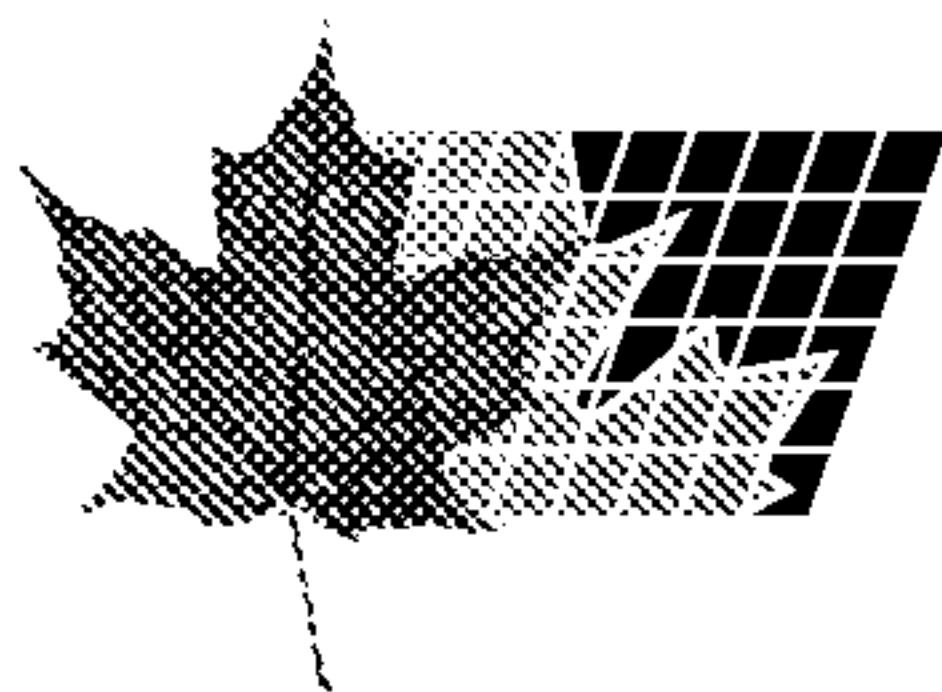




(11) (21) (C) **2,071,837**
(86) 1990/10/16
(87) 1992/04/17
(45) 2001/01/02

(72) Deihl, Joseph A., US

(73) Mayor Pharmaceutical Laboratories, Inc., US

(51) Int.Cl.⁵ A61K 33/30, A61K 31/68, A61K 31/375, A61K 9/12

(54) **METHODES ET COMPOSITIONS POUR UN TRAITEMENT
AUX VITAMINES ET AUX MINERAUX**

(54) **VITAMIN-MINERAL TREATMENT METHODS AND
COMPOSITIONS**

(57) A new use is provided for a particularly specified spray composition. Such spray composition includes at least one of a soluble vitamin, (e.g., Vitamin C) and a soluble mineral, and a non-toxic zinc compound as an essential active agent, as well as, optionally, a soluble flavouring agent, and a non-toxic solvent for the soluble vitamin or for the soluble mineral, or for the optional flavouring agent. Such new use is for introducing at least one of a soluble vitamin and a soluble mineral as well as the non-toxic zinc compound, into an animal through the oral cavity. Methods of preparing such spray compositions for such use are also provided.



ABSTRACT

5 A new use is provided for a particularly specified spray composition. Such spray composition includes at least one of a soluble vitamin, (e.g., Vitamin C) and a soluble mineral, and a non-toxic zinc compound as an essential active agent, as well as, optionally, a soluble flavouring agent, and a non-toxic solvent for the soluble vitamin or for the soluble mineral, or for the optional flavouring agent. Such new use is for introducing at least one of a soluble vitamin and a soluble mineral as well as the non-toxic zinc compound, into an animal through the oral cavity. Methods of preparing such spray compositions for such use are also provided.

(a) **TITLE OF THE INVENTION**

VITAMIN-MINERAL TREATMENT METHODS AND COMPOSITIONS

(b) **TECHNICAL FIELD TO WHICH THE INVENTION RELATES**

5 This invention relates to the use of spray compositions for introducing vitamins and/or minerals into the human body.

(c) **BACKGROUND ART**

10 The closest prior art to the present invention is U.S. Patent No. 4,525,341, issued June 25, 1985, to J.A. Bechl. This patent disclosed methods for administering vitamins to humans by spraying a liquid vitamin composition into the mouth. The vitamin(s) were present in these compositions in a diet supplemental amount. The sprayable compositions contained a breath freshener and, optionally, a flavouring agent. The liquid carrier was a non-toxic alcohol, or an aqueous alcohol or water.

15 Urbach described the clinical use of Vitamin A buccal tablets in the treatment of leucoplakia and lichen planus in Bull. Ass. Milit. Derm 6: 17, 1957.

The local therapy of oral leucoplakia with Vitamin A troches was described by Mulay and Urbach in AMA Arch. Dem. and Syph. 78: 637-58, 1958.

20 Eby, Davies and Halcomb reported that zinc gluconate lozenges, which were dissolved in the mouth every two wakeful hours after an initial double dose, shortened the average duration of common colds by seven days. Problems with palatability, taste distortion, mouth irritation, emetic properties and nausea, however, were reported. (See Antimicrobial Agents and Chemotherapy, Vol 25, No. 1, Jan. 1985, p. 20-24 and also USA Patent No. 4,956,385).

25 The intra-nasal introduction of diverse drugs including Vitamin B₁₂ metoclopramide (cancer chemotherapeutant), insulin, LHRH hormone (contraceptive), lidocaine (headache medicine), alpha-interferon and enviroxime (rhinoviricides) and measles and flu vaccines, have also been suggested and tested,. Some of these treatments induced side effects, e.g., irritation and nasal bleeding.

Thus, the prior art disclosed that vitamins and other medicinal compositions can be administered by mucosal absorption from a composition which is sprayed into the oral cavity, and that nasal administration of certain similar compositions may be feasible. However, the prior art failed to teach or fairly suggest the use of certain specific combinations of vitamins/minerals, administered in a specific, controlled fashion, to achieve particular medical and/or biochemical effects without adverse side effects. In particular, the prior art did not disclose the pharmacological effect of topical application of certain vitamin, mineral or vitamin-mineral oral spray compositions in the treatment of oral lesions. Further, the prior art failed to disclose specific administration regimens for vitamin sprays to achieve specific pharmacologic and nutritional results.

(d) DESCRIPTION OF THE INVENTION

Accordingly, an object of a principal aspect of the present invention is to provide an improved new use of compositions for administering at least one of vitamins, vitamin-mineral and mineral compositions into the human body to achieve specific pharmacological and/or nutritional results.

An object of another aspect of the invention is to provide the new use of such compositions which can be self-practised and be administered by human patients with only limited instructions and minimal supervision by medically-trained personnel.

An object of a further aspect of the invention is to provide a new use of compositions which may be conveniently employed to administer at least one of vitamins, vitamin-mineral and mineral compositions with minimal side effects.

An object of a further aspect of the invention is to provide a method for the preparation of compositions which are specially adapted for such uses.

By a first broad aspect of this invention, the use is provided of a spray composition comprising (i) at least one of a soluble vitamin and a soluble mineral, (ii) a non-toxic zinc compound; and (iii) a non-toxic solvent for the vitamin or the soluble mineral, for introducing at least one of the soluble vitamin and the soluble mineral, as well as the non-toxic zinc compound, into an animal through the oral cavity.

By one variant of this first use of this invention, the use is for introducing Vitamin A and the non-toxic zinc compound into an animal through the oral cavity.

By another variant of this first use of this invention, the use is for introducing Vitamin B₁₂ and the non-toxic zinc compound into an animal through the oral cavity.

5 By a second aspect of this invention, the use is provided of a composition comprising (i) Vitamin C; (ii) a non-toxic zinc compound; and (iii) a non-toxic solvent for the Vitamin C, for introducing the Vitamin C and the non-toxic zinc compound into an animal through the oral cavity, as well as for the treatment of the common cold.

10 By a variant of the first aspect of this invention, or of the second aspect of this invention, this second new use of this invention, the composition includes a flavouring agent.

By a second variant of the first aspect of this invention, or of the second aspect of this invention, this second new use of this invention, the composition includes sodium bicarbonate.

15 By a third variant of the first aspect of this invention, or of the second aspect of this invention, and/or the above variants thereof, the composition includes glycerine.

By a fourth variant of the first aspect of this invention, or of the second aspect of this invention, and/or the above variants thereof, the composition includes potassium sorbate.

20 By a third aspect of this invention, a method is provided for the preparation of a composition comprising: (i) at least one of a soluble vitamin and a soluble mineral, (ii) a non-toxic zinc compound, and (iii) a non-toxic solvent for the vitamin or the soluble mineral, the method comprising the steps of establishing a desired total dose for administration during a daily dosage period; selecting a concentration of the at least one
25 of the soluble vitamin and the soluble mineral agent, as well as the non-toxic zinc salt, in the non-toxic solvent for the vitamin or the soluble mineral, the concentration being one which will provide the desired total dose when administered in aerosol form as a series of aliquot doses at predetermined spaced intervals during waking hours into the oral cavity; and charging the composition to a spray dispenser.

By one variant of this third aspect of the invention, the step of selecting a concentration of the at least one of the soluble vitamin and the soluble mineral agent, as well as the non-toxic zinc salt, further includes the steps of determining the concentration by empirical tests, and translating the tests to the aliquot dosage and a pattern of repetition of such dosages, to maintain the desired minimum body concentration of the at least one of the soluble vitamin as well as the soluble mineral agent, and the non-toxic zinc salt.

By a fourth aspect of this invention, a method is provided for the preparation of a composition comprising: (i) Vitamin C; (ii) a non-toxic zinc compound, and (iii) a non-toxic solvent for the Vitamin C, the method comprising the steps of: establishing a desired total dose of the Vitamin C as well as a non-toxic zinc salt as an essential agent, in the non-toxic solvent, the desired dose being one which will provide the desired total dose when administered in aerosol form as a series of aliquot doses at predetermined spaced intervals during waking hours into the oral cavity; and charging the composition to a spray dispenser.

By one variant of this fourth aspect of the invention, the step of selecting a concentration of the Vitamin C and the non-toxic zinc salt, further includes the steps of: determining the concentration by empirical tests; and translating the tests to the aliquot dosage and a pattern of repetition of such dosages, to maintain the desired minimum body concentration of the at least one of the soluble vitamin and the soluble mineral agent, as well as the non-toxic zinc salt.

By a second variant of this fourth aspect of the invention, the method includes the step of including sodium bicarbonate in the selected concentration or the established dose.

By a third variant of this fourth aspect of the invention, the method includes the step of including glycerine in the selected concentration or in the established dose.

By a fourth variant of this fourth aspect of the invention, the method includes the step of including potassium sorbate in the selected concentration or in the established dose.

By a fifth broad aspect of this invention, a composition is provided when prepared according to the methods as described above, in combination with instructions to spray a series of aliquot doses at predetermined spaced intervals during waking hours into the oral cavity of a patient, for the use as described above.

One novel use of the spray compositions of aspects of this invention is that of treating common colds by oral administration of the spray composition disclosed herein which includes, as an essential ingredient, a solution of a non-toxic zinc compound.

(e) AT LEAST ONE MODE FOR CARRYING OUT THE INVENTION

The invention will now be described with such particularity as to enable any person skilled in the pertinent art to practice the invention without extensive experimentation.

In the administration of biologically-active agents, including drugs, medicines and other compositions which are administered for pharmacological effect, it is normally required that a minimum concentration of the agent be established in the body, e.g., in the tissue or blood stream, and that such minimum concentration be maintained for a predetermined time period, as required to obtain the desired effect. Typically, these requirements are determined by empirical tests and the test results are translated to a dosage and a pattern of repetition of such dosages as required to maintain the desired minimum body concentration of the agent. According to the prior art, such timed aliquot dosages have been administered orally, intravenously, intradermally or by inhalation to ultimately provide the desired total dosage. However, according to present knowledge, the regimen of timed aliquot doses, substantially spaced throughout the wakeful period, has not been practised via mucosal absorption of the agent from solutions thereof which are sprayed into the oral cavity.

According to the broadest aspects of the present invention, desired total dosages of specific soluble vitamin compositions are predetermined by appropriate clinical studies in which the compositions are sprayed into the oral cavity. Similarly, suitable aliquot dosages and administration intervals are predetermined based on observed clinical effects,

after the spray administration of such compositions, e.g., by blood and/or tissue analysis and similar techniques. Having so predetermined the concentration of the vitamin and/or

mineral solution and the spray dosage and interval, the use of these spray compositions can be practiced by persons having only limited medical training and even by the patients themselves.

5 To improve the palatability of such spray compositions, it is preferred to include suitable flavouring agents which may include any suitable flavouring agents which are soluble in the spray compositions in the spray composition. For example, flavouring agents, e.g., sucrose, fruit juices, e.g., orange, apple, grape and pineapple juices and concentrates, may be effectively employed.

10 The liquid carrier for the vitamin and/or mineral agents in the spray is chosen with reference to chemical compatibility with the active agents, including the ability to dissolve such agents, and non-toxicity as well as secondary factors, e.g., taste, volatility, etc. The solvents for the active vitamin and/or minerals can include, for example, water, aqueous alcohols or 200-proof spirits.

15 The spray can be formed by any suitable technique, including conventional air pump atomizers and conventional compressed gas atomizers. The specific type of dispenser is not highly critical and will be chosen with reference to the specific desired effects, e.g., whether the spray is intended for a general application to the buccal mucosa for optimum absorption of the active agents into the blood stream or for local application to specific sites in the oral cavity to achieve topical effects. The selection of specific atomizer apparatus can be made by routine experimentation by persons skilled in the art, 20 having regard for this disclosure.

Specific pharmacological effects which can be obtained in accordance with the use of the spray compositions according to aspects of this invention, include acceleration of healing of oral lesions by topical applications of retinoid, the biologically-active form of Vitamin A. Additional specific biological effects of the spray retinoid compositions 25 include the treatment of night blindness, immunostimulation, and free radical scavenging.

Retinyl propionate, which is dissolved in the spray, is hydrolysed to retinol after oral mucosal absorption. Retinol is then transported into blood plasma, bound to an alpha one-globulin which protects it from metabolism and delivers it to specific sites on the

target cell surface. Another protein carrier then aids in the penetration of the vitamin into the cell where its biological activity takes place.

The biological activities of the retinoid are diverse. For example, in the epithelium, Vitamin A plays a major role in the induction and differentiation of mucus secreting an keratinizing tissue. Immunostimulation effects are obtained by therapeutic levels of Vitamin A which increase circulating T-cells.

Another specific biological effect which may be attained according to the use of the spray compositions according to aspects of this invention, is the reduction in severity of common colds by intraoral application of non-toxic zinc solutions which exhibit rhinoviricidal activity. The inclusion of Vitamin C in such compositions improves the effectiveness of such treatment.

The use of other specific vitamin and/or mineral compositions which can be advantageously used according to aspects of this invention will readily occur to those skilled in the art, having regard for this disclosure.

Working Examples

The following examples will serve to illustrate the practice of aspects of the present invention to those skilled in the art and to identify the presently preferred embodiments and best modes of practice of the present invention. These working examples are intended as illustrations of the practice of aspects of the invention and not as limitations of the scope thereof.

EXAMPLE 1

This example illustrated the preparation of a sprayable Vitamin A composition. Table 1 identifies the final compositions by ingredient and weight percentage.

Table 1

	<u>Ingredients</u>	<u>Parts by Weight</u>
	Alcohol SDA038B (200 proof)	77.0
	Vitamin A Propionate 2.5 MIO I.U./g	18.4
5	Vitamin E Acetate Oil USP, FCC)	
	D.L. - Alpha Tocopheryl Acetate)	4.96
	Flavour (cherry extract)	0.564

The Vitamin A is slowly added to the pre-measured alcohol and is completely dissolved. The tocopheryl is then slowly added until it is completely dissolved and the resultant solution is gently agitated for 15-20 minutes, after which the flavouring is added and is uniformly dissolved in the final mixture.

EXAMPLE II

This example illustrates the preparation of a suitable sprayable zinc-Vitamin C composition. Table II identifies the final compositions by ingredient and weight percentage.

Table 2

	<u>Ingredients</u>	<u>Parts by Weight</u>
	Pharmaceutical grade water (carrier)	54.53
20	Ascorbic Acid	1.64
	Sodium Bicarbonate	0.14
	Glycerine	6.8
	Potassium Sorbate	0.0765
	ETDA	0.0082
25	Zinc Gluconate	1.09
	L-Lysine	0.55
	Glycine	0.55
	Flavouring (Fruit Juice)	0.27
	Flavouring (Sucrose)	32.79
30	Flavour Enhancer (MAGNASWEET _{TM} GA-110)	0.27

5 The water at 85-92°F is measured into a sterile stainless steel vat. The glycerine and potassium sorbate are added to the water. The ascorbic acid and bicarbonate are separately mixed in a portion of the solution from the vat to stabilize the ascorbic acid and this solution is then added to the main batch in the vat. The following ingredients are then added singly with stirring to obtain complete solution thereof before the next
10 ingredient is added: EDTA, zinc gluconate, L-lysine/glycerine, fruit juice/sucrose, and flavour enhancer.

EXAMPLE III

20 Table 3**B**

5 The water at 86-92°F is measured into a sterile stainless steel vat. The SORBISTAT K_{TM}, glycerine, sucrose and fruit juice are then slowly added and completely dissolved before the next ingredient is added. The cyanocobalamin is then added slowly and completely dissolved, leaving a clear deep red solution after approximately 30 minutes. Meanwhile, the emulsifier and peppermint oil are mixed to a subtle cloudy mixture, which requires approximately 20 minutes. Then this cloudy mixture is slowly added to the contents of the vat with final mixing.

EXAMPLE IV

10 This example illustrates the use of a Vitamin A spray of Example I in the treatment of oral lesions.

Procedure

15 Forty-nine adult patients with oral lesions were treated for a period of four weeks with a topical spray of the Vitamin A-alcohol formulation of Example I. The spray was contained in an aerosol container five inches in length and two inches in circumference. Females of child-bearing age were asked to take appropriate birth control measures while on the study and for two week period after stopping the medication.

Patients were instructed to spray the lesions eight times daily. The total dosage of Vitamin A which was delivered to the lesions in this fashion was 200,000 u/day.

20 Table I illustrates the number of patients with each disease treated.

TABLE 1

Number of patients with oral lesions.

	<u>Disease</u>	<u>Number</u>
	Pemphigus	4
25	Leukoplakia	12
	Glossitis	3
	Geographic Tongue	6
	Lichen Planus	14
	Aphthous Stomatitis	10

30 Six patients did not return for follow-up.

The status of the disease and the response to treatment was evaluated by the same investigator weekly for a period of four weeks.

It was emphasized to the patients with leukoplakia that the condition might be precancerous and that other modalities of therapy were available.

5 A double blind procedure was not used since the effect of topical Vitamin A in oral lesions has been known for many years and only the effect of the application and delivery system was of relevance.

Results

10 Forty-three of the forty-nine patients completed the four week course of treatment. Table II illustrates the percentage of improvement in the patients that completed the four week course of treatment.

Table II
Percentage of improvement at end of four week period
in each disease category.

15	<u>Disease</u>	<u>Number of Patients</u>	<u>Percent Improved</u>
	Pemphigus	3	60
	Leukoplakia	10	50
	Glossitis	2	80
	Geographic Tongue	6	95
20	Lichen Planus	12	65
	Aphthous Stomatitis	10	75

EXAMPLE V

25 The procedure of Example II was repeated except that ascorbic acid was omitted from the composition.

EXAMPLE VI

The procedure of Example II was repeated except that zinc gluconate was omitted from the composition.

EXAMPLE VII

The procedure of Example II was repeated except that both ascorbic acid and zinc gluconate were omitted from the composition.

5

EXAMPLE VIII

The compositions of Examples II, V, VI and VII were administered by spraying every two hours during wakeful periods into the mouths of patients having the symptoms of common colds. The total daily doses administered were approximately 300mg. zinc gluconate in the compositions of Examples II and V.

10

After seven days of these treatments the results are:

<u>Spray Compositions</u>	<u>% Patients Asymptomatic</u>
EX.II	85
EX.V	75
EX.VI	60
EX.VII	45

15

B

CLAIMS

1. The use of a composition comprising:
 - (i) at least one of a soluble vitamin and a soluble mineral;
 - (ii) a non-toxic zinc compound; and
 - (iii) a non-toxic solvent for said vitamin or said soluble mineral,for introducing at least one of said soluble vitamin and said soluble mineral as well as said non-toxic zinc compound into an animal through the oral cavity.
2. The use of a composition comprising:
 - (i) Vitamin C;
 - (ii) a non-toxic zinc compound; and
 - (iii) a non-toxic solvent for said Vitamin C,for introducing said Vitamin C and said non-toxic zinc compound into an animal through the oral cavity, and for the treatment of the common cold.
3. The use as claimed in claim 1 or claim 2, as a spray composition.
4. The use as claimed in claims 1 to 3, including the use of a flavouring agent.
5. The use as claimed in claim 1 or claim 3 or claim 4, when dependent on claim 1, for introducing Vitamin A and said non-toxic zinc compound into an animal through the oral cavity.
6. The use as claimed in claim 1, or claim 3 or claim 4, when dependent on claim 1, for introducing Vitamin B₁₂ and said non-toxic zinc compound into an animal through the oral cavity.
7. The use according to claims 1 to 6, including the use of sodium bicarbonate.
8. The use according to claims 1 to 7, including the use of glycerine.
9. The use according to claims 1 to 8, including the use of potassium sorbate.
10. A method for the preparation of a composition comprising: (1) at least one of a soluble vitamin and a soluble mineral, (ii) a non-toxic zinc compound, and (iii) a non-toxic solvent for said vitamin or said soluble mineral, said method comprising the steps of establishing a desired total dose for administration during a daily dosage period; selecting a concentration of said at least one of said soluble vitamin and said soluble

mineral agent, as well as said non-toxic zinc salt, in said non-toxic solvent for said vitamin or said soluble mineral, said concentration being one which will provide the desired total dose when administered in aerosol form as a series of aliquot doses at predetermined spaced intervals during waking hours into the oral cavity; and charging said composition to a spray dispenser.

11. A method for the preparation of a composition comprising: (i) Vitamin C; (ii) a non-toxic zinc compound, and (iii) a non-toxic solvent for said Vitamin C, said method comprising the steps of: establishing a desired total dose of said Vitamin C as well as a non-toxic zinc salt as an essential agent, in said non-toxic solvent, said desired dose being one which will provide the desired total dose when administered in aerosol form as a series of aliquot doses at predetermined spaced intervals during waking hours into the oral cavity; and charging the composition to a spray dispenser.

12. A method according to claim 10, wherein said step of selecting a concentration of said at least one of said soluble vitamin and said soluble mineral agent, and said non-toxic zinc salt, further includes the steps of:

determining the concentration by empirical tests; and

translating said tests to the aliquot dosage and a pattern of repetition of such dosages, to maintain the desired minimum body concentration of said at least one of said soluble vitamin and said soluble mineral agent, as well as said non-toxic zinc salt.

13. A method according to claim 11, wherein said step of selecting a concentration of said Vitamin C and said non-toxic zinc salt, further includes the steps of:

determining the concentration by empirical tests; and

translating said tests to the aliquot dosage and a pattern of repetition of such dosages, to maintain the desired minimum body concentration of said at least one of said soluble vitamin and said soluble mineral agent, as well as said non-toxic zinc salt.

14. The method according to claims 10 to 13, including the step of including sodium bicarbonate in said selected concentration, or in said established dose.

15. The method according to claims 10 to 14, including the step of including glycerine in said selected concentration, or in said established dose.

16. The method according to claims 10 to 15, including the step of including potassium sorbate in said selected concentration, or in said established dose.

17. A composition when prepared according to the method of claims 10 to 16, in combination with instructions to spray a series of aliquot doses at predetermined spaced intervals during waking hours into the oral cavity of a patient, as claimed in claims 1 to 9.