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Acidic and buffered skin-care compositions comprising nicotinamid and an absorbing agent

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DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ROSETTI, MATILDA ET AL: "Effect of certain pyridines on urease activity" XP002324692 retrieved from STN Database accession no. 1976:115677
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(54) Title: ACIDIC AND BUFFERED SKIN-CARE COMPOSITIONS COMPRISING NICOTINAMID AND AN ABSORBING AGENT

(57) Abstract: The invention relates to acidic and buffered skin-care compositions comprising nicotinamid and an absorbing agent, selected from titanium dioxide, titanium dioxide treated with a silicone derivative or fatty acids, zinc oxide treated with a silicone derivative or fatty acids and mixtures thereof. The invention relates also to medicaments comprising said compositions used for treating and/or preventing minor skin irritations, especially diaper dermatitis. The invention relates lastly to the use of said compositions as anti-urease agents.

Acidic and buffered skin-care compositions comprising nicotinamid and an absorbing agent

The invention relates to skin-care compositions comprising nicotinamid and an absorbing agent. The invention relates also to medicaments comprising said compositions, being advantageously used for treating and/or preventing minor to moderate skin irritations.

Few infants escape one or more episodes of diaper dermatits, which in its most commun form represents an irritant contact dermatitis. The diapered skin of enfants is frequently exposed to a warm, moist environnement, and increased hydratation of skin is known to cause increased friction and abrasion, increases permeability and elevated microbial counts.

It is believed that ammonia is implicated in the genesis of diaper dermatitis. More recently, it has been reported that ammonia may play an indirect role, involving an interaction between urine and feces. The direct effect on skin can be attributed to fecal enzymes, particularly proteases and lipases, that become more active and thus more damaging as the pH increases. The pH increase is the result of ammonia production from urinary urea through the action of fecal urease. Urine and feces are commonly present in the diaper at the same time, and exposure of the skin to these materials for several hours is not uncommon, particularly in the overnight diaper, providing suitable conditions and ample time for this interaction and resulting skin damage to occur. So, it is believed that lipases and proteases are skin irritants that may be involved in the induction of diaper dermatitis (Etiologic factors inndiaper dermatitis: the role of urine, Ronald W. Berg et al, Pediatric Dermatology, Vol. 3 No 2. 102-106).

In addition to its potential to make feces an irritant, urine may also contain materials that irritate skin directly, particularly after prolonged exposure.

For many years, research has been conducted into causes of, and remedies for, minor skin rashes in humans. Such rashes are, generally, caused by allergies, exposures of the skin to periods of cold weather, or exposure to hot, humid conditions, such as washing dishes or the like, or exposure to irritating materials in topical products or ingredients (e. g., retinoiod, hydroxy acids, keto acids). These rashes can also be caused by excessive dryness of the skin without adequate skin moisturization.

While the causes may vary, the symptoms usually involve minor skin irritating skin eruptions, chaffing and chapping accompanied by burning, stinging, pain and discomfort. Over the years, numerous attempts have been made to develop topical creams, ointments and pharmaceuticals to relieve or soothe the pain and/or itchiness typically associated with such skin irritations.

The patent application WO99/47141 describes compositions, intented for the treatment of minor skin irritations, containing a safe and effective amount of natural or synthetic vitamin B3 compounds as an anti-irritant agent. The compositions comprise as essential components a vitamin B3 component and a dermatologically acceptable carrier. The compositions may comprise optional components but the disclosed compositions do not comprise an absorbing agent. The compositions have a pH of from about 4 to about 7.

The patent application WO99/63982 discloses a method for treating diaper dermatitis in a human which comprises the steps of:

(A) providing a therapeutic diaper dermatitis wound healing composition comprising:

(a) a therapeutically effective amount of an inhibitor of mono-adenosine diphosphate-ribosyl transferase to inhibit adenosine diphosphate-ribosylation of vascular endothelial growth factor;

(b) a buffering agent to maintain the pH of dermatitis in a range from about 5 to about 8; and

(c) an anti-inflammatory agent; and

(B) contacting the therapeutic diaper dermatitis wound healing composition with diaper dermatitis in a human.

Notwithstanding such disclosures in the area of skin care, there remains a need for additional compositions providing improved symptomatic relief of minor skin irritations.

The regular use of an acidic preparation containing nicotinamid as urease-inhibitor would prevent the rise of the pH and protect the skin by maintening its physiological pH around 5.5.

It is, therefore, an objective of this invention to provide acidic and buffered topical skin preparations for alleviating the symptoms of minor skin eruptions, redness, itchiness, dryness, rashes, and chapping in mammals, especially humans.

The invention relates to an acidic and buffered composition comprising:

a) 0.1 % to 4%, by weight of the composition, of nicotinamid; and

b) 5 % to 20 %, by weight of the composition, of an absorbing agent selected from the group consisting of titanium dioxide, titanium dioxide treated with a silicone derivative or fatty acids, zinc oxide treated with a silicone derivative or fatty acids and mixtures thereof.

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According to a first aspect of the invention there is provided an acidic and buffered skin care composition comprising:

a) 0.3 % to 2.5 %, by weight of the composition, of nicotinamide;

b) 10 % to 30 % by weight of the composition of mixtures of absorbing agents selected from the group consisting of starch, talc, kaolin, aluminium stearate, magnesium carbonate, titanium dioxide, titanium dioxide treated with a silicone derivative or fatty acids, zinc oxide treated with a silicone derivative or fatty acids;

c) 3 % to 10 % by weight of the composition of dexpanthenol;

d) vitamin E;

e) one or more buffering agents; and

f) 40 to 90 % of a dermatologically acceptable carrier,

wherein the buffering agents are citrates, phosphates or mixtures thereof providing a pH range of 4.4 to 6 in the composition.

According to a second aspect of the invention there is provided use of a composition according to the first aspect as an anti-urease agent.

According to a third aspect of the invention there is provided use of a composition according to the first aspect, for the manufacture of a medicament for treating and/or preventing diaper dermatitis.

According to a fourth aspect of the invention there is provided a method for treating and/or preventing diaper dermatitis, the method comprising administering to a subject in need thereof a composition according to the first aspect.

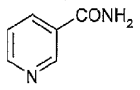
As used herein, "acidic composition" means that said composition has a pH value which is lower than 7.

A buffered composition is formulated to provide a capacity of resistance to an increase of pH induced by the addition of an alkaline agent. The composition may be buffered by the addition of buffering agents which include but are not limited to citrates (disodium citrate/trisodium citrate) or phosphates (potassium dihydrogen phosphate and disodium hydrogen phosphate). Preverence is given to a buffered composition comprising disodium citrate, trisodium citrate potassium dihydrogen phosphate, disodium hydrogen phosphate or mixtures thereof.

The buffer capacity can be quantified by the volume of alkaline solution added to reach a fixed pH.

According to the invention, the composition has advantageously a pH value in the range of 4 to 7, more advantageously from 4.4 to 6.0, even more advantageously from 5.0 to 6.0.

Nicotinamid is a vitamin B_3 compound having the following formula:



Salts of the vitamin B_3 compound are also useful herein. Nonlimiting examples of salts of the vitamin B_3 compound useful herein include organic or inorganic salts, such as inorganic salts with anionic inorganic species (e. g., chloride, bromide, iodide, carbonate), and organic carboxylic acid salts (including mono-, di-and tri-C_1-C_{18} carboxylic acid salts, e. g., acetate, salicylate, glycolate, lactate, malate, citrate). These and other salts of the nicotinamid can be readily prepared by the man skilled in the art.

As used herein, absorbing agents are finely powdered materials incorporated in high concentration in semi-solid preparations (pastes) inducing absorptive characteristics to the preparations. Several methods are described in the litterature to quantify their absorptive feature by measuring the quantity of water absorbed either after incubation or through water permeable film (Juch; Rufi; Surber; in Dermatology 1994; 189 :373-377 and Rae in Brit. J. Dermat. 1947;59,338-39). Absorbing agents according to the invention include but are not limited to zinc oxide, titanium dioxide, starch, talc, kaolin, aluminium stearate, magnesium carbonate or a mixture thereof which are the most commonly used absorbing agents. Preverence is given to a composition comprising talc, titanium dioxide, titanium dioxide treated with a silicone derivative or fatty acids, zinc oxide treated with a silicone derivative or fatty acids or mixtures thereof.

According to the invention, when the absorbing agent is titanium dioxide treated with a silicone derivative or zinc oxide treated with a silicone derivative, the silicon derivative is advantageously selected from the group consisting of methicone, dimethicone and cyclopentasiloxane. When the absorbing agent is titanium dioxide treated with fatty acids or zinc oxide treated with fatty acids, the fatty acids are advantageously selected from the group consisting of stearic acid, mystiric acid and mixtures thereof. According to one embodiment of the invention, the absorbing agent is titanium dioxide. Advantageously, titanium dioxide is used in anatase crystalline form with an average primary crystal size ranging from 0.2 to 0.4 µm.

According to one embodiment of the present invention, the composition comprises 5 % to 20 %, by weight of the composition, of one of said absorbing agents, advandageously 5 % to 15 % by weight of the composition, of one of said absorbing agents. If a mixture of absorbing agents is used the total amount of the absorbing agents in the composition is 5 % to 40 %, preferably 10 % to 30 %, more preferably 15% to 25 % by weight of the composition.

The composition advantageously comprises 0.1 % to 4 %, preferably 0.3 to 2.5 %, by weight of the composition, of nicotinamid.

The composition may further comprise physiological skin lipids which include but are not limited to ceramide, cholesterol, palmitic acid and linoleic acid; other vitamins, in particular specific vitamins to help healing process which include but are not limited to dexpanthenol and vitamin E; anti-pruritic agents which include but are not limited to glycine; moisturising agents which include but are not limited to glycerin, sorbitol and xylitol. According to one advandageously embodiment of the invention, the composition comprises dexpanthenol and vitamin E.

According to one embodiment of the present invention, the composition comprises dexpanthenol in an amount of 3 % to 10 %, preferably 4 % to 8 % by weight of the composition.

The composition may further comprise a vitamin C compound in combination with or instead of nicotinamid.

According to an advantageous embodiment of the invention, the composition does not comprise ethanol or preservatives; the composition is preservative and ethanol free. The composition may comprise a synthetic or a natural emulsifier which include but are not limited to cetearylglucoside, cocoylglucoside, bis-PEG/PPG-16/16 PEG/PPG-16/16 dimethicone, tribehenin PEG-20 esters, glyceryl stearate, PEG-75 stearate, ceteth-20, Ceteareth-12, ceteareth-20, steareth-

20, polyglyceryl-3-diisostearate, polyglyceryl-2-dihydroxystearate, PEG-30 dipolyhydroxystearate, cetyl PEG/PPG-10/1 dimethicone, bis PEG/PPG-14/14 dimethicone.

Other conventional skin care product additives may also be included in the composition of the present invention which include but are not limited to iscosifying agents and emulsion stabilizers like xanthan gum, cetearyl alcohol, PVP, PEG-75, sodium alginate, carbomer, guar gum, emollients like caprilic/capric triglycerides, squalane, dimethicone, water resistant and film former agents like PVP eicosene Copolymer, C20-22 alkyl phosphate/C20-22 alcohols, colorants like iron oxides.

The composition complies with the EP standards for efficacy of antimicrobial preservation, what means that after inoculation of 10^5 to 10^6 micro-organisms the log reduction must be the following :

	2 days	7 days	14 days	28 days
Bacteria criteria A	2	3	-	No Increase (NI)
Bacteria criteria B	-	-	3	(NI)
Fungi criteria A	-	-	2	(NI)
Fungi criteria B	-	-	1	(NI)

Table 1

The composition of the present invention also contains a dermatologically acceptable carrier. The expression "dermatologically-acceptable carrier", as used herein, means that the carrier is suitable for topical application to the skin, has good aesthetic properties, is compatible with the actives of the present invention and any other components, and will not cause any untoward safety or toxicity concerns. A safe and effective amount of carrier is from about 40% to about 90%, preferably from about 45% to about 85%, more preferably from about 50% to about 80% by weight of the composition.

The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to, oil-in-water (e.g. emulgel), water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicone emulsions, are useful herein. Preferred cosmetically and/or pharmaceutically acceptable topical carriers include oil-in-water emulsions.

These emulsions can also be delivered in the form of sprays using either mechanical pump containers or pressurized aerosol containers using conventional propellants. These carriers can also be delivered in the form of a mousse. Other suitable topical carriers include anhydrous liquid solvents such as oils, and silicones; aqueous-based single phase liquid solvents; and thickened versions of these anhydrous and aqueous-based single phase solvents.

The composition of the present invention is generally prepared by conventional methods such as are known in the art of making topical compositions.

Such methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum, and the like. Non-limiting examples of the product form can be a cream, paste, gel, emulsion, lotion, ointment, solution, liquid, mousse, foam etc.

The composition is useful for treating or preventing minor skin eruptions, redness, itchiness, dryness, rashes, and chapping in mammals, especially humans.

The composition is advantageously topically applied to the skin.

The invention also relates to a medicament comprising a composition as described above.

The medicament is useful for treating or preventing the irritation of mammalian skin.

The medicament is useful for treating or preventing skin eruptions, itchiness, rashes, and chapping in mammals, especially humans. The medicament is particularly intented for the treatment and/or the prevention of diaper dermatitis.

The medicament is advantageously topically applied to the skin. The medicament may be in the form of a cream, paste, skin lotion, gel or the like which is intended to be left on the skin. The amount of the medicament which is applied, the frequency of application and the period of use will vary widely depending upon the level of irritation reduction desired.

The invention further relates to the use of the above-described composition as an anti-urease agent, ie the above-described composition may be used for inhibit the urease activity.

The following examples further describe and demonstrate embodiments within the scope of the present invention.

Example 1: formulae comprising Nicotinamid according to the present invention

	1A	1B	1C	1D	1E	1F	1G	1H
Ingredients	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
Uncoated titanium dioxide	4	10	10	10	10	10	10	10
Coated zinc oxide	1	-	-	-	-	-	-	-
talc	-	15	15	15	15	15	15	15
total insoluble powders	**5**	**25**	**25**	**25**	**25**	**25**	**25**	**25**
Water	34.8	27	26	25.5	21	27.5	30	35
Moisturizing Agents	25	15	15	15.5	20	15	15.5	10
Glycine and derivates	3.4	4	4	4	4	4	3	3
nicotinamid	1	2	2	2	2	2	2	2
Viscosifying agents	0.8	1	2	2	2	2	3	3
Buffering agents	-	5.77	5.77	5.77	5.77	4.45	1.35	1.35
total aqueous phase	**65**	**55**	**55**	**55**	**55**	**55**	**55**	**55**
Emollients	25	15	15	15	15	15	15	15
Emulsifying agents	5	5	5	5	5	5	5	5
total lipid phase	**30**	**20**	**20**	**20**	**20**	**20**	**20**	**20**

Table 2

	2A	2B	2C	2D	2E	2F	2G	2H
Ingredients	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
Uncoated titanium dioxide	-	-	-	-	-	10	10	-
Coated titanium dioxide	10	10	10	10	10	-	-	10
talc	10	10	10	10	10	10	10	10
total insoluble powders	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Water	46	45.5	46.5	51.5	47	42.5	47.5	43.1
Moisturizing agents	15.5	15.5	15.5	10.5	15.5	15.5	10.5	15.5
Glycine and derivates	2.5	2.5	2.5	2.5	2.5	3	3	2.7
nicotinamid	2	2	1	1	0.5	2	2	2
Viscosifying agents	3	3	3	3	3	3	3	3
Buffering agents	1	1.5	1.5	1.5	1.5	2	2	1.7

	2A	2B	2C	2D	2E	2F	2G	2H
total aqueous phase	**70**	**70**	**70**	**70**	**70**	**68**	**68**	**68**
Emollients	7	7	7	7	7	7	7	7
Emulsifying agents	3	3	3	3	3	5	5	5
total lipid phase	**10**	**10**	**10**	**10**	**10**	**12**	**12**	**12**

Table 3

	3A	3B	3C	3D	3E
Ingredients	% w/w	% w/w	% w/w	% w/w	% w/w
Uncoated titanium dioxide	-	10	10	-	10
Coated titanium dioxide	10	-	-	10	-
talc	10	10	10	10	10
total insoluble powders	**20**	**20**	**20**	**20**	**20**
Water	42.5	42.5	47.5	43.1	43.1
Moisturizing agents	15.5	15.5	10.5	15.5	15.5
Glycine and derivates	3	3	3	2.7	2.7
nicotinamid	2	2	2	2	2
Viscosifying agents	3	3	3	3	3
Buffering agents	2	2	2	1.7	1.7
total aqueous phase	**68**	**68**	**68**	**68**	**68**
Emollients	7	7	7	7	7
Physiological skin lipids	0.06	0.06	0.006	0.006	0.006
Emulsifying agents	5	5	5	5	5
total lipid phase	**12**	**12**	**12**	**12**	**12**

Table 4

		4A	4B	4C	4D	4E	4F	4G	4H
Ingredients (INCI NAME)	**COMMERCIAL NAME**	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
TITANIUM DIOXIDE	UNCOATED TITANIUM DIOXIDE	4	10	10	10	10	10	10	10
ZINC OXIDE CYCLOPENTASILOXANE DIMETHICONE MYRISTIC ACID	COATED ZINC OXIDE SAS-UFZO-450/D5	1	-	-	-	-	-	-	-

		4A	4B	4C	4D	4E	4F	4G	4H
Ingredients (INCI NAME)	COMMERCIAL NAME	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
TALC	TALC	-	15	15	15	15	15	15	15
	TOTAL INSOLUBLE POWDERS	**5**	**25**	**25**	**25**	**25**	**25**	**25**	**25**
AQUA	WATER	34.8	27	26	26	21	27.5	30	35
SORBITOL	SORBITOL	20	-						
XYLITOL	XYLITOL	-	10	10	10	15	10	10	5
PANTHENOL	DEXPANTHENOL	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
PANTOLACTONE	PANTOLACTONE	-	-	0.5	0.5	0.5	0.5	0.5	0.5
GLYCINE	GLYCINE	1.4	2	2	2	2	2	2	2
NICOTINAMIDE	VITAMINE PP / B3	1	2	2	2	2	2	2	2
SILICA	AEROSIL 200	-	1	2	2	2	2	3	3
CAPRYLOYL GLYCINE	LIPACIDE C8G	1.0	1.0	1.0	2.0	2.0	2.0	1.0	1.0
UNDECYLENOYL GLYCINE	LIPACIDE UG	1.0	1.0	1.0	-	-	-	-	-
POTASSIUM PHOSPHATE	POTASSIUM PHOSPHATE	-	-	-	-	-	-	0.65	0.65
DISODIUM PHOSPHATE	DISODIUM PHOSPHATE	-	-	-	-	-	-	0.7	0.7
XANTHAN GUM	KELTROL K	0.8	-	-	-	-	-	-	-
SODIUM CITRATE	TRISODIUM CITRATE	-	3.14	3.14	3.14	3.14	3.14	-	-
DISODIUM CITRATE	DISODIUM CITRATE	-	2.63	2.63	2.63	2.63	1.315	-	-
	TOTAL AQUEOUS PHASE	**65**	**55**	**55**	**55**	**55**	**55**	**55**	**55**
CAPRYLIC /CAPRIC GLYCERIDES	TRIGLYCERIDES C8-C10 5545	7	3	4	4	4	4	4	4
SQUALANE	PHYTOSQUALANE	6	1	2	2	2	2	2	2
DIMETHICONE	DIMETHICONE Q7-9120 100 cSt	5	4	2	2	2	2	2	2
CETEARYL ALCOHOL	LANETTE O	5	2	2	2	2	2	2	2
CETEARYL ALCOHOL COCOGLUC	MONTANOV 82	5	5	5	5	5	5	5	5

		4A	4B	4C	4D	4E	4F	4G	4H
Ingredients (INCI NAME)	COMMERCIAL NAME	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
TOCOPHERYL ACETATE	VITAMINE E	2	2	2	2	2	2	2	2
OLEIC/LINOLEIC/LINOLENIC GLYC	VIAMERINE 4000	-	3	3	3	3	3	3	3
	TOTAL LIPID PHASE	**30**	**20**	**20**	**20**	**20**	**20**	**20**	**20**

Table 5

		5A	5B	5C	5D	5E	5F	5G	5H
Ingredients (INCI NAME)	COMMERCIAL NAME	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
TITANIUM DIOXIDE	UNCOATED TITANIUM DIOXIDE PHARMA GRADE HOMBITAN ANATASE FF	-	-	-	-	-	10	10	-
TITANIUM DIOXIDE DIMETHICONE	COATED TITANIUM DIOXIDE C47-060-10	10	10	10	10	10	-	-	10
TALC	TALC	10	10	10	10	10	10	10	10
	TOTAL INSOLUBLE POWDERS	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
AQUA	WATER	46	45.5	46.5	51.5	47	42.5	47.5	43.1
XYLITOL	XYLITOL	10	10	10	5	10	10	5	10
PANTHENOL	DEXPANTHENOL	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
PANTOLACTONE	PANTOLACTONE	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
GLYCINE	GLYCINE	2	2	2	2	2	2	2	2
NICOTINAMIDE	VITAMINE PP / B3	2	2	1	1	0.5	2	2	2
SILICA	AEROSIL 200	3	3	3	3	3	3	3	3
CAPRYLOYL GLYCINE	LIPACIDE C8G	0.5	0.5	0.5	0.5	0.5	1.0	1.0	0.7
UNDECYLENOYL GLYCINE	LIPACIDE UG	-	-	-	-	-	-	-	-

		5A	5B	5C	5D	5E	5F	5G	5H
Ingredients (INCI NAME)	COMMERCIAL NAME	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
POTASSIUM PHOSPHATE	POTASSIUM PHOSPHATE	0.65	1.0	1.0	1.0	1.0	1.0	1.0	1.0
DISODIUM PHOSPHATE	DISODIUM PHOSPHATE	0.35	0.5	0.5	0.5	0.5	1.0	1.0	0.7
	TOTAL AQUEOUS PHASE	**70**	**70**	**70**	**70**	**70**	**68**	**68**	**68**
CAPRYLIC /CAPRIC GLYCERIDES	TRIGLYCERIDES C8-C10 5545	1	1	1	1	1	1	1	1
SQUALANE	PHYTOSQUALANE	1	1	1	1	1	1	1	1
DIMETHICONE	DIMETHICONE Q7-9120 100 cSt	1	1	1	1	1	1	1	1
CETEARYL ALCOHOL	LANETTE O	2	2	2	2	2	2	2	2
CETEARYL ALCOHOL COCOGLUC	MONTANOV 82	3	3	3	3	3	3	3	3
TOCOPHERYL ACETATE	VITAMINE E	2	2	2	2	2	2	2	2
C20-22 ALKYL PHOSPHATE AND C20-22 ALCOHOLS	SENSANOV WR	-	-	-	-	-	2	2	2
	TOTAL LIPID PHASE	**10**	**10**	**10**	**10**	**10**	**12**	**12**	**12**

Table 6

		6A	6B	6C	6D	6E
Ingredients (INCI NAME)	COMMERCIAL NAME	% w/w	% w/w	% w/w	% w/w	% w/w
TITANIUM DIOXIDE	UNCOATED TITANIUM DIOXIDE PHARMA GRADE HOMBITAN ANATASE FF	-	10	10	-	10

Ingredients (INCI NAME)	COMMERCIAL NAME	6A % w/w	6B % w/w	6C % w/w	6D % w/w	6E % w/w
TITANIUM DIOXIDE DIMETHICONE	COATED TITANIUM DIOXIDE C47-060-10	10	-	-	10	-
TALC	TALC	10	10	10	10	10
	TOTAL INSOLUBLE POWDERS	**20**	**20**	**20**	**20**	**20**
AQUA	WATER	42.5	42.5	47.5	43.1	43.1
XYLITOL	XYLITOL	10	10	**5**	10	10
PANTHENOL	DEXPANTHENOL	5.0	5.0	5.0	5.0	5.0
PANTOLACTONE	PANTOLACTONE	0.5	0.5	0.5	0.5	0.5
GLYCINE	GLYCINE	2	2	2	2	2
NICOTINAMIDE	VITAMINE PP / B3	2	2	2	2	2
SILICA	AEROSIL 200	3	3	3	3	3
CAPRYLOYL GLYCINE	LIPACIDE C8G	1.0	1.0	1.0	0.7	0.7
POTASSIUM PHOSPHATE	POTASSIUM PHOSPHATE	1.0	1.0	1.0	1.0	1.0
DISODIUM PHOSPHATE	DISODIUM PHOSPHATE	1.0	1.0	1.0	0.7	0.7
	TOTAL AQUEOUS PHASE	**68**	**68**	**68**	**68**	**68**
CAPRYLIC /CAPRIC GLYCERIDES	TRIGLYCERIDES C8-C10 5545	1	1	1	1	1
SQUALANE	PHYTOSQUALANE	1	1	1	1	1
DIMETHICONE	DIMETHICONE Q7-9120 100 cSt	1	1	1	1	1
CETEARYL ALCOHOL	LANETTE O	2	2	2	2	2
CETEARYL ALCOHOL COCOGLUC	MONTANOV 82	3	3	3	3	3
TOCOPHERYL ACETATE	VITAMINE E	2	2	2	2	2
C20-22 ALKYL PHOSPHATE AND C20-22 ALCOHOLS	SENSANOV WR	2	2	2	2	2
CERAMIDE	CERAMIDE	0.01	0.01	0.001	0.001	0.001

		6A	6B	6C	6D	6E
Ingredients (INCI NAME)	COMMERCIAL NAME	% w/w	% w/w	% w/w	% w/w	% w/w
CHOLESTEROL	CHOLESTEROL	0.03	0.03	0.003	0.003	0.003
PALMITIC ACID	PALMITIC ACID	0.01	0.01	0.001	0.001	0.001
LINOLEIC ACID	LINOLEIC ACID	0.01	0.01	0.001	0.001	0.001
	TOTAL LIPID PHASE	**12**	**12**	**12**	**12**	**12**

Table 7

Example 2: Buffer capacity of the compositions according to the invention

The buffer capacity can be quantified by the volume of alkaline solution added to reach a fixed pH.

Protocol : Test is done by titrimetry

Dilute 10 g of cream up to 100 ml with water

Titrate 50 ml of solution with 0.1 M ammonia to reach a pH of 8

Record the volume

Results : the results are given in table 8

	5B	5F	5H	4F
Glycine	2%	2%	2%	2%
Disodium Phosphate	0.5%	1.0%	0.7%	-
Potassium phosphate	1.0%	1.0%	1.0%	-
Disodium citrate	-	-	-	1.315%
Trisodium citrate	-	-	-	3.14%
Lipacide C8G	0.5%	1%	0.7%	1%
Lipacide UG	0%	0%	0%	1%
pH (at start)	5.3	5.1	5.3	5.3
Results: in ml of ammonia 0.1M to reach pH 8	**4.9**	**7.8**	**5.6**	**6.5**

Table 8

Proposed specification : more than 3.0 ml, preferably more than 4.5 ml of ammonia 0.1M to reach pH 8.

These results confirm that the compositions according to the invention could be called buffered compositions.

Example 3: Inhibition of urease

The purpose of this example is to test the inhibitory effect of some molecules on the activity of urease. Suitable conditions (T°, time, concentration) for which urease produces amounts of measurable ammonia were determined. In the same conditions, increasing concentrations of nicotinamid are added.

METHOD

Principle: Enzyme activity is determined by incubation of the sample with urease and subsequent determination of released ammonia using an indophenol reaction along with parallel standardisation with ammonia.

Solutions:

- Buffers

a) "Buffer pH 12": 30 g Na citrate
30 g Na_3 phosphate
3 g EDTA >>>ad 1000 ml H_2OmQ

b) "Acetate buffer": 0.2 m in H_2OmQ >>>adjusted to pH 5.5

- Reagents (stock solutions)

1) "Urease stock": 2.5 mg/ml in H_2OmQ (-20°C)
2) "Urea stock": 10 % urea w/v in H_2OmQ (4°C)

- Reagents (working solutions)

3) "Reagent A": 6.0 g phenol
20 mg sodium nitroprusside >>> ad 100 ml H_2OmQ
4) "Reagent B": 16 g NaOH solid
7.0 ml sodium hypochlorite 13 % >> ad 1000 ml H_2OmQ
5) "Urea-acetate": Urea stock (2) in acetate buffer (b) to 4 % w/v
6) "Samples": 25 mg/ml in acetate buffer (b)
7) "Standard": 100 mg/L in H_2OmQ
8) "Urease": Urease stock (1) in H_2OmQ to 0.4 mg/L

Method Overview: Suitable urease and ammonia concentrations were determined by preliminary tests to get a linear signal (between 0 and 1.2 O.D. at 630 nm) after 30' of colorimetric reaction.

Serial dilutions of the samples were prepared in order to obtain a significant inhibition curve. An ammonia standard curve was also prepared in parallel. Each test was performed in duplicate. The well volume is 100 µL. All sample and urea solutions were adjusted to pH 5.5. We used 3 blank values and a zero inhibition point:

- zero inhibition test : 25 µL 4% w/v urea + 50 µL urease 0.4mg/ml + 25 µL acetate buffer

- sample blanks : 25 µL sample 25 mg/ml + 25 µL urea + 50 µL acetate buffer

- urease blank: 50 µL urease 0.4 mg/ml + 50 µL acetate buffer

- standard blank : 25 µL 4% w/v urea + 75 µL acetate buffer

Sample curves included 8 concentrations (dilution 2/5 from 25 mg/ml to 0.01 mg/ml) :

- sample tests : 25 µL sample (for each concentration) + 25 µL 4% w/v urea + 50 µL urease 0.4 mg/ml

The standard curves included also 8 concentrations (two-fold dilution from 100 mg/L to 0.8 mg/ml)

- standard tests : 50 µL standard (for each concentrations) + 25 µL 4% w/v urea + 25 µL acetate buffer

The microplate was incubated for 15' at room temperature after urease addition (enzymatic reaction) and then incubated for 30' after addition of reagent A and reagent B (60 µL and 90 µL respectively >> indophenol colorimetric reaction).

The absorbance was then read at 630 nm

RESULTS:

Each result corresponds to the average of the two replicates. For the samples, blank is the sum of urease blank and sample blank. For the standards, blank is the standard blank.

Wells	ABSORBANCE (630 nm)
blank Nicotinamid	0.038
blank urease	0.049
blank Standard	0.061
urease (zero inhibition)	1.3755

Table 9

Nicotinamid

Wells	Concentration	Absorbance (630 nm)	Absorbance-Blank (630 nm)
A	6.25	0.072	-0.015
B	2.5	0.0835	-0.0035
C	1	0.1065	0.0195
D	0.4	0.151	0.064
E	0.16	0.2595	0.1725
F	0.064	0.497	0.41
G	0.0256	0.7325	0.6455
H	0.01024	1.058	0.971
Urease	0	1.3755	1.2885

Table 10

Standad

Wells	Concentration	Absorbance (630 nm)	Absorbance-Blank (630 nm)
A*	100	NA	NA
B	50	0.9535	0.8925
C	25	0.543	0.482
D	12.5	0.309	0.248
E	6.25	0.1865	0.1255
F	3.125	0.124	0.063
G	1.5625	0.093	0.032
H	0.78125	0.0775	0.0165
Blank	0	0.061	0

* 100 mg/ml was not used due to the high variabilty between duplicate absorbance values (1.102-1.574)

Table 11

In the test conditions significant inhibition of urease activity is observed between 0.01 and 1 mg/ml; above this last concentration, total inhibition of urease is obtained.

Example 4: Inhibition of the Jack Bean UREASE activity by the compositions according to the invention

The purpose of this example is to compare the inhibition of urease activity by a cream placebo and a cream containing 0.5%, 1%, 2% nicotinamid.

Optimal conditions to reach sufficient inhibitory effect will be investigated.

Product: formulae 5B, 5C, 5E and formula 5E', which is the same as formula 5E provided that it comprises 47.5 % w/w water instead of 47 % w/w and 0% w/w nicotinamid instead of 0.5 % w/w, have been tested.

- Method

Reagent and buffer preparation

a) Sodium Acetate Buffer 0.33 ph 5.5 ("buffer")

b) Ammonium standard: NH_4Cl X mg/l
(diluted with buffer or diluted sample; X depending on the test)

c)	"Buffer pH 12":	Na_3PO4 12 H_2O	30 g/l
		Na_3citrate 2 H_2O	30 g/l
		EDTA	3 g/l
d)	Reagent A:	phenol	6 g/100 ml
		sodium nitroprusside	25 mg/100 ml
		ad "Buffer pH 12" to complete volume	
e)	Reagent B:	NaOH	16 g/l
		NaClO 13 %	7.0 ml/l
		ad dd H_2O to complete volume	
f)	Urea 4 %	Urea 40 g/l	
		ad buffer to complete volume	
g)	Urease-stock	Jack Bean Urease	2,5 mg/ml
		reconstituted with ddH_2O	
h)	Urease (working solution)	Urease-stock	50 µl/50 ml
		diluted with buffer	

i)	Nicotinamid control	Nicotinamid	50 mg/l
		ad buffer to complete volume	

Composition: Sample with 2%, 1%, 0.5%, 0% nicotinamid

- General Method : Urease inhibition assay

Each assay is divided in three steps :

1) Sample preparation

2) Detection

3) Absorbance readings at 630 nm

1) Sample preparation

Sample and placebo were diluted in buffer (Sodium Acetate Buffer 0.33 M pH 5.5).

2) Detection : Urease assay

Each test tube contained	250 µl urea 4 %
	250 µl urease 2,5 mg/l
	500 µl diluted sample or diluted placebo

Each tube was incubated 15' at room temperature with urease.

30 µl of HCl 30% and 400 µl chloroform were added in each tube.

The tubes were centrifugated 15' 10000 RPM.

The supernatant was removed.

100 µl supernatant, 60 µl of Reagent A and 90 µl of Reagent B were added in each well and incubated 1h at room temperature.

3) Absorbance reading at 630 nm

Absorbance was read at 630 nm.

Urease blank average value was substracted from each "activity tubes" values.

Averages and RSD was calculated for each series.

- Results and discussion

In this study, serial dilutions of cream (placebo, nicotinamid 0.5 % and 2%) were tested for inhibitory effect on urease activity. The method described in example 3 was applied. In a second step, inhibitory effects of cream placebo or containing 0.5 %, 1% and 2 % nicotinamid were compared.

1. Research for cream dilution with optimal inhibitory effect :

The two major consequences of the cream dilutions are a lower matrix effect and a reduction of the nicotinamid concentration. This inhibitory effect of nicotinamid was shown by comparison of results obtained for the placebo and the sample. The optimal dilution will be chosen for its best ratio between placebo and sample inhibitory effect. 200, 400, 600 and 800 fold dilutions of cream - nicotinamid 2% were tested. 100, 200 and 300 fold dilutions were tested for the cream - nicotinamid 0.5%. For each dilution, duplicates were prepared and tested in quadruplicate. Average and RSD were calculated for each series (8 results).

Results are shown in figurs 1 and 2. Figur 1 describes, for a cream comprising 2% nicotinamid, the O.D. values at 630 nm after 60' respectively for

1- sample – dilution 800×
1'- placebo – dilution 800×
2- sample – dilution 600×
2'- placebo – dilution 600×
3- sample – dilution 400×
3'- placebo – dilution 400×
4- sample – dilution 200×
4'- placebo – dilution 200×

Figur 2 describes, for a cream comprising 0.5% nicotinamid, the O.D. values at 630 nm after 60' respectively for

1- sample – dilution 300×
1'- placebo – dilution 300×

2- sample – dilution 200×

2'- placebo – dilution 200×

3- sample – dilution 100×

3'- placebo – dilution 100×

All together, these results suggest that 200 fold dilution is the more effective condition of assay.

2. Inhibitory effects of diluted cream placebo or diluted cream containing 0.5 %, 1% and 2 % nicotinamid

200 fold dilutions of each cream formulations and placebo were tested for their inhibitory effect on urease activity. For each dilution, duplicates were prepared and tested in quadruplicate. Average and RSD were calculated for each series (8 results).

Result are shown in figur 3, which describes the O.D. values at 630 nm after 60' respectively for

1- placebo – dilution 200×

2- cream with 0.5% nicotinamid – dilution 200×

3- cream with 1% nicotinamid – dilution 200×

4- cream with 2% nicotinamid – dilution 200×

The O.D. difference between diluted cream placebo and diluted cream containing 0.5 % nicotinamid is more pronounced than O.D. differences between diluted samples containing 0.5 % - 1% and 2 % nicotinamid. However, the inhibitory effect appears to increase gradually with the nicotinamid concentration.

- Conclusion

All together, these results strongly suggest that a cream containing 0.5%, 1%, 2% nicotinamid inhibit gradually urease activity.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

The claims defining the invention are as follows:

1. Acidic and buffered skin care composition comprising:

   a) 0.3 % to 2.5 %, by weight of the composition, of nicotinamide;

   b) 10 % to 30 % by weight of the composition of mixtures of absorbing agents selected from the group consisting of starch, talc, kaolin, aluminium stearate, magnesium carbonate, titanium dioxide, titanium dioxide treated with a silicone derivative or fatty acids, zinc oxide treated with a silicone derivative or fatty acids;

   c) 3 % to 10 % by weight of the composition of dexpanthenol;

   d) vitamin E;

   e) one or more buffering agents; and

   f) 40 to 90 % of a dermatologically acceptable carrier,

   wherein the buffering agents are citrates, phosphates or mixtures thereof providing a pH range of 4.4 to 6 in the composition.

2. Composition according to claim 1, wherein the buffering agents are disodium citrate, trisodium citrate, potassium dihydrogen phosphate, disodium hydrogen phosphate or mixtures thereof.

3. Composition according to claim 1 or 2, wherein the composition comprises 15 % to 25 %, by weight of the composition, of said mixture of absorbing agents.

4. Composition according to any one of claims 1 to 3, wherein one of the absorbing agents is titanium dioxide.

5. Composition according to any one of claims 1 to 4, wherein the composition further comprises physiological skin lipids, other vitamins, anti-pruritic agent and/or moisturising agents.

6. Composition according to any one of claims 1 to 5, wherein the composition is an oil-in-water emulsion.

7. Composition according to any one of claims 1 to 6, wherein the composition is preservative and ethanol free.

8. Composition according to any one of claims 1 to 7 having a buffer capacity such that when 10 g of the composition is diluted in 100 ml water and 50 ml thereof is titrated with an aqueous solution of 0.1 M ammonia, more than 3 ml of the ammonia solution is needed to reach a pH of 8.

9. Composition according to any one of claims 1 to 8, wherein the nicotinamide is present at 0.5 % to 2 % by weight of the composition.

10. Composition according to any one of claims 1 to 9 for use as medicament.

11. Composition according to claim 10, wherein the medicament is used for treating and/or preventing diaper dermatitis.

12. Use of a composition according to any one of claims 1 to 11 as an anti-urease agent.

13. Use of a composition according to any one of claims 1 to 9, for the manufacture of a medicament for treating and/or preventing diaper dermatitis.

14. A method for treating and/or preventing diaper dermatitis, the method comprising administering to a subject in need thereof a composition according to any one of claims 1 to 9.

15. A composition according to claim 1 and substantially as herein described with reference to the Examples.

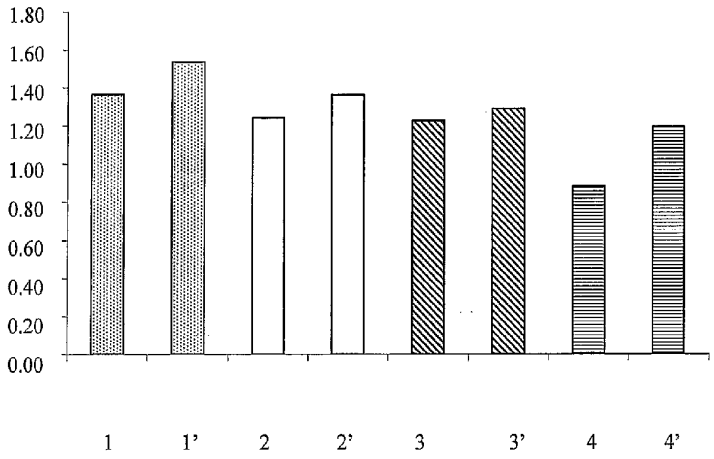


Fig. 1

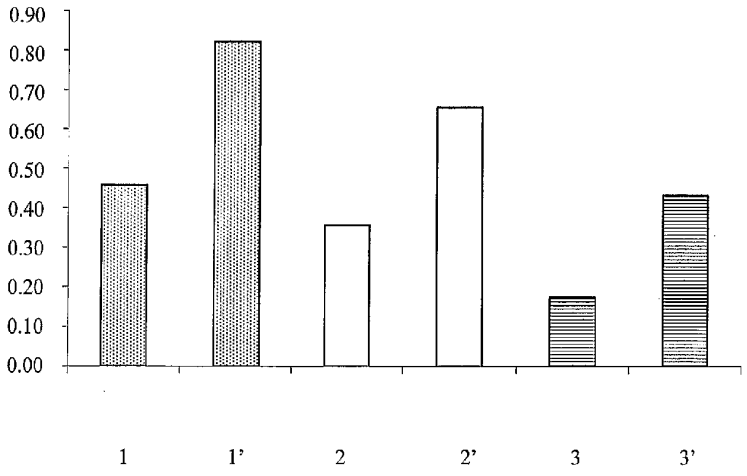


Fig. 2

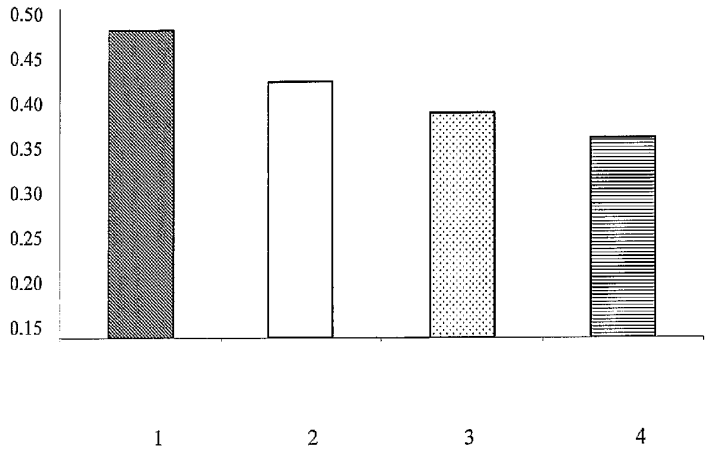


Fig. 3