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(54) Title: TOPICAL COMPOSITIONS

(57) Abstract: The present invention provides new topical pharmaceutical or cosmetic compositions for the prevention and treatment of irritation of mucous cells, or skin cells, comprising a combination of: xylitol, myoinositol or mannitol or any combination of these; glycerol and/or urea; water; in the absence of any oil in water or wax in water emulsion.

TOPICAL COMPOSITIONS

FIELD AND BACKGROUND OF THE INVENTION

The present invention provides a new combination of topically active substances, for the prevention and alleviation of cell damage, caused by preservatives, detergents or drugs, used in topical pharmaceutical, cosmetic or veterinary compositions.

Many substances are applied topically to the skin or mucous membranes of humans or animals in order to alter the subject's appearance, to protect the subject from the environment, or to produce a biological change in the skin or other tissue for therapeutic, preventive or cosmetic purposes. These substances may generically be termed "topical products" and include such topically applied substances as cosmetics, over-the-counter and prescription topical drugs, and a variety of other products such as soaps and detergents.

Topical products occur in a variety of forms, including solids, liquids, suspensions, semisolids (such as creams, gels, pastes or "sticks"), powders or finely dispersed liquids such as sprays or mists. Examples of topical products commonly classified as "cosmetics" include skin care products such as creams, lotions, moisturizers and "treatment cosmetics" such as exfoliants and/or skin cell renewal agents; fragrances such as perfumes and colognes, and deodorants; shaving-related products such as creams, "bracers" and aftershaves; depilatories and other hair removal products; skin cleansers, toners and astringents; pre-moistened wipes and washcloths; tanning lotions; bath products such as oils; eye care products such as eye lotions and makeup removers; foot care products such as powders and sprays; skin colorant and make-up products such as foundations, blushes, rouges, eye shadows and liners, lip colors and mascaras; lip balms and sticks; hair care and treatment products such as shampoos, conditioners, colorants, dyes, bleaches, straighteners and permanent wave products; baby products such as baby lotions, oils, shampoos, powders and wet wipes; feminine hygiene products such as deodorants and douches; skin or facial peels applied by dermatologists or cosmeticians; and others. Examples of topical products commonly classified as "topical drugs" are many and varied, and include over-the-counter and/or

prescription products such as antiperspirants, insect repellents, sunscreens and sunburn treatments, anti-acne agents, antibiotics, topical respiratory agents, ocular drugs such as eyedrops and saline solutions, therapeutic retinoids, anti-dandruff agents, external analgesics such as capsaicin products, topical contraceptives, topical drug delivery systems, gastrointestinal agents such as suppositories, enemas and hemorrhoid treatments, reproductive system agents such as vaginal treatments, oral treatments such as lozenges, and many other products with therapeutic or other effects. Other topical products include hand, facial and body soaps and detergents and other forms of skin cleansers, as well as household detergents and many other household products such as solvents, propellants, polishes, lubricants, adhesives, waxes and others which are either applied topically or are topically exposed to the body during normal use.

In a large number of cases, topical products contain chemicals which may produce "irritation," including various inflammation symptoms or signs, when applied to the skin or mucosa. The present invention is directed to compositions for inhibiting the irritation associated with such topical products.

The occurrence, frequency and nature of topical-product-induced irritation often varies from user to user. The severity of irritation to the susceptible user may range from subclinical to mild to severe. Typical symptoms of "irritation" include itching (pruritus), stinging, burning, tingling, "tightness," erythema (redness) or edema (swelling). The irritation response may be due to the direct effect on the skin of certain topical product chemicals or to a response by the immune system directed toward the chemicals alone or in combination with skin components (e.g. antigens).

Many ingredients used in topical products are known irritants or are potentially irritating, especially to people with "sensitive skin". These irritating ingredients include fragrances, preservatives, solvents, propellants and many other ingredients that might otherwise be considered inert components of the products. Additionally, many topical product active ingredients, including chemicals that may also be classified as drugs, produce irritation when applied to the skin. These include, but are not limited to, such ingredients as exfoliants and skin cell renewal agents, anti-acne drugs, antiperspirant compounds, antihistamines, anti-inflammatory agents, skin protective agents, insect repellent chemicals, sunscreens and many others. Where

more than one chemical irritant is present, their irritating effects may be additive. Furthermore, chemical ingredients may react with one another, or in the environment of the skin, to form new chemicals which are irritating. The vehicles in which the active drug ingredients are formulated may also produce irritation in sensitive people.

Whatever the exact cause of irritation, many attempts have been made to reduce the irritation potential of topical products by identifying chemicals which tend to cause irritation and reducing their concentration or eliminating them from the products. Many of these products are advertised to consumers as "hypoallergenic" or the like to designate a product's reduced tendency to cause irritation in consumers with sensitive skin. Many skin and mucosal irritation responses, however, are not allergic in origin. In any event, it is often not feasible or practical to identify or eliminate all of the irritating chemical(s), particularly when the irritating chemical(s) are the active ingredient of the product or are required for formulation, preservative or other functional reasons.

It is an object of the present invention to provide an effective topical composition, for combating damaging effects of irritants to mucous and skin cells.

The present invention relates to topical compositions for combating damaging effects of preservatives or other irritants , found, e.g. in multi-dose eye drops, to mucous cells, especially in the corneal cells and simultaneously beneficial to those tissues. It was found that glycerol counteracts corneal cell damage caused by preservatives such as benzalkonium chloride, cetrimonium bromide, sodium ethylene diamine tetraacetate, etc. Not all the polyhydroxy compounds have such anti-irritant properties. Moreover, it is known that isotonic sodium chloride is toxic to the corneal cells, whereas isotonic glycerol is not toxic. (Follmann, P. et. al. Szemészet 141, 305-308, 2004.)

In addition two physicochemical parameters are very important for a good topical composition: increased viscosity and increased spread of the solution.

Increased viscosity is achieved by high molecular weight (equal to more than 0.5 million Dalton) polymers. Increased spread is achieved by surface active agents, however after chronic use the surface active agents usually have damaging effects. (See Animal Studies,a).

It has now been found according to the present invention that all of the above mentioned problems of irritation by preservatives, detergents and other cell damaging agents disappear, and the beneficial effects are preserved or increased, by using a combination of xylitol, myoinositol or mannitol with glycerol and/or urea, preferably together with a surface active agent.

The advantages resulting from the addition of a surface active agent include a decrease in the surface tension of the aqueous solution, thereby increasing the spread. Thus it has now been found, that polysorbate 80 even at a concentration of 0.002% increases the diminished Break Up Time (BUT) in dry eye patients. (It is accepted that 10 sec. or less BUT indicates dry eye syndrome) (See Human Studies 1).

Thus, according to the present invention there are now provided topical pharmaceutical or cosmetic compositions for the prevention and treatment of irritation of mucous cells, or skin cells, comprising a combination of:

- xylitol, myoinositol or mannitol or any combination of these;
- glycerol and/or urea;
- water;
- in the absence of any oil in water or wax in water emulsion.

The present invention provides topical pharmaceutical or cosmetic compositions for the prevention and treatment of irritation of mucous cells, comprising a combination of:

- 1.5-5.5% xylitol, myoinositol or mannitol or any combination of these;
- 0.9-2.0% glycerol;
- less than 0.01% inorganic salts;
- water;
- in the absence of any oil in water or wax in water emulsion.

The present invention further provides topical pharmaceutical or cosmetic compositions, for the prevention and treatment of irritation of skin cells, comprising a combination of :

- 5-18 % xylitol, myoinositol or mannitol or any combination of these;
- 5-10% glycerol and/or urea;
- water;
- in the absence of any oil in water or wax in water emulsion.

More specifically the present invention preferably provides a non-irritant topical cosmetic or pharmaceutical composition for mucous cells or for the skin, as defined above, for the prevention of cell damage caused by preservatives, detergents or drugs in topically used cosmetic, pharmaceutical or veterinary compositions.

In especially preferred embodiments of the present invention there is provided a non-irritant topical cosmetic or pharmaceutical composition for mucous cells or for the skin, as defined above, further comprising at least one pharmaceutically active agent in solution, or in suspension but not in emulsion.

In preferred embodiments of the present invention there is provided a non-irritant topical cosmetic or pharmaceutical composition for mucous cells or for the skin, as defined above, further comprising at least one viscosity enhancing agent.

While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention of these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of proving what is believed to be the most useful and readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

Examples

Example 1: Moisturizing eye drops

Sodium hyaluronate	0.03 gm.
Povidone	2.0 gm.
Glycerol	1.0 gm.
Mannitol	3.2 gm.
Cetrimide	0.01 gm.
NaOH	q.s. to pH 7.0
H_2O	to 100 ml.

Example 2: Moisturizing eye drops

Glycerol	1.3 gm.
Xylitol	2.2 gm.
Benzalkonium Chloride	0.01 gm.
NaOH	q.s. to pH 7.0
H_2O	to 100 ml.

Example 3: Moisturizing eye drops unit dose form for single application

Sodium hyaluronate	0.03 gm.
Povidone	2.0 gm.
Glycerol	1.0 gm.
Myoinositol	3.2 gm.
NaOH	q.s. to pH 7.0
H_2O	to 100 ml.

Example 4: Moisturizing anti-inflammatory eye drops

Glycerol	1.3 gm.
Xylitol	2.2 gm.
Sodium diclofenac	0.1 gm.
Benzalkonium chloride	0.01 gm
NaOH	q.s. to pH 7.2
H_2O	to 100 ml.

Example 5: Moisturizing anti-inflammatory eye drops unit dose for single application

Glycerol	1.0gm.
Mannitol	1.6 gm.
Xylitol	1.6gm .
Sodium diclofenac	0.1 gm.
NaOH	q.s. to pH 7.2
H_2O	to 100 ml.

Example 6: Moisturizing Gel for skin

Glycerol	8.0 gm.
Mannitol	5.0 gm.
Urea	5.0 gm.
Glycine	5.0 gm
Methylparaben	0.1 gm.
Propylparaben	0.01 gm.
Polyacrylate 980 adjusted to pH 4.5	0.7 gm.
H_2O	to 100 ml

Example 7: Moisturizing Gel for skin

Glycerol	10.0 gm.
Xylitol	8.0 gm.
Urea	5.0 gm.
Glycine	5.0 gm
Methylparaben	0.1 gm.
Propylparaben	0.01 gm.
Polyacrylate 980 adjusted to pH 4.5	0.7 gm.
H_2O	to 100 ml.

Example 8: Moisturizing Gel for skin

Glycerol	8.0 gm.
Myoinositol	4.5 gm.
Xylitol	3.5gm
Urea	5.0 gm.
Glycine	5.0 gm
Methylparaben	0.1 gm.
Propylparaben	0.01 gm.
Polyacrylate 980 adjusted to pH 4.5	0.7 gm.
H_2O	to 100 ml.

Example 9: Moisturizing Gel with Phytosphingosine suspension for skin

Glycerol	8.0 gm.
Xylitol	7.0 gm

Polyethylene glycol 3350	2.0 gm
Phospholipids	0.25 gm
Phytosphingosine in suspension	0.2 gm.
Polyacrylate 980 or 974	1.0 gm.
Methylparaben	0.1 gm.
Propylparaben	0.01 gm.
H_2O	to 100 ml.

Suitable preservatives, suspending agents, excipients and other additives can be incorporated. The preferred pH (to be adjusted) of the compositions of examples 6 to 9 is pH 4.0 to 6.0 .

Methods:

Human studies

a. 23 dry eye patients received in both eyes 1drop of Fluorescein-Novesin mixture. After 30 seconds the right eye was treated with 1 drop from the treatment bottle. The patient was asked to blink 2-3 times, then the fluorescein BUT was measured. Afterwards the left eye was treated with 1 drop from the Control bottle, the patient was asked to blink 2-3 times. Then the fluorescein BUT was measured.

Materials: Control – 0.9% NaCl (saline); surface tension 72 mN/m

Treatment = as Control + 0.002% Tween 80; surface tension 49 mN/m (dyn/cm)

Results:

Left eye – Control	Right eye – Treatment
7.7 ± 0.4 sec	12.7 ± 1.5 sec

Paired differences 5.0 ± 1.4 sec ($p \sim 0.001$)

b. Examination of treatment, of conjunctival damage, in dry eye syndrome.

One month study, use of the eye drops three times a day:

Left eye = essentially isotonic Glycerol (marketed product) (L).

Right eye = 50% isotonic Glycerol + 50% isotonic Xylitol (R).

. Patient No	Rose Bengal score (Oxford Scale)			
	Before		One month	
	R	L	R	L
1	3	3	1	2
2	2	3	0	2
3	2	3	0	2
4	3	3	1	2
5	1	3	1	2
mean	2.2	3.0	0.6	2

Patient No.	Personal Satisfaction			
	Before		One month	
	R	L	R	L
1	0	0	2	1
2	0	0	2	1
3	0	0	2	1
4	0	0	2	1
5	0	0	2	1
mean	0	0	2	1

0= not satisfied	1= better	2= much better

Essentially the same results were obtained, by using Myoinositol instead of Xylitol.

Animal Studies

a. 3 rabbits were treated for 3 months twice daily with eye drops, adjusted to pH 7.0. The average cross section of the epithelial corneal cells and the percentage of damaged cells were evaluated by electromicroscopy.

Treatment	Cross section in μ^2	Damaged cells %
None	590	16
0.9% NaCl	542	28
0.01% Benzalkonium Chloride + 0.9% NaCl	538	29
0.01% Benzalkonium Chloride + 2.5% Glycerol	699	14
0.01% Cetrimonium Bromide + 0.9% NaCl	591	27
0.01% Cetrimonium Bromide + 2.5% Glycerol	625	19
0.1% Na_2 EDTA + 0.9% NaCl	531	15
0.1% Na_2 EDTA + 2.5% Glycerol	616	17
0.025% Polysorbate 80 + 0.9% NaCl	440	25
0.025% Polysorbate 80 + 2.5% Glycerol	600	18
2.5% Glycerol	605	17
0.01% Benzalkonium Chloride + 4.5% Xylitol	554	19
0.01% Benzalkonium Chloride + 5.4% Myoinositol	584	19
0.01% Benzalkonium Chloride + 5.4% Mannitol	570	21

b. Prevention of dry skin (irritation) caused by 2% sodium lauryl sulphate (Method: modification of Sagiv et al. Skin Res. Technol. 6, 37, 2000)

Daily topical application of molar or isotonic polyols in deinonized water, half an hour before application of 2% sodium lauryl sulphate in deinonized water(SLS), on one of the two shaved flanks of guinea pigs, for three consecutive days, was examined in order to prevent SLS induced "Dry skin syndrome". Skin dryness and erythema were measured four days later in vivo:

Name	Concentration	Corneometer	Mexameter
Glycerol	1M	5.5 ± 1.9 (E)	4.1 ± 3.3 (E)
Glycerol	0.3M	25.9 ± 1.7 (NE)	27.4 ± 2.2 (NE)
Xylitol	0.3M	2.8 ± 1.0 (E)	0.2 ± 0.4 (E)
Myoinositol	0.3M	0.3 ± 1.1 (E)	5.1 ± 0.9 (E?)
Mannitol	0.3M	2.2 ± 1.6 (E)	1.7 ± 0.5 (E)

Treatment of dry skin induced by 2% sodium lauryl sulphate (Sagiv et al. Skin Res. Technol. 6, 37, 2000)

Name	Concentration	Corneometer	Mexameter
Glycerol	1M	3.2 ± 1.7 (E)	1.5 ± 3.0 (E)
Glycerol	0.3M	3.3 ± 2.3 (E)	21.2 ± 0.9 (NE)
Xylitol	0.3M	1.3 ± 1.1 (E)	1.2 ± 0.9 (E)
Myoinositol	0.3M	0.7 ± 1.8 (E)	1.0 ± 0.9 (E)
Mannitol	0.3M	1.4 ± 0.6 (E)	-0.1 ± 0.3 (E)

E = Effective = No significant difference or little difference between the treated and untreated side.

NE = Not effective = Very much and significant difference between the treated and untreated side.

It was claimed that to be sure in efficacy both the "Corneometer" and "Maxameter" measurements have to be "Effective" (Sagiv et al. Skin Res. Technol. 6, 37, 2000).

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

1. A topical pharmaceutical or cosmetic composition for the prevention and treatment of irritation of mucous cells, or skin cells, comprising a combination of :

   a) xylitol, myoinositol or mannitol or any combination of these;

   b) glycerol and/or urea;

   c) water;

   d) in the absence of any oil in water or wax in water emulsion.

2. A topical pharmaceutical or cosmetic composition for the prevention and treatment of irritation of mucous cells, or skin cells, comprising a combination of :

   a) 1.5-25% xylitol, myoinositol or mannitol or any combination of these;

   b) 0.9-10% glycerol and/or urea;

   c) water;

   d) in the absence of any oil in water or wax in water emulsion.

3. A topical pharmaceutical or cosmetic composition for the prevention and treatment of irritation of mucous cells, comprising a combination of :

   a) 1.5-5.5% xylitol, myoinositol or mannitol or any combination of these;

   b) 0.9-2.0% glycerol;

   c) less than 0.01% inorganic salts;

   d) water;

   e) in the absence of any oil in water or wax in water emulsion.

4. A topical pharmaceutical or cosmetic composition according to claim 3, comprising 1.5-3.0% xylitol and 0.9-1.8% glycerol.

5. A topical pharmaceutical or cosmetic composition according to claim 3, comprising 1.8-3.6% myoinositol and 0.9-1.8% glycerol.

6. A topical pharmaceutical or cosmetic composition according to claim 3, comprising 1.8-3.6% mannitol and 0.9-1.8% glycerol.

7. A topical pharmaceutical or cosmetic composition according to claim 3, comprising 1-2% xylitol, 1.5-3% mannitol and 0.9-1.8% glycerol.

8. A topical pharmaceutical or cosmetic composition, for the prevention and treatment of irritation of skin cells, comprising a combination of :

   a) 5-18 % xylitol, myoinositol or mannitol or any combination of these;

   b) 5-10% glycerol and/or urea;

   c) water;

   d) in the absence of any oil in water or wax in water emulsion.

9. A topical pharmaceutical or cosmetic composition according to claim 8, comprising 5-18 % xylitol and 5-10% urea.

10. A topical pharmaceutical or cosmetic composition according to claim 8, comprising 5-18 % myoinositol and 5-10% urea.

11. A topical pharmaceutical or cosmetic composition according to claim 8, comprising 5-18 % mannitol and 5-10% urea.

12. A topical pharmaceutical or cosmetic composition according to any of claims 1-11, further comprising an agent, to lower the surface tension of the solution to less than 90% of that of water.

13. A topical pharmaceutical or cosmetic composition according to any of claims 1-11, for the prevention and alleviation of cell damage caused by preservatives, detergents or drugs, used in topical pharmaceutical cosmetic or veterinary compositions.

14. A topical pharmaceutical or cosmetic composition according to any of claims 1-11, further comprising pharmaceutically acceptable excipients or additives.

15. A topical pharmaceutical or cosmetic composition according to any of claims 1-11, further comprising at least one pharmaceutically active agent in solution.

16. A topical pharmaceutical or cosmetic composition according to any of claims 1-11, further comprising at least one pharmaceutically active agent in suspension.

17. A topical pharmaceutical or cosmetic composition according to any of claims 1-11, further comprising at least one viscosity enhancing agent.

18. A topical pharmaceutical or cosmetic composition according to any of claims 3-7, for preventing and treating irritation of the mucous membranes of the eye caused by allergies, chemical pollutants, or physical irritants, manifested by redness, tearing, burning, discomfort or itching.

19. A topical pharmaceutical or cosmetic composition, according to any of the preceding claims, substantially as herein described, with reference to any of the examples.

20. A topical pharmaceutical or cosmetic composition, substantially as herein described, with reference to any of the examples.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2006/000537

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/10 A61K47/26 A61K47/18 A61Q19/00
A61K8/34 A61K8/60 A61K8/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IWAO, JUNICHI ET AL: "Allergy-inhibiting ophthalmic solutions containing cyproheptadine or its salts" XP002398971 retrieved from STN Database accession no. 111:63983 abstract & JP 63 270625 A2 (SANTEN PHARMACEUTICAL CO., LTD., JAPAN) 8 November 1988 (1988-11-08) ----- -/--	1-20

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Sproll, Susanne

INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MORITA, TAKAKAZU ET AL: "Stable pirenoxine ophthalmic solutions" XP002398972 retrieved from STN Database accession no. 113:46324 abstract & JP 02 078619 A2 (SANTEN PHARMACEUTICAL CO., LTD., JAPAN) 19 March 1990 (1990-03-19)	1,2, 8-17,19, 20
X	EP 1 354 580 A (SHISEIDO COMPANY LIMITED) 22 October 2003 (2003-10-22) abstract; example 44	1,2, 8-17,19, 20
A	US 5 089 255 A (GAFFAR ET AL) 18 February 1992 (1992-02-18) example 1	1-20
A	US 2004/191332 A1 (CHANG JAMES N [US] ET AL) 30 September 2004 (2004-09-30) the whole document	1-20
A	WO 02/49615 A (ALCON UNIVERSAL LTD; CHOWHAN, MASOOD; CHEN, HUAGANG; ALCON, INC) 27 June 2002 (2002-06-27) page 9; example 1	1-20
A	US 5 597 559 A (OLEJNIK ET AL) 28 January 1997 (1997-01-28) the whole document	1-20
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