Do you own any "classic" vacuum tube audio products or a new high-end vacuum tube product? If you would like to share your experiences with these products or just throw in your two-cents on the virtues of vacuum tube technology, post to my [Vacuum Tube Audio Forum](#).

Top Related Searches [Home Theater Applications](#) [True Audiophiles](#) [Pro Logic II](#) [Rockford Fosgate](#) [Vacuum Tubes](#) [Digital Curve](#)

3. The objections listed above are not intended to be exhaustive. Registrant objects to each of the prefatory statements, definitions, and instructions, and Petitioner's Requests to the extent that they impose obligations upon Registrant that exceed those required by the Federal Rules of Civil Procedure, the Federal Rules of Evidence, Title 37 of the Code of Federal Regulations, any order of the Trademark Trial and Appeal Board, or any other applicable law.

Registrant incorporates by reference to each and every Response to Petitioner's Requests herein, the General Objections set forth above.

SUPPLEMENTAL RESPONSES TO REQUESTS FOR ADMISSIONS

Request for Admission No. 1:

Registrant did not use the term Restoraderm in commerce in connection with any product prior to February 28, 2002.

Response:

Subject to and without waiving the general objections, Registrant responds as follows: Admitted.

Request for Admission No. 2:

Registrant did not use the term Restoraderm in commerce in connection with any product prior to February 11, 2002.

Response:

Subject to and without waiving the general objections, Registrant responds as follows: Admitted.

Request for Admission No. 3:

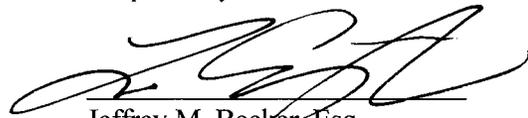
Registrant did not use the term Restoraderm in commerce in connection with any product prior to September 11, 2001.

Response:

Subject to and without waiving the general objections, Registrant responds as follows: Admitted.

Date: April 24, 2013

Respectfully submitted,



Jeffrey M. Becker, Esq.

Lisa N. Congleton, Esq.

Attorneys for Registrant

HAYNES AND BOONE, LLP

2323 Victory Avenue, Suite 700

Dallas, Texas 75219

Telephone: 214-651-5262

Facsimile: 214-200-0765

lisa.congleton@haynesboone.com

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD**

Exhibit T155 Skold v. Galderma Cancellation No. 92052897

Thomas Sköld
Petitioner,

v.

Galderma Laboratories, Inc.
Registrant.

§
§
§
§
§
§

Cancellation No.: 92052897

Mark: RESTORADERM

Reg. Nos.: 2,985,751 and 3,394,514

**REGISTRANT’S SUPPLEMENTAL RESPONSE TO PETITIONER
SKÖLD’S FIRST AND SECOND SETS OF INTERROGATORIES AND
REQUESTS FOR PRODUCTION OF DOCUMENTS AND THINGS**

Pursuant to the provisions of: (a) 37 C.F.R. §§ 2.116(a) and 2.120, Rule 33 of the Federal Rules of Civil Procedure, T.B.M.P. §§ 403.02 and 408.01; and (b) 37 C.F.R. §§ 2.120, Rule 34 of the Federal Rules of Civil Procedure and T.B.M.P. §§ 403.03 and 408.01, Galderma Laboratories, Inc. (“Registrant”) herewith responds to Thomas Sköld’s (“Petitioner”) First and Second Sets of Interrogatories (“Interrogatory” or “Interrogatories”) and Requests for Production of Documents and Things (“Request” or “Requests”) as follows:

GENERAL OBJECTIONS

1. Registrant objects to Petitioner’s Interrogatories and Requests to the extent that they seek to impose obligations beyond those imposed by Rule 26 of the Federal Rules of Civil Procedure. In particular, Rule 26(b) limits the scope of discovery to “any matter, not privileged, which is relevant to the subject matter involved in the pending action.”

2. Registrant objects to any specific Interrogatory or Request to the extent that it seeks information subject to (i) the attorney-client privilege, (ii) the attorney work product doctrine, (iii) the protection afforded consulting experts pursuant to Federal Rule of Civil Procedure 26(b)(4)(B), (iv) the self-critical analysis privilege, (v) the investigative privilege, (vi) the party communications privilege, (vii) the witness statement privilege, or (viii) any other privilege or protection afforded by state or federal law. To the extent that an Interrogatory or Request can be construed as seeking information subject to such privileges, or any other privilege afforded by law, Registrant hereby claims such privilege and/or invokes the attorney work product doctrine.

3. Registrant objects to any specific Interrogatory or Request to the extent it calls for information that is publicly available to Petitioner because such Interrogatory or Request is unduly burdensome, oppressive, and annoying since Petitioner has access to such information.

4. Registrant objects to any specific Interrogatory or Request to the extent that it seeks information other than that which may be obtained through a reasonably diligent search of its records.

5. Registrant objects to each Interrogatory or Request to the extent that it seeks information not within Registrant's possession, custody, or control.

6. Registrant objects to the use of "all," "each," and the like in Petitioner's Interrogatories and Requests, to the extent same renders the Interrogatories and Requests overly broad and unduly burdensome. Unless otherwise indicated by objection, Registrant will provide information and documents that Registrant was able to locate as a result of a comprehensive search of Registrant's business records. However, where the scope of information requested is unduly burdensome, Registrant will respond by representative information only, as sanctioned by the Board. To the extent that Registrant produces any such document, it does not concede that the document produced is relevant to this action. Respondent produces the documents without waiving or intending to waive any objection to competency, relevancy, or admissibility as evidence of any matter referred to or made the subject of any answer provided, including at the trial of this action.

7. Registrant objects to the Petitioner's definition of "identify," when used in reference to a natural individual, as including the individual's home address, on grounds that such information is not reasonably calculated to lead to the discovery of admissible evidence. Where Registrant has identified, and where it will identify, an individual, Registrant will provide that individual's business address only, if the individual has a known business address.

8. Registrant objects to Petitioner's definition of "identify" and "identification" when used with respect to a document for which Registrant claims privilege as overly broad, unduly burdensome, oppressive, not reasonably calculated to lead to the discovery of admissible evidence, and harassing.

9. Registrant objects to any specific Interrogatory or Request to the extent that it seeks information pertaining to Registrant's non-use of, or intent not to resume use of, the trademark RESTORADERM. The Board's order of November 8, 2012, dismissing with prejudice Petitioner's claim of abandonment of Registrant's U.S. Trademark Registration No. 2,985,751, conclusively forecloses an argument that the information objected to is either relevant to this matter or reasonably calculated to lead to the discovery of admissible evidence.

10. Registrant objects to Instruction No. 3 to the extent that it purports to impose obligations upon Registrant that exceed those required by the Federal Rules of Civil Procedure, the Federal Rules of Evidence, Title 37 of the Code of Federal Regulations, any order of the Trademark Trial and Appeal Board, or any other applicable law, particularly because it cites Rules 4:17-7 and 4:17-8, which do not

refer to any known rules of procedure or evidence applicable to Board proceedings or in federal litigation as governing Registrant's duties and obligations relating to discovery responses.

11. Registrant objects to Definition Nos. 1 and No. 2, defining the terms "2002 Agreement" and "2004 Agreement," respectively, as vague and ambiguous as the defined terms refer to documents not identified with specificity. In this regard, Registrant notes that, while Registrant is aware of a 2002 agreement entitled "Co-Operation, Development and Licensing Agreement" and a 2004 agreement entitled "Asset Purchase and Product Development Agreement," the parties have not yet stipulated that a particular version or copy of each such agreement is true and correct or that the parties' references to the "2002 Agreement" or the "2004 Agreement" identify such true and correct copies of the originals. Subject to and without waiving the foregoing objection, Registrant states that, for purposes of Registrant's responses herein, Registrant relies upon documents found in its own records, including an agreement entitled "Co-Operation, Development and Licensing Agreement" dated February 11, 2002 and an agreement entitled "Asset Purchase and Product Development Agreement" dated August 19, 2004, and refers to them as Petitioner does as the "2002 Agreement" and the "2004 Agreement," respectively.

12. Registrant expressly reserves the right to amend, supplement, or change its responses and objections to Petitioner's Interrogatories and Requests with information learned in the course of further investigation and discovery.

13. The objections listed above are not intended to be exhaustive. Registrant objects to each of the prefatory statements, definitions, and instructions, and Petitioner's Interrogatories and Requests to the extent that they purport to impose obligations upon Registrant that exceed those required by the Federal Rules of Civil Procedure, the Federal Rules of Evidence, Title 37 of the Code of Federal Regulations, any order of the Trademark Trial and Appeal Board, or any other applicable law.

Registrant incorporates by reference to each and every Response to Petitioner's Interrogatories and Requests herein, the General Objections set forth above.

RESPONSES TO INTERROGATORIES

Interrogatory No. 4:

Describe in detail how the term “Restoraderm” was first conceived of.

Response:

Registrant objects to this Interrogatory on the grounds that it is vague and ambiguous. Registrant further objects to the extent this Interrogatory seeks information that is neither relevant to this matter, nor reasonably calculated to lead to the discovery of admissible evidence.

Subject to and without waiving the foregoing objections and the general objections, Registrant responds as follows. Registrant has no knowledge regarding how the term “Restoraderm” was first conceived of.

Interrogatory No. 5:

Describe each product that has been marketed under the mark “Restoraderm”.

Response:

Registrant objects to this Interrogatory on the grounds that it is vague and ambiguous, especially with respect to the meaning of the term “marketed.” Registrant further objects to the extent this Interrogatory seeks information that is neither relevant to this matter, nor reasonably calculated to lead to the discovery of admissible evidence.

Subject to and without waiving the foregoing objections and the general objections, Registrant responds as follows. Registrant advertises, offers for sale, and sells two RESTORADERM-branded products in the United States in retail stores nationwide: RESTORADERM Skin Restoring Body Wash and RESTORADERM Skin Restoring Moisturizer. The products were specifically designed to work together as a daily regimen to provide continuous relief for those struggling with atopic dermatitis and/or eczema-prone skin.

Interrogatory No. 6:

State the date of, and describe in detail the circumstances of, Registrant's first use of the mark "Restoraderm" in commerce in connection with the sale, offering for sale, distribution, or advertising of a dermatology product.

Response:

Subject to and without waiving the general objections, Registrant responds as follow. Registrant began using the mark "Restoraderm" in commerce in connection with the sale, offering for sale, distribution, or advertising of a dermatology product at least as early as May 27, 2005. Additional details regarding the circumstances of such first use can be found in the Statement of Use filed by CollaGenex Pharmaceuticals, Inc. on June 6, 2005 in connection with U.S. Trademark Registration No. 2,985,751, which is of record in this proceeding pursuant to 37 C.F.R. 2.122(b).

Interrogatory No. 7:

State the date of, and describe in detail the circumstances of, Registrant's first use of the mark "Cetaphil Restoraderm" in commerce in connection with the sale, offering for sale, distribution, or advertising of a dermatology product.

Response:

Registrant objects to this Interrogatory on the grounds that it is vague and ambiguous. Registrant specifically objects that the phrase "the mark 'Cetaphil Restoraderm'" is vague and ambiguous.

Subject to and without waiving the foregoing objections and the general objections, Registrant responds as follows. Registrant began using the mark "Cetaphil Restoraderm" in commerce in connection with the sale, offering for sale, distribution, or advertising of a dermatological product at least as early as January 2010, as described in the Declaration of Cindy Kee filed in support of Registrant's Motion for Summary Judgment on April 27, 2012.

Interrogatory No. 8:

Describe in detail all facts and identify all documents and things showing that the mark Restoraderm was irrevocably assigned in either the 2002 or 2004 Agreement, which facts, document or things are in addition to the 2002 Agreement and the 2004 Agreement themselves.

Response:

Registrant objects to this Interrogatory on the ground that complete compliance with “all facts and . . . all documents and things” is overly broad and unduly burdensome. Registrant further objects to the extent this Interrogatory seeks information that is neither relevant to this matter, nor reasonably calculated to lead to the discovery of admissible evidence. Moreover, Registrant objects to the extent that the Interrogatory calls for a legal conclusion.

Subject to and without waiving the foregoing objections and the general objections, Registrant responds as follows. Petitioner’s documents SKOLD-000775 – SKOLD-000810 and an email from Petitioner dated August 18, 2004, which Petitioner produced to Registrant in connection with this proceeding, evidence that the parties intentionally excluded the RESTORADERM trademark from the 2004 Agreement and that the parties decided to do so because both parties explicitly acknowledged that CollaGenex had always owned the RESTORADERM trademark and, therefore, there was no need for CollaGenex to purchase the RESTORADERM trademark from Petitioner.

Further, the behavior of, and correspondence between, the parties beginning in late 2001 and extending through to the initiation of the current proceeding supports Registrant’s allegations that, pursuant to the 2002 Agreement, all trademark rights in the RESTORADERM mark arising before or after the execution the 2002 Agreement were and would thereafter be owned solely by CollaGenex. Such behavior is evidenced by numerous documents Petitioner has produced. In this regard, Registrant reiterates its objection that compliance with “all facts and . . . all documents and things” is overly broad and unduly burdensome.

Interrogatory No. 9:

Describe in detail all facts and identify all documents and things showing that the mark Restoraderm was assigned in either the 2002 Agreement or the 2004 Agreement, without contingency that the full measure of contemplated consideration being paid, which facts, document or things are in addition to the 2002 Agreement and the 2004 Agreement themselves.

Response:

Registrant objects to this Interrogatory on the ground that complete compliance with “all facts and . . . all documents and things” is overly broad and unduly burdensome. Registrant further objects to the extent this Interrogatory seeks information that is neither relevant to this matter, nor reasonably calculated to lead to the discovery of admissible evidence. Moreover, Registrant objects to the extent that the Request calls for a legal conclusion.

Subject to and without waiving the foregoing objections and the general objections Registrant responds as follows. Facts responsive to this Interrogatory No. 9 are encompassed in Registrant’s response to Interrogatory No. 8.

Interrogatory No. 26:

Describe all facts and identify all documents and things relating to Galderma’s decision that it could retain the Restoraderm trademark it nominally acquired from CollaGenex.

Response:

Registrant objects to this Interrogatory on the grounds that it is vague and ambiguous. Registrant further objects to this Interrogatory on the ground that complete compliance with “all facts and . . . all documents and things” is overly broad and unduly burdensome. Moreover, Registrant objects to this Interrogatory to the extent that it is premised upon certain factual and legal conclusions that are at issue in this Cancellation. Registrant specifically objects to the use of the term “nominally” to describe Registrant’s acquisition of the RESTORADERM trademark, and the use of the phrase “decision that it

could retain the Restoraderm trademark” to characterize the circumstances surrounding Registrant’s acquisition and ownership of the RESTORADERM trademark.

As discussed by counsel for the parties, Registrant responds to this Interrogatory No. 26 based on its understanding that Interrogatory No. 26 pertains generally to the circumstances surrounding Registrant’s acquisition and ownership of the RESTORADERM trademark.

Subject to and without waiving the foregoing objections and the general objections, Registrant responds as follows. The 2002 Agreement between CollaGenex and Petitioner stated that CollaGenex was the sole owner of the trademark RESTORADERM during the term of the 2002 Agreement and thereafter, thereby negating any need for Registrant to make a decision regarding the retention of the trademark RESTORADERM.

Interrogatory No. 27:

Describe all facts and identify all documents and things relating to Galderma’s decision to relinquish the patent estate assigned to Sköld by the Assignment of Patents dated February 22, 2010 and the product identified for return to Sköld in the Jim Wallace email dated February 8, 2010.

Response:

Registrant objects to this Interrogatory on the grounds that it is vague and ambiguous. Registrant specifically objects that the documents referred to as “Assignment of Patents dated February 22, 2010” and “Jim Wallace email dated February 8, 2010” are not identified with specificity.

Registrant further objects to this Interrogatory on the ground that complete compliance with “all facts and . . . all documents and things” is overly broad and unduly burdensome. Moreover, Registrant objects to the extent this Interrogatory seeks information that is neither relevant to this matter, nor reasonably calculated to lead to the discovery of admissible evidence.

Subject to and without waiving the foregoing objections and the general objections, Registrant responds as follows. As of February 22, 2010, it was Registrant’s understanding that the patent estate identified in the Assignment of Patents entered into between Registrant and Petitioner dated as of

February 22, 2010 was among the assets purchased pursuant to the 2004 Agreement. Following Registrant's termination of the 2004 Agreement, Registrant believed that paragraph 8.5(b) of the 2004 Agreement required it to assign the patent estate to Petitioner.

Interrogatory No. 30:

Describe all facts and identify all documents and things relating to any inquiries to Galderma from third parties, including consumers, indicating or suggesting confusion between Registrant's Mark and the technology and compositions that Petitioner terms RESTORADERM Technology or the these third parties associate with Petitioner.

Response:

Registrant objects to this Interrogatory on the grounds that it is vague and ambiguous. Registrant further objects to this Interrogatory on the ground that complete compliance with "all facts and . . . all documents and things" is overly broad and unduly burdensome. Moreover, Registrant objects to the extent this Interrogatory seeks information that is neither relevant to this matter, nor reasonably calculated to lead to the discovery of admissible evidence.

Subject to and without waiving the foregoing objections and the general objections, Registrant responds as follows. Registrant is aware of no facts, documents, or things responsive to this Interrogatory No. 30.

Date: April 24, 2013

Respectfully submitted,



Jeffrey M. Becker, Esq.

Lisa N. Congleton, Esq.

Attorneys for Registrant

HAYNES AND BOONE, LLP

2323 Victory Avenue, Suite 700

Dallas, Texas 75219

Telephone: 214-651-5262

Facsimile: 214-200-0765

lisa.congleton@haynesboone.com

VERIFICATION

I hereby swear that I have reviewed the above and foregoing *Registrant's Supplemental Response to Petitioner Sköld's First and Second Sets of Interrogatories and Requests for Production of Documents and Things*, I have personal knowledge of the information provided in these requests, and I believe the answers are true and correct to the best of my knowledge.

Art Clapp
Director of Business Development of
Galderma Laboratories, L.P.

Sworn to and subscribed before me on this _____ day of April, 2013.

Notary Public

Printed Name of Notary
Commission Expires _____

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD**

Thomas Sköld
Petitioner,

v.

Galderma Laboratories, Inc.
Registrant.

§
§
§
§
§
§

Cancellation No.: 92052897

Mark: RESTORADERM

Reg. Nos.: 2,985,751 and 3,394,514

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on this 24th day of April, 2013, the foregoing *Registrant's Supplemental Response to Petitioner Sköld's First and Second Sets of Interrogatories and Request for Production of Documents and Things* was served on Petitioner's counsel of record, via email to the following:

Arthur E. Jackson
Moser IP Law Group
artjcksn@gmail.com
docketing@mtiplaw.com



Lisa N. Congleton

PUBLIC

Exhibit **T155**
Skold v. Galderma
Cancellation No. 92052897

Declaration of Cindy Kee

EXHIBIT B



Atopic dermatitis: Deficiencies can lead to a compromised skin barrier

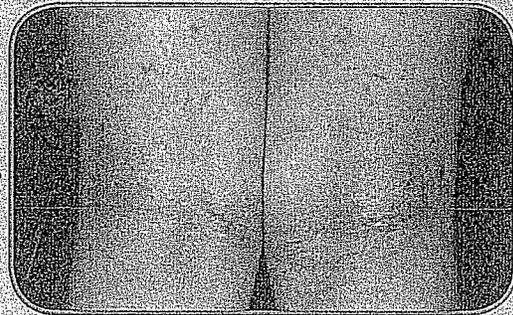
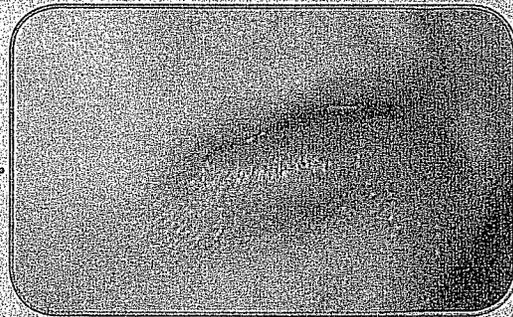
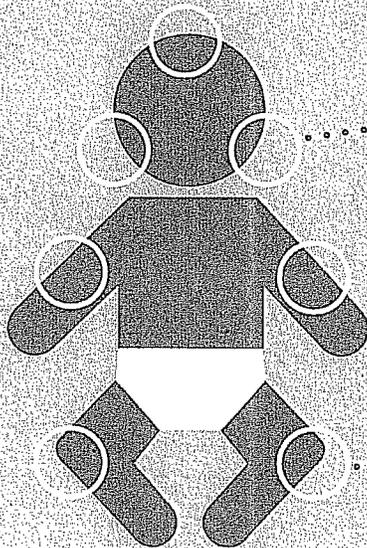


Filaggrin and ceramide deficiencies can occur in atopic dermatitis^{1,2}

- These deficiencies can lead to a compromised skin barrier^{1,2}
- Symptoms (dry, itchy rash) are the result of a compromised skin barrier³
 - These symptoms can lead to sleeplessness and irritability

In children, atopic dermatitis can occur all over the body

Patches commonly appear on the scalp, face and in the bends of the joints (knees and elbows)⁴



Photos provided by Dr. Joseph Bikowski



Cetaphil® RestoraDerm® products: uniquely formulated to meet the needs of atopic dermatitis patients



Patented technologies help replenish the skin barrier

Filaggrin technology™ works to improve hydration, which helps restore skin barrier function^{2,3,5}

Ceramide technology enhances the skin's natural ability to retain moisture⁶

Proven to significantly restore skin barrier function
(compared with baseline) over 4 weeks

- Decreased transepidermal water loss (TEWL)⁵
- Increased hydration as assessed by corneometry⁵

Provides proven symptom relief for your patients

- Soothes the dry, itchy skin of eczema⁵
- Proven highly tolerable on atopic skin⁵



Cetaphil® RESTORADERM®

PUBLIC

ATOPIC DERMATITIS: Results in skin barrier dysfunction

Filaggrin: A protein deficiency in atopic skin

~ Filaggrin deficiency compromises barrier function, leaving skin vulnerable to irritants and allergens¹

Ceramides: Lipid deficiency in atopic skin

~ Reduced levels of ceramides 1 and 3 cause excess water loss and a damaged skin barrier¹

Cetaphil® RESTORADERM® Skin Restoring Moisturizer and Body Wash: The first and only products with ceramide AND Filaggrin technology™

Filaggrin technology™ helps restore moisture to help rebuild the damaged skin barrier^{1,2}

Ceramide technology increases ceramides 1, 2 and 3³

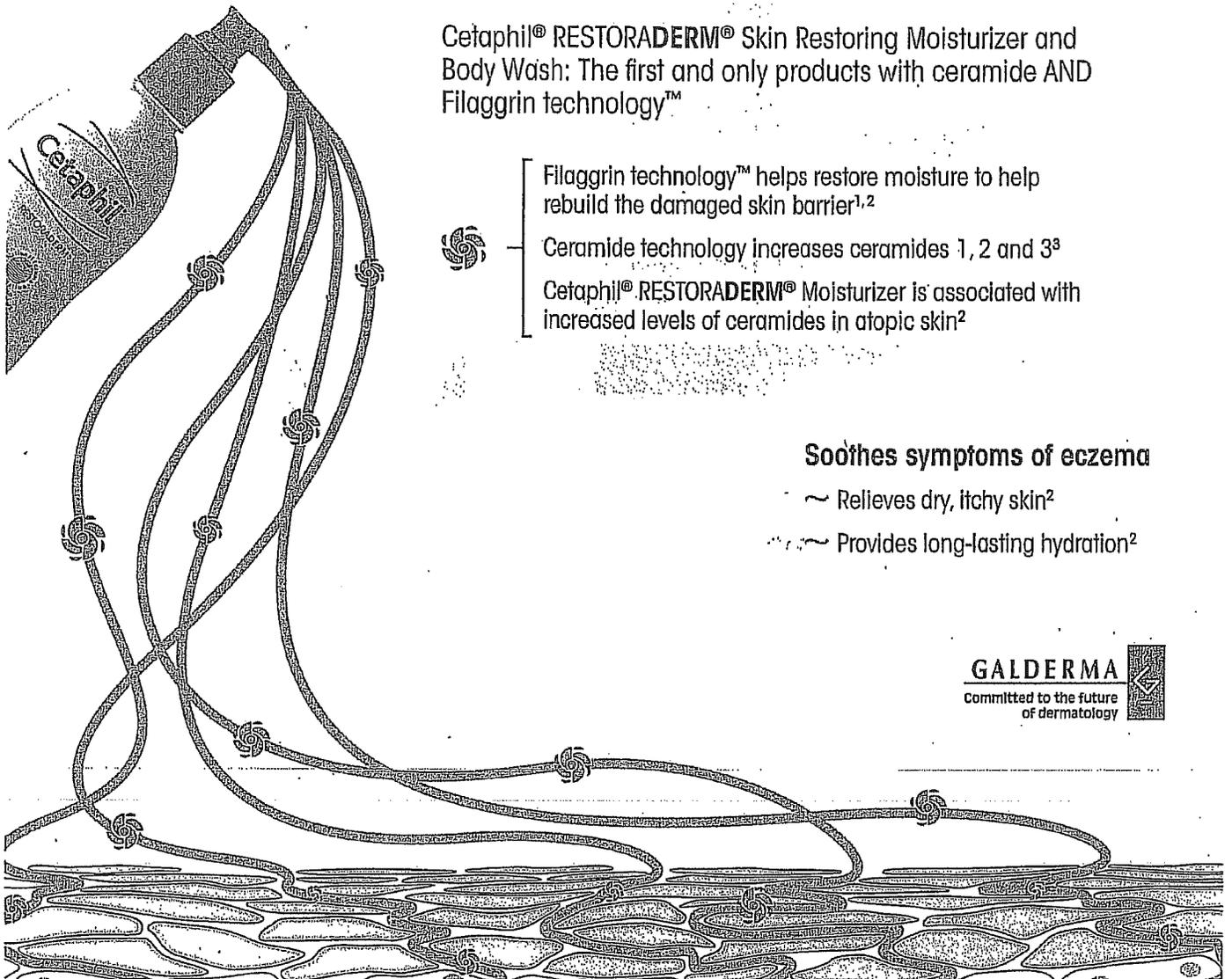
Cetaphil® RESTORADERM® Moisturizer is associated with increased levels of ceramides in atopic skin²

Soothes symptoms of eczema

~ Relieves dry, itchy skin²

~ Provides long-lasting hydration²

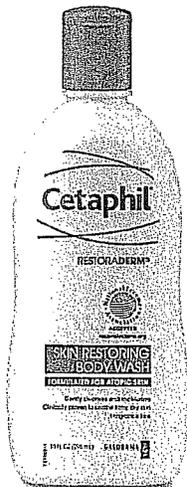
GALDERMA
Committed to the future
of dermatology



Proven results in ^{PUBLIC} atopic patients



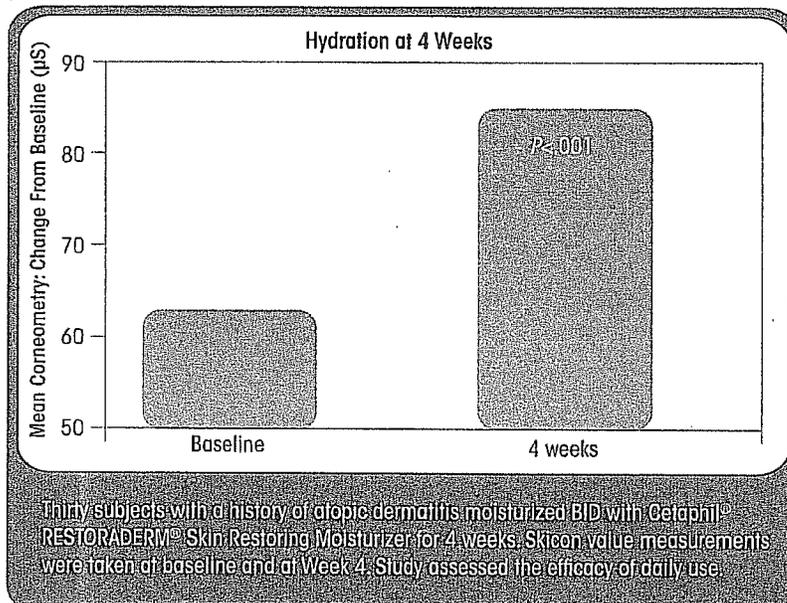
Safe for use in children as young as 3 months²



Cetaphil® RESTORADERM® Skin Restoring Moisturizer

- ~ Reduces and prevents dryness to help break the itch-scratch-itch cycle²
- ~ Clinically proven to help restore skin barrier function²
- ~ Provides long-lasting hydration for atopic skin²

▶ Significantly increased hydration after 4 weeks²



Gentle enough to bathe atopic skin— Cetaphil® RESTORADERM® Skin Restoring Body Wash²

- ~ Encapsulates skin-nourishing oils in a soap-free foaming wash²
- ~ Helps soothe itch and reduces redness, dryness and irritation²
- ~ Maintains skin barrier function and prevents transepidermal water loss²

Cetaphil® RESTORADERM® products are proven non-irritating on atopic skin²

- ~ Contain no preservatives, fragrances, nut oils, parabens or lanolin²
- ~ High patient satisfaction—up to 92% of patients reported they would continue using Cetaphil® RESTORADERM®²



Cetaphil®
RESTORADERM®
Replenish. Restore. Rebuild.



The National Eczema Association (NEA) Seal of Acceptance is awarded to products that have been created or intended for use by persons with eczema or severe sensitive skin conditions and have satisfied the NEA Seal of Acceptance Criteria. NEA has awarded the Seal of Acceptance to these products with a 4 out of 5 rating. Read the label to determine if these products contain ingredients that may be unsuitable for your skin. Visit nationaleczema.org for more information.

PULL

PUBLIC

Complete formula for atopic skin²

	Formulated for Atopic Skin	Ceramides	Filaggrin Proteins	Niacinamide	Sunflower Seed Oil	Glycerin	Shea Butter
Cetaphil® RESTORADERM® Skin Restoring Moisturizer	✓	✓	✓	✓	✓	✓	✓
Cetaphil® RESTORADERM® Skin Restoring Body Wash	✓		✓	✓	✓	✓	✓
CeraVe® Body Moisturizers and Cleanser		✓				✓	
Eucerin® Calming Crème						✓	
Aveeno® Advanced Care		✓				✓	

Available at locations nationwide, including:

- ~ CVS
- ~ Duane Reade
- ~ Rite Aid
- ~ Walgreens
- ~ Walmart

PULL

Look for Cetaphil® RESTORADERM® in the skin care aisle

- ~ Average retail price: **\$13.99-\$14.99**
- ~ Available in **10 fl oz bottles**



www.cetaphil.com

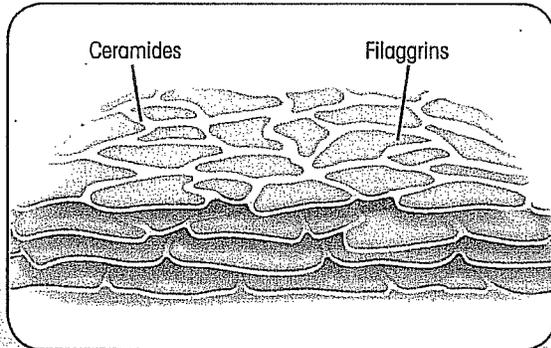
References: 1. Sugarman JL. The epidermal barrier in atopic dermatitis. *Semin Cutan Med Surg.* 2008;27:108-114. 2. Data on file. Galderma Laboratories. All trademarks are property of their respective owners. © 2011 Galderma Laboratories, L.P. Galderma Laboratories, L.P., 14501 N. Freeway, Fort Worth, TX 76177 CETA-242 Printed in USA 01/11



Cetaphil
RESTORADERM®
Replenish. Restore. Rebuild.

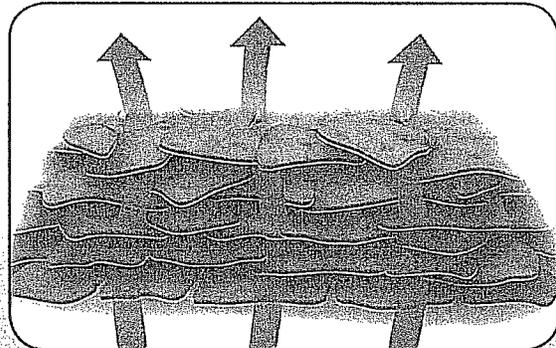
PUBLIC
Atopic dermatitis: The result of a skin barrier dysfunction

HEALTHY SKIN

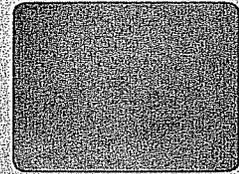


- ~ Ceramides are lipids in the stratum corneum¹
- ~ Filaggrins are proteins in the stratum corneum¹

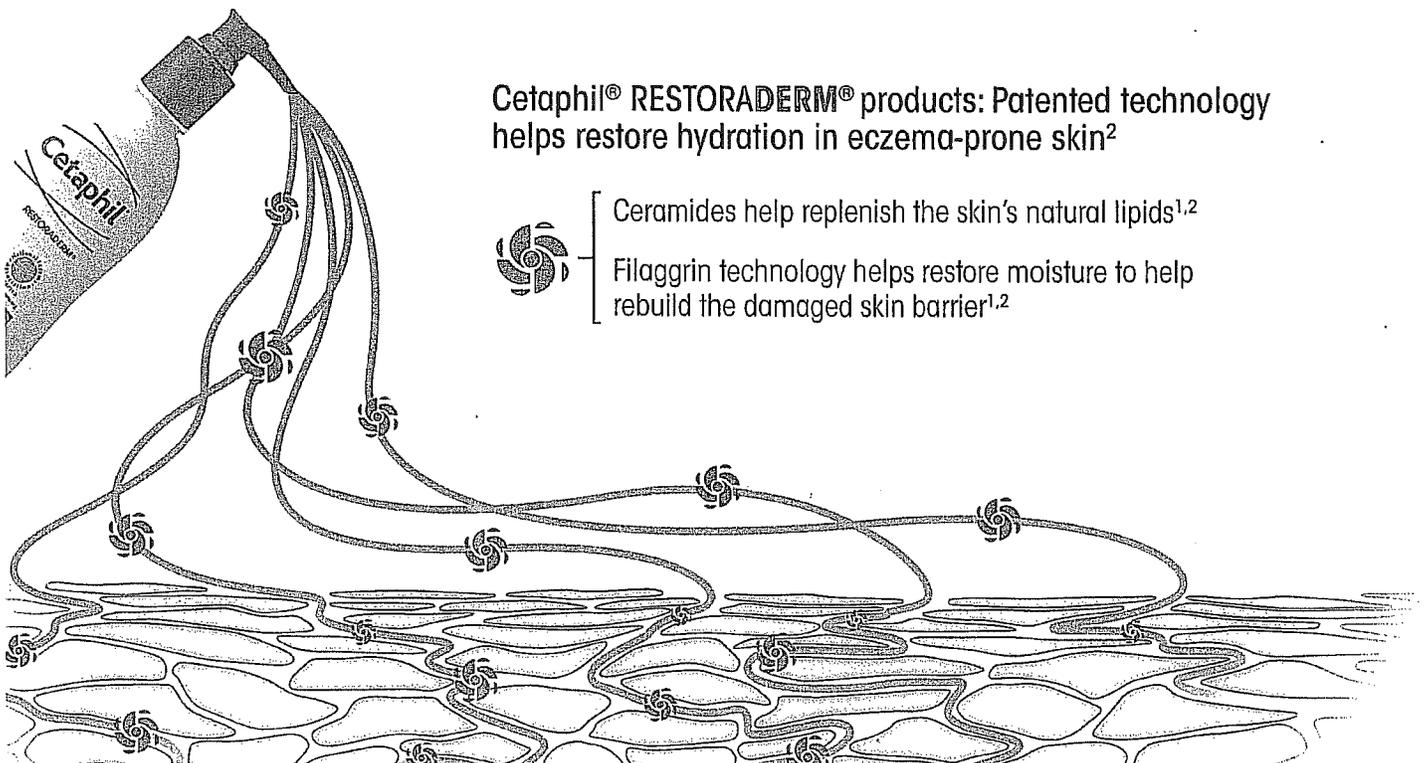
ATOPIC DERMATITIS—A FORM OF ECZEMA



- ~ Reduced levels of ceramides result in damaged skin barrier and excessive water loss¹
- ~ Filaggrin deficiency compromises barrier function, leaving skin vulnerable to irritants and allergens¹



Now replenish skin at the structural level



Cetaphil® RESTORADERM® products: Patented technology helps restore hydration in eczema-prone skin²



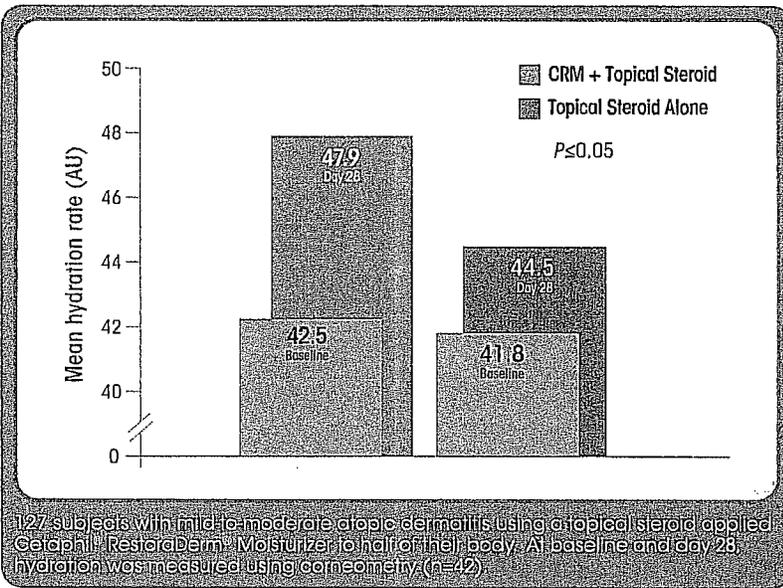
- Ceramides help replenish the skin's natural lipids^{1,2}
- Filaggrin technology helps restore moisture to help rebuild the damaged skin barrier^{1,2}



Improves hydration and decreases overall disease severity

Newly published data³
for Cetaphil® RestoraDerm® Moisturizer

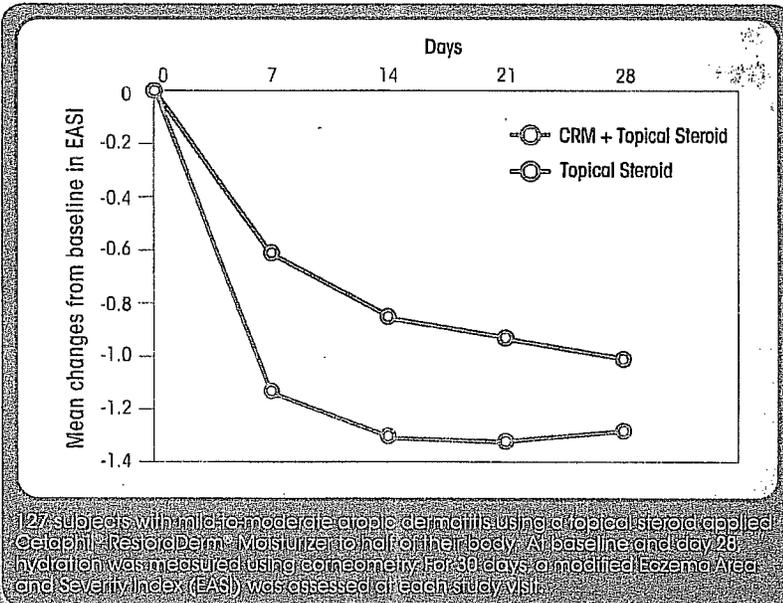
Significant hydration versus topical steroid treatment alone^{3,5}



Cetaphil® RestoraDerm® Moisturizer

Increases hydration when used with a topical steroid³

Decrease in overall disease severity compared with topical steroid treatment alone^{3,5}



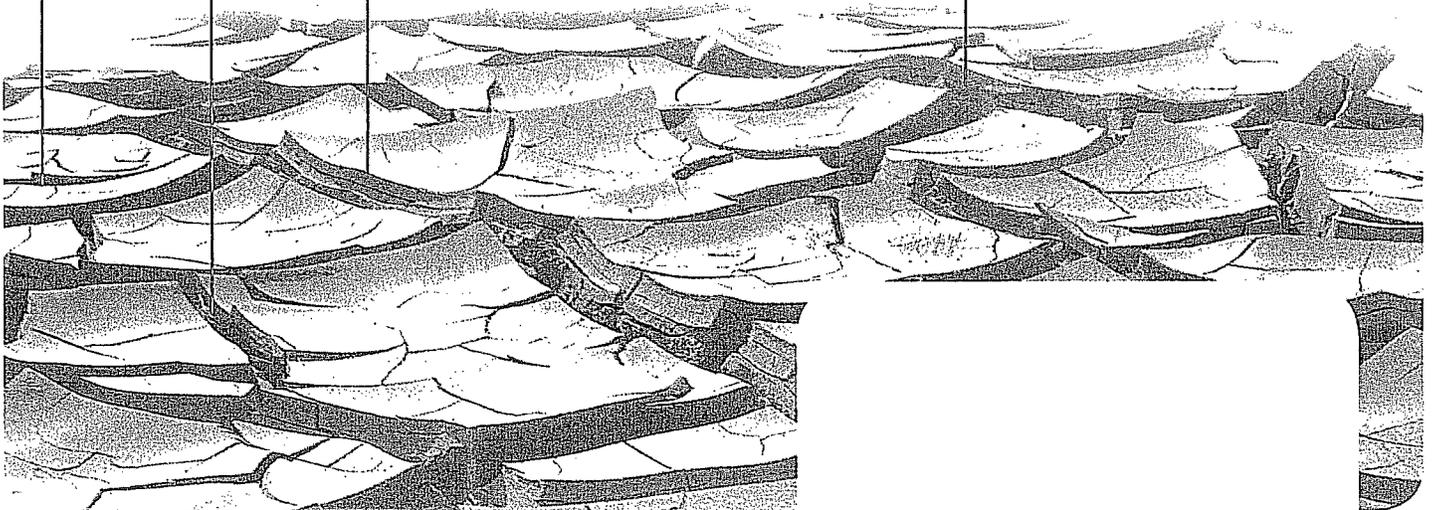
The Eczema Area and Severity Index (EASI)

A tool to measure the severity of atopic dermatitis

Structural deficiencies can lead to a compromised skin barrier in atopic dermatitis

Atopic skin may be deficient in filaggrin proteins and ceramides^{1,2}

- Lack of filaggrin proteins can result in fewer breakdown products¹
 - Filaggrin breakdown products are needed to form natural moisturizing factor (NMF)¹
 - A reduction of filaggrin-generated NMF results in reduced hydration and suppleness in the skin barrier¹
- Reduced levels of ceramides 1 and 3 cause excess water loss from the damaged skin barrier²



Typical atopic dermatitis presentation ▶

PUBLIC

Help rebuild the skin barrier with a skincare regimen including Cetaphil® RestoraDerm® products

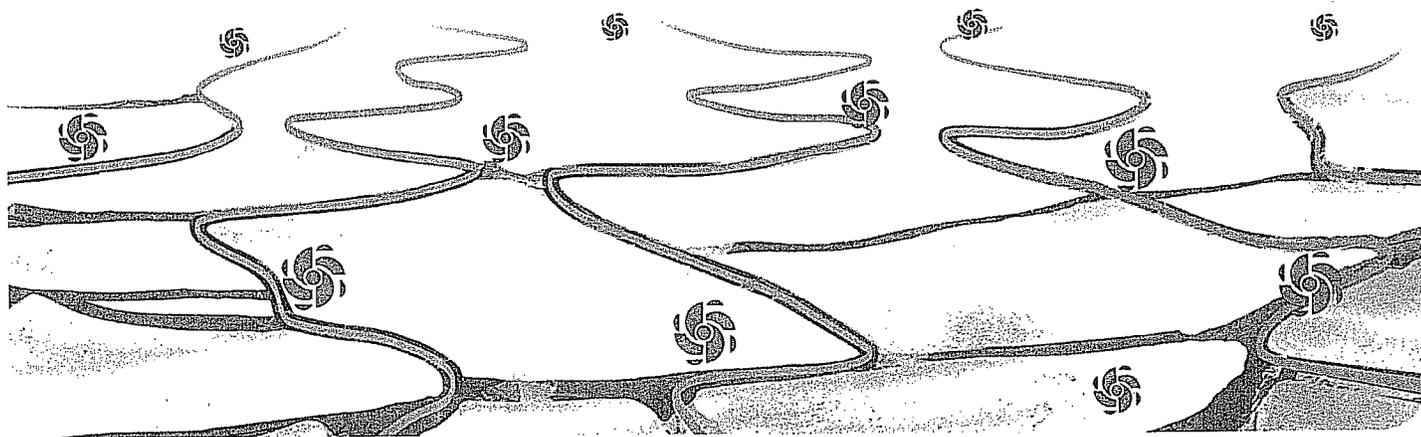
The first and only products with both ceramide and Filaggrin technology™

Filaggrin technology™

- Contains filaggrin breakdown products (sodium PCA and arginine) that help replenish NMF^{2,3}
- Leads to improved hydration, which helps restore skin barrier function⁴

Ceramide technology

- Increases ceramides 1, 2 and 3⁵
- Helps the skin retain moisture⁵



Proven to significantly restore skin barrier function (compared with baseline) over 4 weeks

- Decreased transepidermal water loss (TEWL) and increased hydration as assessed by corneometry⁴

Uniquely formulated to meet the needs of your atopic dermatitis patients

- Soothes the dry, itchy skin of eczema⁴
- Proven highly tolerable on atopic skin⁴



Cetaphil®

RESTORADERM®

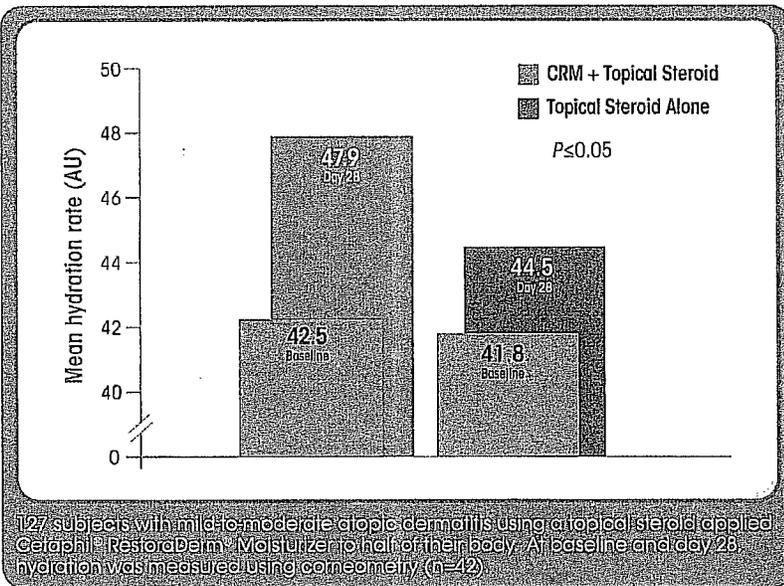


Improves hydration and decreases overall disease severity



Newly published data³
for Cetaphil® RestoraDerm® Moisturizer

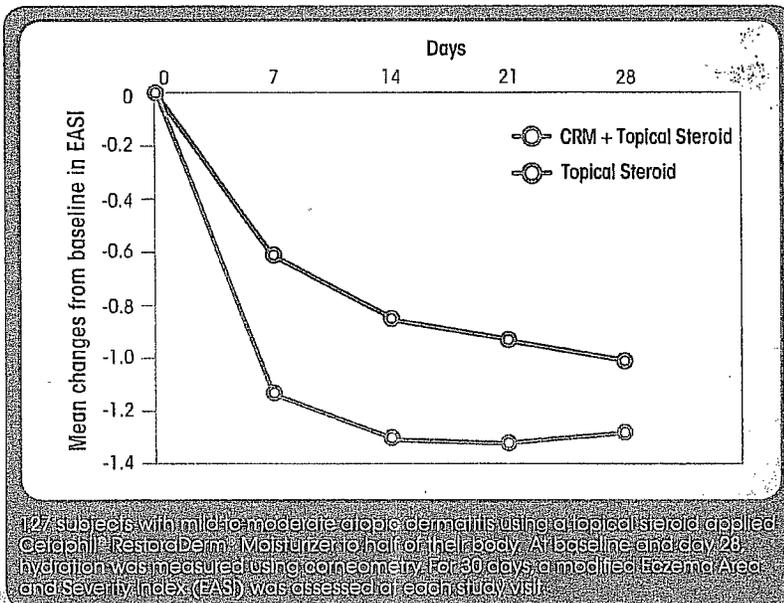
Significant hydration versus topical steroid treatment alone^{3,4}



Cetaphil® RestoraDerm® Moisturizer

Increases hydration when used with a topical steroid³

Decrease in overall disease severity compared with topical steroid treatment alone^{3,4}



The Eczema Area and Severity Index (EASI)

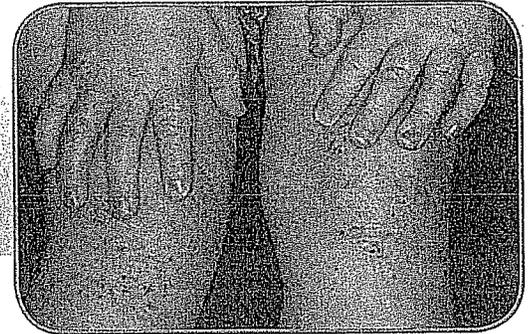
A tool to measure the severity of atopic dermatitis



Recommend Cetaphil® RestoraDerm® Body Wash and Moisturizer:
**the first and only products with both
 ceramide and Filaggrin technology™**



- Unique formulation contains ceramides and filaggrin breakdown products needed to restore and moisturize the compromised skin barrier^{2,5}
- Proven results in atopic patients—soothes the dry, itchy skin of eczema⁴



Typical atopic dermatitis presentation ▶

Photo provided by Dr. Joseph Bikowski

Cetaphil® RestoraDerm® products: SEE. SAMPLE. SEND.



SEE patients with atopic dermatitis



SAMPLE with a recommendation and a coupon for Cetaphil® RestoraDerm® products



SEND patients to CVS®, Walgreens®, Target® or Walmart® to purchase



References: 1. Chandar P, Nole G, Johnson AW. Understanding natural moisturizing mechanisms: Implications for moisturizer technology. *Cutis*. 2009;84(suppl 1):2-15. 2. Sugarman JL. The epidermal barrier in atopic dermatitis. *Semin Cutan Med Surg*. 2008;27:108-114. 3. Simpson E, Dutronc Y. A new body moisturizer increases skin hydration and improves atopic dermatitis symptoms among children and adults. *J Drugs Dermatol*. 2011;10:744-749. 4. Data on file, Galderma Laboratories. 5. Castiel-Higonenc I, Chopart M, Ferraris C. Stratum corneum lipids: specificity, role, deficiencies and modulation. *DCL*. 2004;11(6):401-406.

cetaphil.com



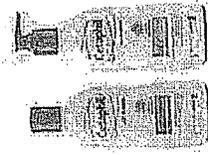
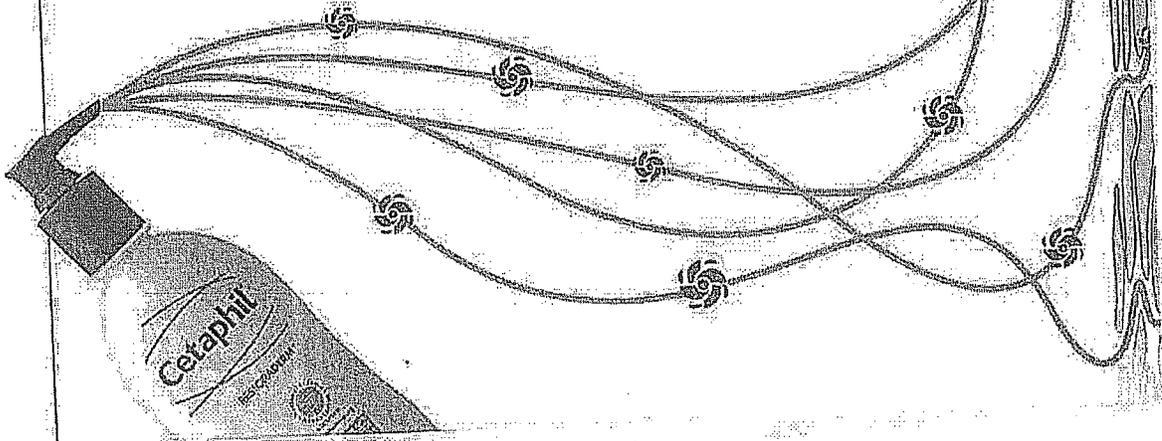
All trademarks are the property of their respective owners.
 © 2012 Galderma Laboratories, L.P.
 Galderma Laboratories, L.P., 14501 N. Freeway, Fort Worth, TX 76177
 CETA-385 Printed in USA 11/11

Cetaphil®
 RESTORADERM®
 Replenish. Restore. Rebuild.

PUBLIC

F O R A T O P I C D E R M A T I T I S

Cetaphil® RESTORADERM®
Daily Skin Care Management for Atopic Patients



Cetaphil®
RESTORADERM®
Replenish. Restore. Rebuild.

- ~ Atopic dermatitis is the most common childhood skin disease, affecting approximately 20% of children in the US
- ~ Approximately 65% of patients develop symptoms in the first year of life

Common skin signs and symptoms

- ~ Dryness ~ Itch ~ Swelling ~ Redness
- ~ Cracking ~ Crusting ~ Scaling

Atopic dermatitis can take a toll on both patient and family

- ~ Lack of sleep ~ Behavioral problems ~ Multiple doctor visits
- ~ Low self-esteem ~ Medication expenses



Question:

What is the most common symptom of atopic dermatitis?

Answer: *Dry, itchy skin*



Cetaphil
RESTOADERM
Replenish. Restore. Rebuild.

Atopic dermatitis: A chronic skin disease with significant impact

- ~ The most common childhood skin disease, affects approximately 20% of children in the US¹
- ~ Approximately 65% of patients develop symptoms in the first year of life²

Common skin signs and symptoms²

- ~ Dryness ~ Itch ~ Swelling ~ Redness
- ~ Cracking ~ Crusting ~ Scaling

Atopic dermatitis can take a toll on both patient and family^{2,3}

- ~ Lack of sleep
- ~ Low self-esteem
- ~ Behavioral problems
- ~ Medication expenses
- ~ Multiple doctor visits

In a skin care survey, approximately 52% of mothers described their children with eczema as being irritable.¹

From the survey Skin Care Preferences and Dealing With Eczema, conducted with over 1000 mothers of children with eczema in the US in June 2010.

Atopic Dermatitis



Cetaphil
RESTOADERM
Replenish. Restore. Rebuild.

- ~ A lipid is a fat or oil that has moisture-binding properties
- ~ A protein is composed of amino acids and is associated with growth, repair and maintenance of cells
- ~ The stratum corneum contains lipids and proteins called ceramides and filaggrin
- ~ Atopic skin is deficient in filaggrin and ceramides, resulting in a damaged skin barrier
- ~ Reduced level of ceramides results in a damaged skin barrier and excessive water loss
- ~ Filaggrin deficiency compromises barrier function, leaving skin vulnerable to irritants and allergens

Question:

Deficiencies in what two elements are associated with atopic dermatitis?

Answer: Filaggrin and ceramides

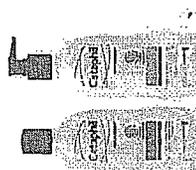
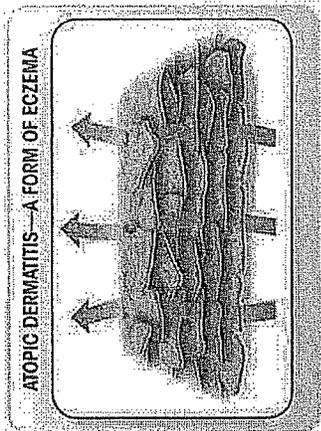
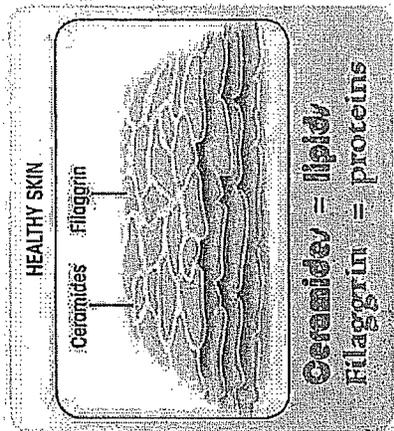


Two key elements of healthy skin

- ~ A lipid is a fat or oil that has moisture-binding properties^{4,5}
- ~ A protein is composed of amino acids and is associated with growth, repair and maintenance of cells⁴
- ~ The stratum corneum contains lipids and proteins called ceramides and filaggrin⁶

Atopic skin is deficient in filaggrin and ceramides

- ~ Reduced level of ceramides results in a damaged skin barrier and excessive water loss⁶
- ~ Filaggrin deficiency compromises barrier function, leaving skin vulnerable to irritants and allergens⁶



Cetaphil
RESTORADERM[™]
Replenish. Restore. Rebuild.

Ceramides
and Filaggrin

Medication is often prescribed to atopic patients. Daily skin care also plays an important role in the management of atopic dermatitis. Deficiencies in moisture and barrier protection are key factors in atopic skin.

- ~ The first and only products with ceramide and Filaggrin technology™, **Cetaphil® RESTORADERM®** products' patented technology helps restore hydration in atopic skin
- ~ Filaggrin technology™ restores moisture to help rebuild the damaged skin barrier
- ~ Ceramides help replenish the skin's natural lipids
- ~ **Cetaphil® RESTORADERM® Skin Restoring Moisturizer** is clinically proven to help restore skin barrier function
 - Improves surface hydration as early as day 1
 - Provides long-lasting hydration for atopic skin
- ~ **Cetaphil® RESTORADERM® Skin Restoring Body Wash** encapsulates skin-nourishing oils in a soap-free foaming wash
 - Helps soothe itch and reduce redness, dryness and irritation
 - Significantly decreases burning, stinging, scaling and flaking



Question:

What unique technology in Cetaphil® RESTORADERM® products restores moisture to help rebuild the damaged skin barrier?

Answer: Filaggrin technology™



Cetaphil

RESTORADERM®
Replenish/Restore/Rebuild

Ceramide & Filaggrin
Technology/Technology

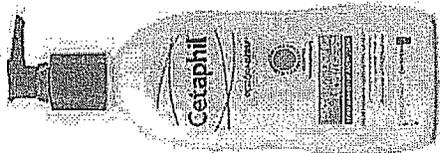
Medication is often prescribed to atopic patients. Daily skin care also plays an important role in the management of atopic dermatitis. Deficiencies in moisture and barrier protection are key factors in atopic skin.

The first and only products with ceramide and Filaggrin technology™, Cetaphil® RESTORADERM® products' patented technology helps restore hydration in atopic skin

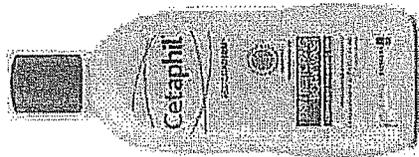


Filaggrin technology™ restores moisture to help rebuild the damaged skin barrier¹

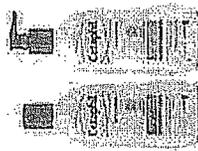
Ceramides help replenish the skin's natural lipids⁶



- ~ Helps restore skin barrier function¹
- ~ Improves surface hydration¹
- ~ Provides long-lasting hydration¹



- ~ Soap-free foaming wash
- ~ Helps soothe itch and reduce redness, dryness and irritation¹
- ~ Significantly decreases burning, stinging and scaling¹



Cetaphil
RESTORADERM®
Replenish. Restore. Rebuild.

Ceramide & Filaggrin
Technology Efficacy

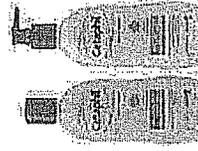
- ~ The safety and tolerability of **Cetaphil® RESTORADERM®** products were evaluated in 53 patients, aged 3–36 months, with atopic tendencies
- ~ Patients were bathed and moisturized at least once a day, but no more than twice daily for 4 weeks
- ~ Additionally, skin barrier function, or transepidermal water loss (TEWL), and hydration (corneometry) were measured in triplicate at baseline and at weeks 2 and 4, at least 2.5 hours after application of product
- ~ Approximately 90% of subjects had no scaling or dryness after using **Cetaphil® RESTORADERM® Moisturizer and Body Wash**
- ~ 92% reported that the regimen was non-irritating
- ~ 87% of survey respondents in the study agree that the regimen relieves itchy skin



Question:

Cetaphil® RESTORADERM® products have been proven safe for use in children as young as _____?

Answer: 3 months



Cetaphil

RESTORADERM
Replenish. Restore. Rebuild.

Pediatric Itch Study

Pediatric Usage Study

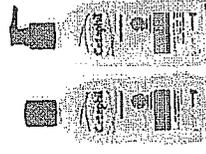
Safety and tolerability demonstrated in Cetaphil® RESTORADERM® Skin Restoring Moisturizer and Body Wash

Study design

- ~ Safety and tolerability evaluated in 53 patients, aged 3-36 months, with atopic tendencies¹
- ~ Patients bathed and moisturized at least once a day, but no more than twice daily, for 4 weeks¹
- ~ Additionally, skin barrier function (TEWL) and hydration (corneometry) measured three times: at baseline, week 2 and week 4¹

Proven tolerability, with a high degree of patient satisfaction

- ~ Approximately 90% of subjects had no scaling or dryness after use¹
- ~ 92% reported that the regimen was non-irritating¹
- ~ 87% of survey respondents in the study agree that the regimen relieves itchy skin¹



Cetaphil
RESTORADERM®
Replenish. Restore. Rebuild.

Pediatric Usage Study

- ~ **Cetaphil® RESTORADERM® Skin Restoring Moisturizer and Body Wash** improve skin barrier function
- ~ **Cetaphil® RESTORADERM®** products significantly decreased TEWL scores when compared with baseline measurements at 2 weeks and 4 weeks of treatment
- ~ **Cetaphil® RESTORADERM® Skin Restoring Moisturizer and Body Wash** improve hydration
- ~ **Cetaphil® RESTORADERM®** products significantly increased hydration compared with baseline measurements, as assessed by corneometry



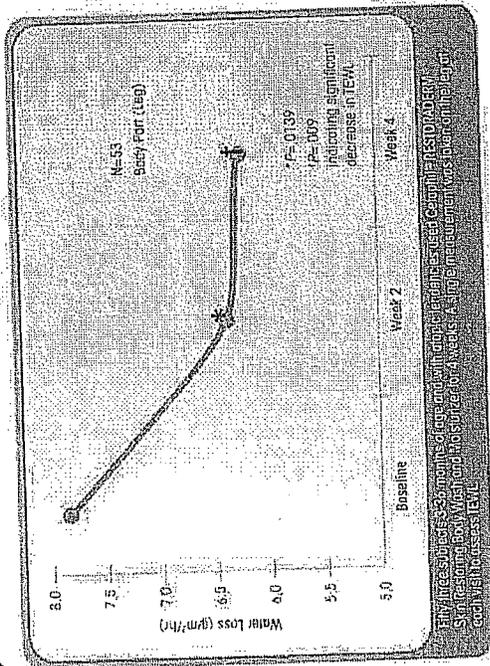
Cetaphil
RESTORADERM

Replenish. Restore. Rebuild.

Periatric Usage Study
Efficacy

Cetaphil® RESTORADERM® Skin Restoring Moisturizer and Body Wash

Improves skin barrier function over 4 weeks!



Improves skin barrier function

Cetaphil® RESTORADERM® Moisturizer and Body Wash significantly decreased TEWL at 2 weeks and 4 weeks compared with baseline!

Improves hydration

Cetaphil® RESTORADERM® products significantly increased hydration compared with baseline measurements as assessed by corneometry!



Cetaphil
RESTORADERM®
Replenish. Restore. Rebuild.

Restoring Skin Study

Cetaphil® RESTORADERM® products

- ~ Proven non-irritating on atopic skin
- ~ Safe for use in children as young as 3 months of age
- ~ Contain no preservatives, fragrances, nut oils, parabens or lanolin
- ~ Steroid free



Question:

True or false: Cetaphil® RESTORADERM® products contain no preservatives, fragrances, nut oils, parabens or lanolin.

Answer: True



Cetaphil®

RESTORADERM®
Replenish. Restore. Rebuild.

Tolerability/
Safety Profile

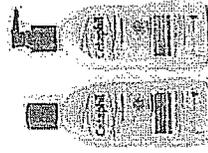
Cetaphil® RESTORADERM® products are proven non-irritating on atopic skin.

- ~ Safe for use in children as young as 3 months
- ~ Contain no preservatives, fragrances, nut oils, parabens or lanolin
- ~ Steroid free

Contact with eyes should be avoided

Complete formula for atopic skin

	Formulated for Atopic Skin	Ceramides	Flaggrin Proteins	Niacinamide	Sunflower Seed Oil	Glycerin	Shea Butter
Cetaphil® RESTORADERM® Skin Restoring Moisturizer	✓	✓	✓	✓	✓	✓	✓
Cetaphil® RESTORADERM® Skin Restoring Body Wash	✓		✓	✓	✓	✓	✓
CeraVe® Body Moisturizers and Cleanser		✓				✓	
Eucerin® Calming Crème						✓	
Aveeno® Advanced Care		✓				✓	



Cetaphil® RESTORADERM®
Replenish. Restore. Rebuild.

"I absolutely love the products. Helped with my itchy dry skin. Will definitely purchase both items."

*User testimonials were gathered as part of a patient-experience program, in which participants were given Cetaphil® RESTORADERM® products by their doctor and asked to share their experiences after 1 week of use (n=408).

Tolerability/
Safety Profile

- ~ The first and only products to contain patented ceramide and Filaggrin technology™
- Ceramides help replenish the skin's natural lipids
- Filaggrin technology™ helps restore moisture to help rebuild the damaged skin barrier
- ~ Clinically proven to help soothe itch and reduce redness, dryness and irritation
- ~ Safe for use in children as young as 3 months of age
- ~ Contain no preservatives, fragrances, nut oils, parabens or lanolin

Make Cetaphil® RESTORADERM® the foundation of a daily skin care regimen for your patients with atopic dermatitis

QUIZ

1 Question: *What is the most common symptom of atopic dermatitis?*

Answer: Dry, itchy skin

2 Question: *Deficiencies of what two elements are associated with atopic dermatitis?*

Answer: Filaggrin and ceramides

3 Question: *What unique technology in Cetaphil® RESTORADERM® products restores moisture to help rebuild the damaged skin barrier?*

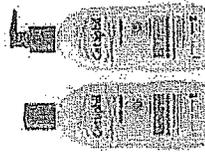
Answer: Filaggrin technology™

4 Question: *Cetaphil® RESTORADERM® products have been proven safe for use in children as young as _____?*

Answer: 3 months

5 Question: *True or false: Cetaphil® RESTORADERM® products contain no preservatives, fragrances, nut oils, parabens or lanolin.*

Answer: True



Cetaphil

RESTORADERM
Replenish. Restore. Rebuild.

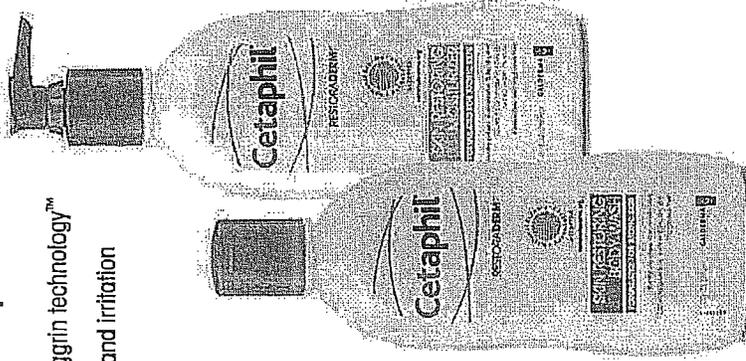
Summary

**Cetaphil® RESTORADERM® Skin Restoring Moisturizer and Body Wash:
Patented technology helps restore hydration in atopic skin**

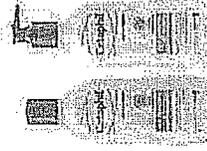
- ~ The first and only products to contain patented ceramide and Filaggrin technology™
- ~ Clinically proven to help soothe itch and reduce redness, dryness and irritation
- ~ Safe for use in children as young as 3 months of age
- ~ Contain no preservatives, fragrances, nut oils, parabens or lanolin

Replenish. Restore. Rebuild.

**Make Cetaphil® RESTORADERM®
the foundation of a daily skin care regimen
for your patients with atopic dermatitis**



Available at locations nationwide



Cetaphil

RESTORADERM®
Replenish. Restore. Rebuild.

Summary

"Better results than any cream or body wash used previously."[†]

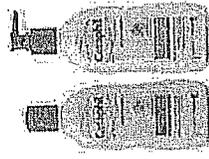
[†]User testimonials were gathered as part of a patient-experience program, in which participants were given Cetaphil® RESTORADERM® products by their doctor and asked to share their experiences after 1 week of use (n=100).

Cetaphil® RESTORADERM® Skin Restoring Moisturizer

- ~ Clinically proven to help restore skin barrier function
- ~ Improves surface hydration as early as day 1
- ~ Provides long-lasting hydration for atopic skin

Cetaphil® RESTORADERM® Skin Restoring Body Wash

- ~ Encapsulates skin-nourishing oils in a soap-free foaming wash
- ~ Helps soothe itch and reduce redness, dryness and irritation
- ~ Significantly decreases burning, stinging and scaling



Cetaphil

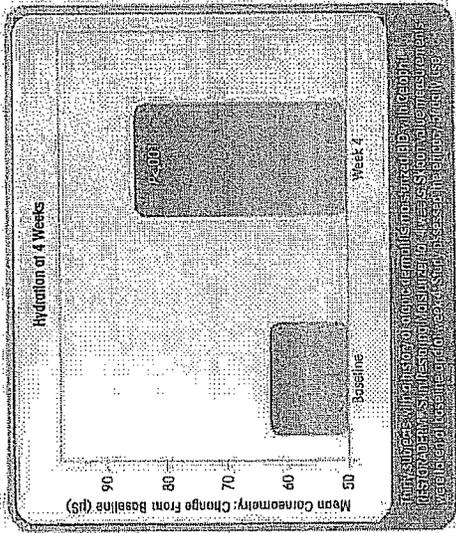
RESTORADERM®
Replenish. Restore. Rebuild.

Backup

**Cetaphil® RESTORADERM®
Skin Restoring Moisturizer**

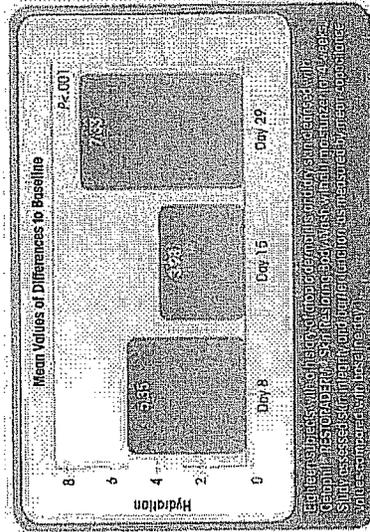
- ~ Helps restore skin barrier function
- ~ Improves surface hydration
- ~ Long-lasting hydration

Significantly increased hydration after 4 weeks!



For subjects with skin on face, chest and arms, hydration was significantly increased with Cetaphil RESTORADERM Skin Restoring Moisturizer. See Statistical Comparison Table for baseline and week 4 values. See Statistical Comparison Table for baseline and week 4 values. See Statistical Comparison Table for baseline and week 4 values.

Cleanses without disrupting skin's ability to retain moisture!



For subjects with skin on face, chest and arms, hydration was significantly increased with Cetaphil RESTORADERM Skin Restoring Body Wash. See Statistical Comparison Table for baseline and day 8, 15, and 29 values. See Statistical Comparison Table for baseline and day 8, 15, and 29 values.



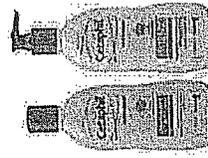
Cetaphil®
RESTORADERM®
Replenish. Restore. Rebuild.

Backup

- ~ Filaggrin is broken down into filaggrin breakdown products (free amino acids)
- ~ These amino acids bond with other chemicals to form natural moisturizing factors (NMFs)
- ~ Filaggrin-generated NMFs hold water to keep the stratum corneum hydrated and supple

Ceramides: The brick and mortar model

- ~ Ceramides are essential to help hold moisture within skin and help cells stay together



Cetaphil

RESTODERM
Replenish. Restore. Rebuild.

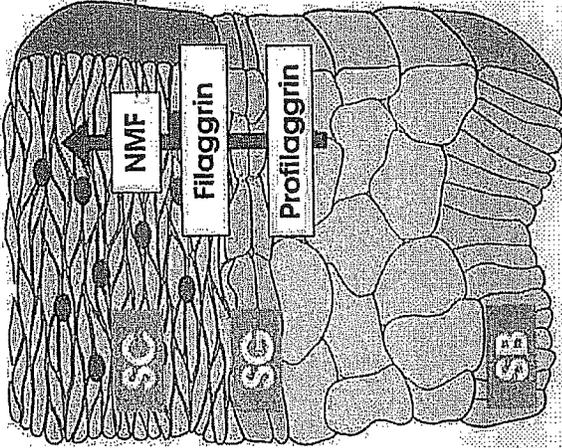
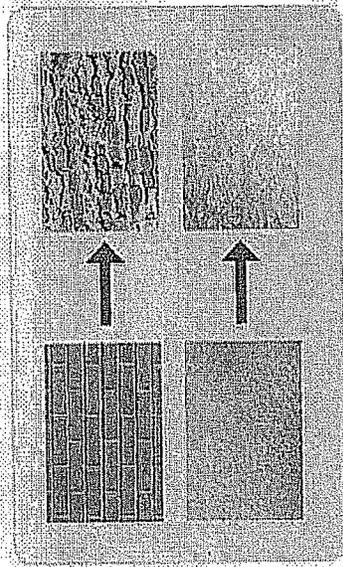
Filaggrin

Filaggrin—a closer look

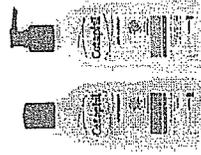
- ~ Filaggrin is broken down into filaggrin breakdown products (free amino acids)
- ~ These amino acids bond with other chemicals to form natural moisturizing factors (NMFs)
- ~ Filaggrin-generated NMFs hold water to keep the stratum corneum hydrated and supple

Ceramides: The brick and mortar model

- ~ Ceramides are essential to help hold moisture within skin and help cells stay together



NMFs are also known as filaggrin breakdown products
 — 40% of NMFs are arginine and sodium PCA



Cetaphil
 RESTORADERM
 Replenish. Restore. Rebuild.

PUBLIC

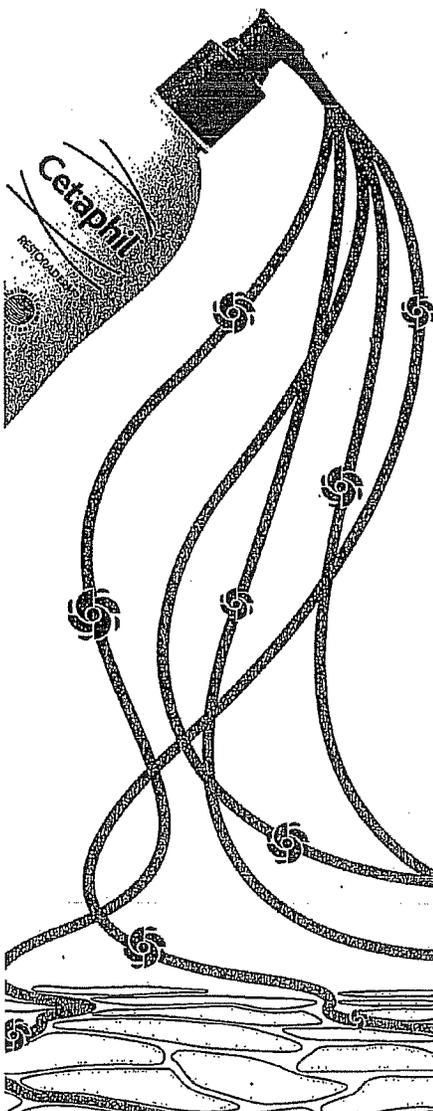
ATOPIC DERMATITIS: Results in skin barrier dysfunction

Filaggrin: A protein deficiency in atopic skin

~ Filaggrin deficiency compromises barrier function, leaving skin vulnerable to irritants and allergens¹

Ceramides: Lipid deficiency in atopic skin

~ Reduced levels of ceramides 1 and 3 cause excess water loss and a damaged skin barrier¹



Cetaphil® RESTORADERM® Skin Restoring Moisturizer and Body Wash: The first and only products with ceramide AND Filaggrin technology™



Filaggrin technology™ helps restore moisture to help rebuild the damaged skin barrier^{1,2}

Ceramide technology increases ceramides 1, 2 and 3³

Cetaphil® RESTORADERM® Moisturizer is associated with increased levels of ceramides in atopic skin²

Soothes symptoms of eczema

~ Relieves dry, itchy skin²

~ Provides long-lasting hydration²

GALDERMA
committed to the future
of dermatology

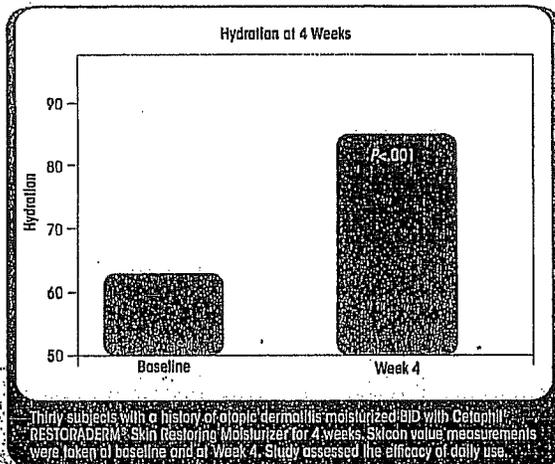


PUBLIC

Proven results in atopic patients

Cetaphil® RESTORADERM® Skin Restoring Moisturizer

▶ Significantly increased hydration after 4 weeks²

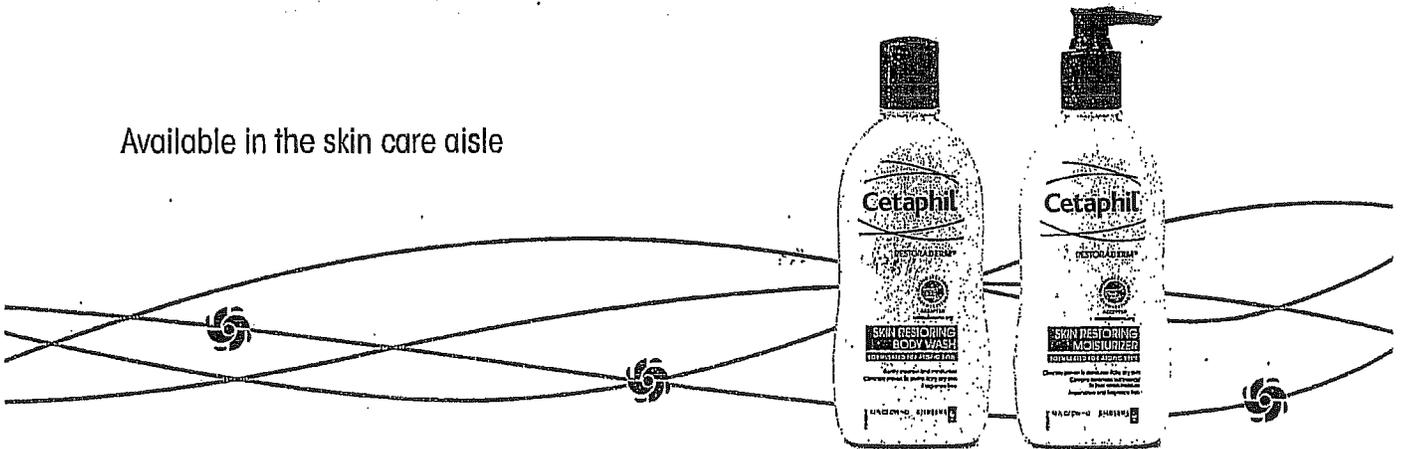


Cetaphil® RESTORADERM® Skin Restoring Moisturizer

- ~ Clinically proven to help restore skin barrier function²
- ~ Improves surface hydration as early as Day 1²
- ~ Provides long-lasting hydration for atopic skin²

Recommend Cetaphil® RESTORADERM® products as part of a daily skin care regimen for atopic skin

Available in the skin care aisle



#1 DERMATOLOGIST RECOMMENDED
BRAND OF CLEANSERS AND MOISTURIZERS

Cetaphil®
RESTORADERM®
Replenish. Restore. Rebuild.

cetaphil.com

GALDERMA
committed to the future
of dermatology



References: 1. Sugarman JL. The epidermal barrier in atopic dermatitis. *Semin Cutan Med Surg.* 2008;27:108-114. 2. Data on file, Galderma Laboratories. 3. Castjal-Higounenc I, Chopart M, Ferraris C. Squalum corneum lipids: specificity, role, deficiencies and modulation. *OCL.* 2004;11(6):401-406.
© 2011 Galderma Laboratories, L.P. Galderma is a registered trademark. Galderma Laboratories, L.P., 14501 N. Freeway, Fort Worth, TX 78177
CETA-296 Printed in USA 05/11