OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(12) (19) (CA) **Demande-Application**

(21) (A1) **2,303,094**
(86) 1999/07/01
(87) 2000/01/13

(72) GANS, EUGENE H., US
(71) GANS, EUGENE H., US

(51) Int.Cl.[7] A61F 2/02, A61K 9/68, A61K 9/28, A61K 9/20
(30) 1998/07/02 (09/109,366) US

(54) **PROCEDES ET COMPOSITIONS PERMETTANT DE PRODUIRE UN EFFET DE REFROIDISSEMENT DANS DES TISSUS**

(54) **METHODS AND COMPOSITIONS FOR PRODUCING A COOLING EFFECT IN TISSUES**

(57) La présente invention concerne une technique permettant de produire des sensations de soulagement et de refroidissement dans des tissus tels que ceux des zones cutanées sensibles et des membranes des muqueuses. Pour produire une sensation de refroidissement appréciable, du diméthyléther peut être appliqué sur les tissus visés sous forme d'un liquide ou d'un gaz produit par un liquide vaporisé, avalé ou appliqué avec un bandage ou un pansement. L'application peut également se faire avec une pastille, un suppositoire ou une autre forme posologique solide qui libère le diméthyléther au niveau du tissu visé. L'intensité et la durée de l'effet de refroidissement appréciable est obtenu lorsque le diméthyléther est appliqué à des concentrations infimes. On a également découvert que cette technique peut améliorer la perception de la saveur des aliments, des boissons et des bonbons.

(57) A technique for the production of soothing and cooling sensations in tissues such as sensitive skin areas and mucous membranes is provided. To produce a sensation of esthetic cooling, dimethyl ether may be applied to the target tissues in the form of a liquid or a gas arising from a liquid that is sprayed, swallowed, or applied with a bandage or other dressing. Alternatively, it may be applied as a lozenge, suppository, or other solid dosage form that releases the dimethyl ether to the target tissue. The intensity and duration of the esthetic cooling effect is obtained when the dimethyl ether is applied at minute concentrations. It has also been discovered that this technique can enhance the perception of flavor of foods, beverages, and candies.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61F 2/02, A61K 9/20, 9/28, 9/68

A1

(11) International Publication Number: **WO 00/01321**

(43) International Publication Date: 13 January 2000 (13.01.00)

(21) International Application Number: PCT/US99/15173

(22) International Filing Date: 1 July 1999 (01.07.99)

(30) Priority Data:
09/109,366 2 July 1998 (02.07.98) US

(71)(72) Applicant and Inventor: GANS, Eugene, H. [US/US]; 514 Harvest Commons, Westport, CT 06880 (US).

(74) Agent: MCNICHOL, William, J., Jr.; Reed Smith Shaw & McClay LLP, 2500 One Liberty Place, Philadelphia, PA 19103–7301 (US).

(81) Designated States: CA, IL, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHODS AND COMPOSITIONS FOR PRODUCING A COOLING EFFECT IN TISSUES

(57) Abstract

A technique for the production of soothing and cooling sensations in tissues such as sensitive skin areas and mucous membranes is provided. To produce a sensation of esthetic cooling, dimethyl ether may be applied to the target tissues in the form of a liquid or a gas arising from a liquid that is sprayed, swallowed, or applied with a bandage or other dressing. Alternatively, it may be applied as a lozenge, suppository, or other solid dosage form that releases the dimethyl ether to the target tissue. The intensity and duration of the esthetic cooling effect is obtained when the dimethyl ether is applied at minute concentrations. It has also been discovered that this technique can enhance the perception of flavor of foods, beverages, and candies.

METHODS AND COMPOSITIONS FOR PRODUCING A COOLING EFFECT IN TISSUES

Field of the Invention

This invention relates to techniques for the production of soothing, cooling sensations in tissues such as sensitive skin areas and mucous membranes.

Background of the Invention

It has long been desired to be able to produce a cooling, soothing sensation in sensitive skin areas, including mucous membranes. In the past this has been achieved by use of substances such as chloroform or camphor. The sensation produced by these substances has been variously described as cooling, penetration, or a sense of spreading or a sense of opening up/cleaning out. This esthetic signaling effect shall be referred to herein as "esthetic cooling." In addition to being mildly pleasurable, this sensation is often genuinely soothing to sensitive or irritated tissues.

Compounds which are known to produce the esthetic cooling effect all suffer from a variety of drawbacks, some of them quite serious. Chloroform was once widely used for this purpose, but is no longer used because of its carcinogenic potential. Camphor and aromatic oils have distinct flavors and odors and are sometimes irritating or sensitizing to certain tissues.

It is therefore highly desirable to find a way to achieve this effect of esthetic cooling that is safe, convenient and effective.

Summary of the Invention

It has been discovered that dimethyl ether (CH_3-O-CH_3) is effective in producing a sensation of esthetic cooling. Dimethyl ether may be applied to the target tissues in the form of a liquid or a gas arising from a liquid that is sprayed, swallowed, or applied with a bandage or other dressing. Alternatively, it may be applied as a lozenge, suppository, or other solid dosage form that releases the dimethyl ether to the target tissue. The intensity and duration of the esthetic cooling effect is obtained when the dimethyl ether is applied at concentrations of as little

as 1.0%, or even lower in formulations where availability and delivery to tissues is heightened or enhanced. It has also been discovered that this technique can enhance the perception of flavor of foods, beverage, and candies.

Detailed Description of the Invention

Dimethyl ether is a well-known and well-characterized chemical entity. Its principal commercial use is as a propellant for aerosols such as hair sprays. See, for example, "A New Era In Aerosol Propellants" J.J. Daily, Drug Cosmet. Ind., Vol. 134, No. 2, Page 40 (1984). Because of its high volatility, it has also been used as a cryogenic agent for removing skin lesions. See U.S. Patent No. 5,516,505. Some of Dimethyl ether's physical properties are shown in Table 1.

Table 1
Physical Properties of Dimethyl Ether

Molecular Weight	44.07
Boiling Point	-24.8°C
Density at 20°C	0.66 g/ml
Solubility in H_2O at 20°C	35 wt %

It has been found that dimethyl ether can be applied to skin and sensitive tissues to produce a sensation of esthetic cooling. This should not be confused with an actual lowering of temperature by means of evaporation or volatilization as described in U.S. Patent No. 5,516,505, as dimethyl ether is capable of producing this effect even in areas where evaporative cooling is not possible, such as the throat. Indeed, some of the preferred embodiments of this invention call for dimethyl ether to be applied in a manner which tends to produce very little evaporative cooling.

Because of its high solubility in water, dimethyl ether is conveniently applied to the target tissue in the form of an aqueous solution. It can also be delivered in other suitable solvents or in systems where the gas is absorbed or entrapped. Aqueous solutions in excess of

30% by weight can be prepared and are useful in this invention. However, solutions of much lower concentration are typically employed.

Dimethyl ether is available from a variety of sources and is marketed by the E.I. DuPont Company under the trade name DYMEL A.

Other components may be added to the aqueous solution of Dimethyl either (DME) in order to advantageously modify its delivery. For instance, compounds such as viscosity builders which prolong its delivery and sensate effect, or compounds such as ethanol, carbon dioxide and others which can speed and heighten its delivery and sensate effect. Additionally, there are compounds known to create their own type of sensate effect on tissues, such as menthol, glycyrrhizin, aromatic oils, capsaicin, and others, which can contribute to DME's unique sensate effect.

An aqueous solution of dimethyl ether was prepared in the following manner. DYMEL A brand dimethyl ether was obtained in the form of a cylinder of compressed gas. A length of tubing was attached to the regulator valve of the tank and run into a 250 milliliter erlenmeyer flask containing 125 milliliters of distilled water. The tubing terminated in a fritted glass gas diffuser. The flask was maintained in an ice water bath to minimize evaporative loss. Dimethyl ether gas was bubbled through the liquid, allowing the dimethyl ether to dissolve in the water. This process was used to produce solutions of approximately 2%, 5% and 10% by weight of dimethyl ether. Aliquots of these solutions were used in the following experiments to demonstrate the ability of dimethyl ether to produce a sensation of esthetic cooling.

A subject sipped a small volume of 2%, 5% and 10% dimethyl ether solutions and reported a distinct, penetrating sensation of esthetic cooling in the mouth and throat. Aliquots of these solutions were diluted to produce 1.0% and 0.5% dimethyl ether solutions and was again sipped by the subject. The sensation of esthetic cooling was still noticeable though less intense.

An aliquot of 2% dimethyl ether solution was diluted to 1.0% and 0.5% and applied to sensitive skin areas including irritated eyelids, psoriatic skin, eczematous skin and fresh surgical sites. In each case, the subject reported a pleasant sensation of esthetic cooling.

Other liquid forms of dimethyl ether solutions have been prepared and found effective in the present invention. Using a solution of dimethyl ether prepared in the manner described above, the following compositions were prepared: Three and 6% dimethyl ether solutions in a benzalkonium chloride anti-bacterial mouthwash, a 3% dimethyl ether solution in a syrup, a 2.0% dimethyl ether solution in a nasal spray of 1% penylephrine decongestant, a 1.0% and 2.5% dimethyl ether solutions in an aqueous phosphate enema solution and a 1.0% and 2.5% dimethyl ether solutions in a 5% vinegar vaginal douche. In each case, the ordinary action of these preparations was supplemented by a pleasant and soothing sensation of esthetic cooling.

Confections, drops, troches, lozenges, gums and the like incorporating dimethyl ether can be formulated. These are useful as cough drops or cough lozenges, and are useful in cases of gum or mouth irritation and oral ulcers or sores. (This can also be accomplished by direct introduction of aqueous solutions of dimethyl ether described above or dimethyl ether solutions together with other solvents.)

Dermatological delivery systems containing dimethyl ether have been compounded by introducing dimethyl ether solution into the following products to obtain 4% concentrations: an oil-in-water moisturizing lotion, an oil-in-water anti-inflammatory hydrocortisone cream, a water-in-oil emulsion skin emollient lotion, and a protective diaper ointment. Each of these dermatological products was used to treat sensitive skin in the areas of the chest, neck, groin, thighs and buttocks, and, in addition to their ordinary therapeutic action, produced a pleasant and soothing sensation of esthetic cooling. The present invention may also be used in topical analgesics, including capsaicin on civamide containing preparations to enhance their effectiveness or appeal.

The effect of esthetic cooling has also been produced using an aqueous solution of dimethyl ether that is sprayed onto the target tissue by means of an aerosol or atomizer. Other application methods within the scope of this invention will be apparent to those skilled in the art upon reading this specification.

The taste sensation produced by various foods was enhanced by the addition of dimethyl ether. For example, the taste of liquors such as Gran Marnier and B&B were enhanced

by the addition of 1% and 2% dimethyl ether. Similar effects can be obtained by introducing satiable concentrations of dimethyl ether into sodas, candies, and confections.

The foregoing examples are non-limiting and the invention is defined only by the following claims.

Claims

1. A method of producing a sensation of esthetic cooling in animal tissue comprising applying an efficacious amount of dimethyl ether to the tissue.

2. The method of claim 1, wherein the dimethyl ether is in the form of an aqueous solution.

3. The method of claim 2, wherein the aqueous solution is sprayed onto the tissue.

4. The method of claim 1, wherein the dimethyl ether is provided in an oil-in-water emulsion.

5. The method of claim 1, wherein the dimethyl ether is provided in a dermatologically acceptable lotion.

6. The method of claim 1, wherein the dimethyl ether is provided in a protective ointment.

7. A method of soothing irritated or inflamed tissue comprising applying an efficacious amount of dimethyl ether to the tissue.

8. The method of claim 7, wherein the dimethyl ether is in the form of an aqueous solution.

9. The method of claim 7, wherein the aqueous solution is sprayed onto the tissue.

10. The method of claim 7, wherein the dimethyl ether is provided in an oil-in-water emulsion.

11. The method of claim 7, wherein the dimethyl ether is provided in a dermatologically acceptable lotion.

12. The method of claim 7, wherein the dimethyl ether is provided in a protective ointment.

13. The method of claim 7, wherein the aqueous solution is sprayed onto the tissue.

14. The method of claim 7, wherein the dimethyl ether is provided in an oil-in-water emulsion.

15. The method of claim 7, wherein the dimethyl ether is provided in a dermatologically acceptable lotion.

16. The method of claim 7, wherein the dimethyl ether is provided in a protective ointment.

17. A composition for the treatment of living tissues comprising an efficacious amount of dimethyl ether and a pharmacalogically acceptable carrier.

18. The composition of claim 17, wherein the carrier is a dermatologically acceptable vehicle.

19. The composition of claim 17, wherein the composition is a lozenge.

20. The composition of claim 17, wherein the composition is a syrup.

21. The composition of claim 17, wherein the composition is a suppository.

22. The method of claim 17, wherein the dimethyl ether is in the form of an aqueous solution.

23. The composition of claim 13, wherein the dimethyl ether is present in a concentration of at least 0.1% by weight

24. The composition of claim 13, wherein the dimethyl ether is present in a concentration of at least 0.5% by weight.

25. The composition of claim 13, wherein the dimethyl ether is present in a concentration of at least 1.0% by weight.

26. The composition of claim 13, wherein the dimethyl ether is present in a concentration of at least 2.0% by weight.

27. A method of enhancing the taste sensation produced by food, comprising adding dimethyl ether to the food.

28. The method of claim 27, wherein the dimethyl ether is present in the food in a concentration of at least 0.1% by weight.

29. The method of claim 28, wherein the concentration of dimethyl ether is at least 1.0% by weight.

30. The method of claim 29, wherein the food is an alcoholic beverage.

31. The method of claim 29, wherein the food is a candy or confection.

32. The method of claim 29, wherein the food is a beverage.