Stable vitamin A forms
Visibly improves the appearance of fine lines,
wrinkles, spots and acnes

Retinoids Family Series

Anti-aging | Maintain Younger-looking Skin

Spec-Chem Group
Sep, 2023 up

CONTENT

Product Introduction

- In 1931 Paul Karrer won the Nobel prize for figuring out the structure of **vitamin A**. Twelve years later, **Retinol** was successfully synthesized and since then, **vitamin A derivatives** started to pop up. Retinol was discovered in 1909, isolated in 1931, and first made in 1947.
- Retinoids are a class of vitamin A (VA) derivatives. Vitamin A refers to retinol in the narrower sense .
- Retinol and its derivatives retinyl palmitate, retinyl acetate and retinyl linoleate occur naturally in the skin.

Classifications of VA and its derivatives

Category	Uses	Representative component
Prescription	For topical prescription drugs (Cosmetics prohibited)	Retinoic acid, isotretinoin, adapalene, tazarotene, etc.
Skin care products	Widely used in skin care products field	Retinol, Retinal, Retinyl palmitate, Retinyl propionate, Retinol retinoate, retinyl linoleate, Retinyl acetate, Hydroxypinacolone retinoate (HPR), Tocopherol retinoate, etc.

Action Mechanism

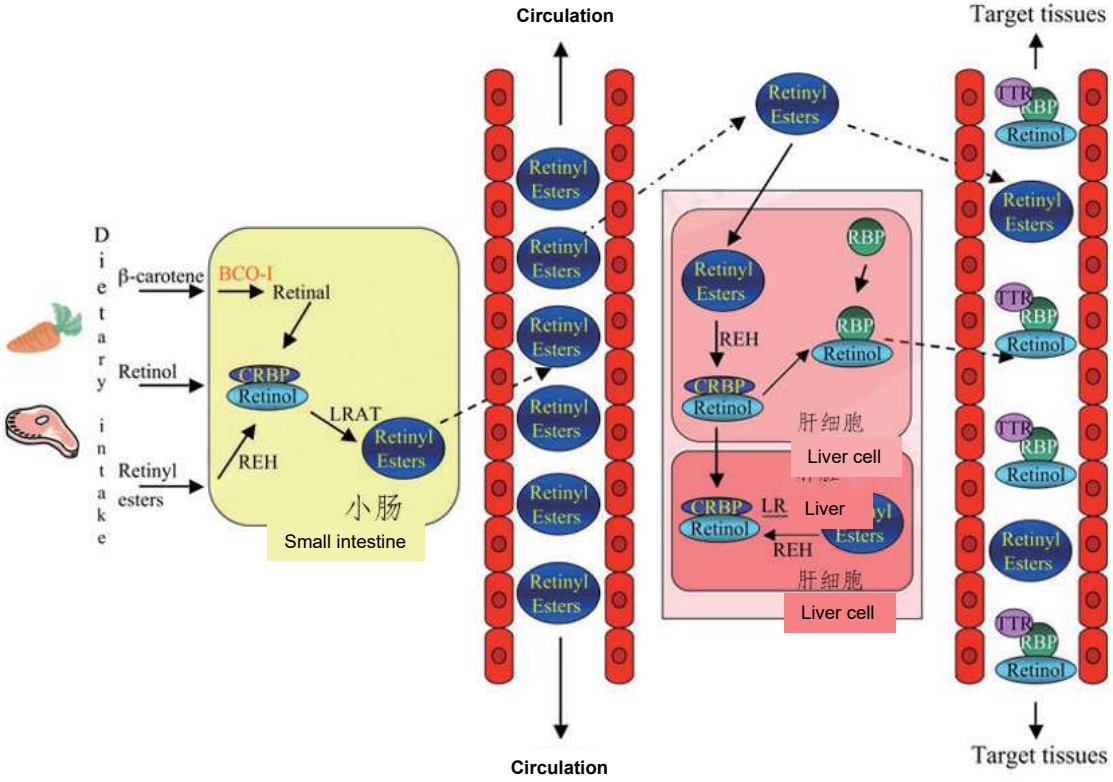


Fig. 1 Absorption and metabolism process of VA in the body

- VA cannot be synthesized from scratch in the body and must be obtained through the diet. The sources mainly include carotenoids (plants) and VA (animal liver).
- Carotenoids from plant sources and VA from animal liver sources are first re-esterified and absorbed in the small intestine to form retinyl esters. A portion is transferred to the liver as retinol esters via coeliac particles and then excreted via bile and the kidneys. A portion is present in the plasma as cellular retinol-binding protein (CRBP) complexes, which are then transported to target organs to perform their respective functions

Action Mechanism

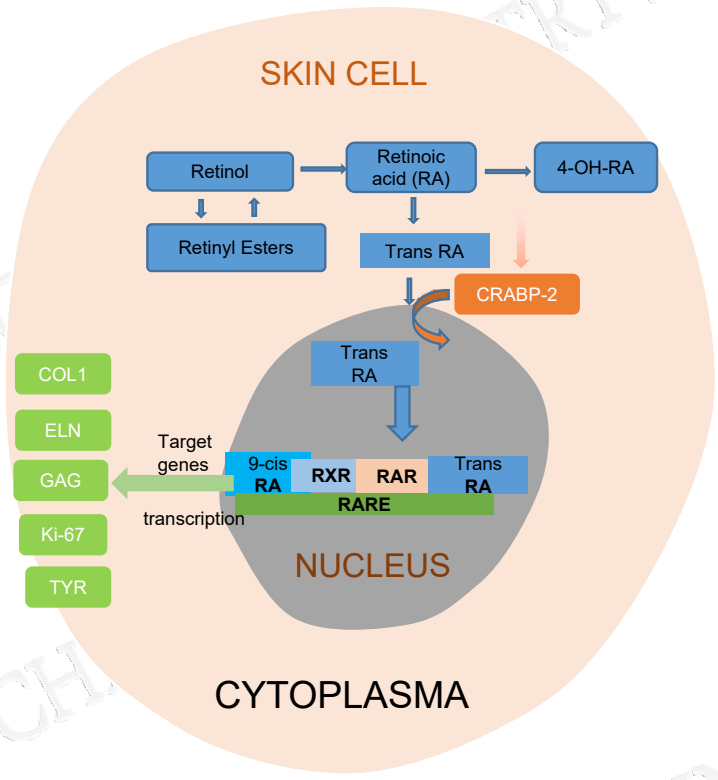
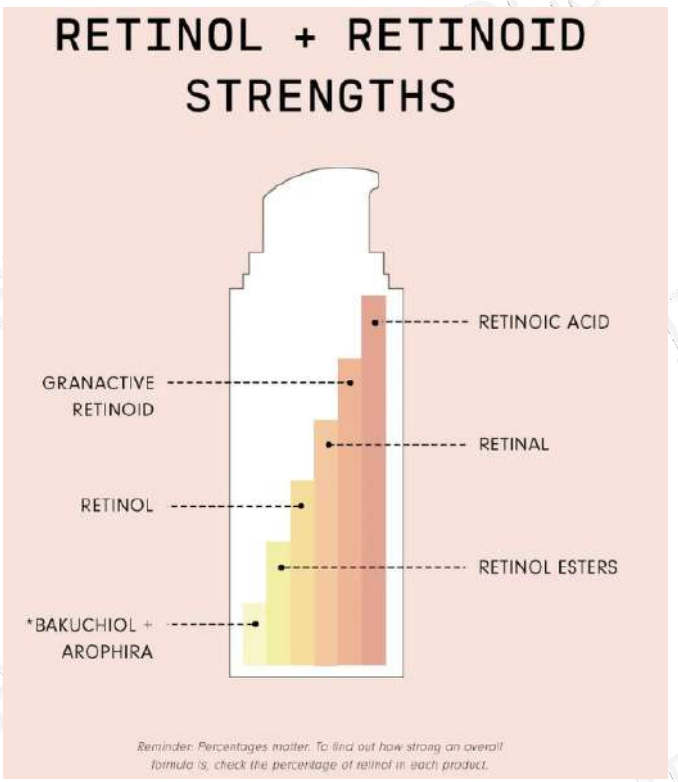


Fig 2. the metablic mechanism of retinol on role on skin cell

- Since it is Retinoic acid that really plays a role in skin anti-aging, any exogenous supplementation of VA needs to be converted to retinoic acid by enzymes on the surface of the skin (with the exception of HPR)
- Retinol/Retinyl esters are converted to retinoic acid (RA) under the action of skin surface enzymes. Abundant retinol is stored in the form of retinyl ester until needed, or degraded as polar metabolites (4-OH-RA) by enzymes.
- Retinoic acid is transported from the cytoplasm to the nucleus by CRABP-2. Retinoic acid binds to the retinoic acid receptor (RAR) which forms a heterodimer with the retinoid X receptor (RXR). This complex acts as a transcription factor on regions called retinoic acid response elements (RARE) and mediates RA-responsive gene expression, such as for type I procollagen (COL1), elastin (ELN), glycosaminoglycan (GAG), tyrosinase (TYR) and Ki-67 protein.
- By regulating and controlling the activation and expression of genes, it regulates cell division and differentiation, stimulates keratinocyte proliferation, promotes epidermal keratinocyte metabolism, and regulates extracellular matrix components, etc.

Action Mechanism



https://versedskin.com/blogs/learn/types-of-retinol

The biological activity is determined by the length and difficulty of the transformation pathway on the skin. And the higher the biological activity of VA and its derivatives, the more irritating they are to the skin.

- **RETINOIC ACID (TRETINOIN)**
  - ✓ The purest form of retinol. Since it doesn't need to be converted, it gets to work right away.
  - ✓ That also means it can be harsh, drying, and irritating for most skin types.
- **GRANACTIVE RETINOID (HYDROXYPINACOLONE RETINOATE)**
  - ✓ **Si**milar to retinoic acid, it does not need to be converted and is incredibly effective.
  - ✓ Much less irritating than tretinoin
- **RETINAL (RETINALDEHYDE)**
  - ✓ Just one conversion step from retinoic acid.
- **RETINYL RETINOATE**
  - ✓ takes one conversion
  - ✓ It converts to part retinoic acid, part retinol.
- **RETINOL**
  - ✓ Convert retinoic acid *twice*
  - ✓ It's the most well-known type, found in a majority of retinol-based skincare products.
- **RETINOL ESTERS** (RETINYL PALMITATE, RETINOL ACETATE, RETINYL PROPIONATE, RETINYL LINOLEATE, etc.)
  - ✓ Take three conversions to reach retinoic acid.
  - ✓ The effectiveness of esters relies on the effectiveness of the molecule selected.

Action Mechanism

Comparison of advantages and disadvantages

Retinoids	Advantages	Disadvantages	Trade Name
Hydroxypinacolone Retinoate (HPR)	Low irritation Strong activity Superior Stability to heat Directly binds to RA Receptor without metabolic transformation	Sensitive to UVs Not applicable to pregnant women	SpecKare® HPR
Retinyl Ester	Low irritation Relatively stable to heat Widespread market recognition	Sensitive to UVs Prone to be oxidized (fatty acid) Relatively low activity Not applicable to pregnant women	SpecWhite® VAC (Retinyl Acetate) SpecKare® VAP 100 (Retinyl palmitate)
Retinol	Relatively strong activity Widespread market recognition	Sensitive to UVs & Heat Prone to be oxidized Potential irritation (without slow-release and Package technology) Not applicable to pregnant women	SpecKare® RRT SpecKare® RRT15 SpecKare® RRT501 SpecKare® RRT502
Retinal	Converting to Retinoic acid in just one step, fast acting	Sensitive to UVs & Heat Prone to be oxidized Poor stability, intermediate Not applicable to pregnant women	-
Retinoic acid (RA)	Potent Activity FDA-approved Drug	Not allowed as cosmetic ingredient Sensitive to UVs & Heat Poor Stability, Strong irritation Not applicable to pregnant women	SpecWhite® VAA

Product Information

Product No.: 11001901
Trade Name: SpecKare® RRT
INCI name: Retinol, Hydroxypropyl Cyclodextrin
CAS No.: 68-26-8, 128446-35-5
Application: Anti-wrinkle, anti-aging, whitening, anti-acne, anti-UV-induced aging spots and etc.
Rec. use level: Daily usage: 0. 1-1.0% ;
medium dosage: 1.0-5.0%;
high dosage: 5.0-10.0%
Storage: Store at room temperature. Keep container tightly closed in a dry and well-ventilated place.
Shelf life: 2 year
Package: 1kg

Items	Specification
Appearance	Yellow powder
Odor	Characteristic
Solubility	Disperse in water
Loss on drying	≤ 2.0%
Active Matter	310000 - 330000 IU/g
Lead	≤ 10 mg/kg
Arsenic	≤ 2 mg/kg
Mercury	≤ 1 mg/kg
Cadmium	≤ 5 mg/kg
Total plate count	≤ 1000 cfu/g
Mould & Yeast	≤ 100 cfu/g

Product Information

Product No.: 11001903
Trade Name: SpecKare® RRT501
INCI name: Retinol, Tocopheryl Acetate
CAS No.: 68-26-8 ,7695-91-2
Application: Anti-wrinkle, anti-aging, whitening, anti-acne, anti-UV-induced aging spots and etc.
Rec. use level: 0.01-2.0%(Refer to local regulations)
Storage: Store in cold place. Keep away from light. Keep container tightly closed in a dry and well-ventilated place.
Recommended temperature: 2 - 10℃
Shelf life: 1 year
Package: 1kg

Items	Specification
Appearance	Yellow to brownish red oily transparent liquid
Identify	Positive reaction
Solubility	Soluble in grease
Refractive index	1.540-1.580
Assay	50±2%
Lead(mg/kg)	≤10.0
Arsenic(mg/kg)	≤2.0
Mercury(mg/kg)	≤1.0
Cadmium(mg/kg)	≤5.0

Product Information

Product No.:	11001904
Trade Name:	SpecKare® RRT502
INCI name:	Retinol, Polysorbate 20, BHA,BHT
CAS No.:	68-26-8 ,9005-64-5, 25013-16-5, 128-37-0
Application:	Anti-wrinkle, anti-aging, whitening, anti-acne, anti-UV-induced aging spots and etc.
Rec. use level:	0.1-2.0% (Refer to local regulations)
Storage:	Keep in cold storage. Keep away from light. Keep container tightly closed in a dry and well-ventilated place. 2-10℃ is recommended.
Shelf life:	1 year
Package:	1kg

Items	Specification
Appearance	Yellow to brownish red oily transparent liquid
Identify	Positive reaction
Purity	≥ 95.0%
Assay	42.75 - 49.50%
BHT	3.15 - 3.50%
BHA	0.90 - 1.10%

Product Information

Product No.: 11001902
Trade Name: SpecKare® RRT15
INCI name: Retinol, Caprylic/Capric Triglyceride, BHT
CAS No.: 68-26-8 ,73398-61-5/65381-09-1, 128-37-0
Application: Anti-wrinkle, anti-aging, whitening, anti-acne, anti-UV-induced aging spots and etc.
Rec. use level: 0.03-5% (Refer to local regulations)
Storage: Keep in cold storage. Keep away from light. Keep container tightly closed in a dry and well-ventilated place. 2-10℃ is recommended.
Shelf life: 1 year
Package: 1kg

Items	Specification
Appearance	Yellow to brownish red oily transparent liquid
Relative density	0.940-0.960
Refractive index	1.460-1.485
Assay	15-15.9%
Lead(mg/kg)	≤10.0
Arsenic(mg/kg)	≤2.0
Mercury(mg/kg)	≤1.0
Cadmium(mg/kg)	≤5.0

Product information

Product No.:	**11001800**
Trade name:	SpecWhite® VAC
INCI name:	Retinyl Acetate
CAS No.:	127-47-9
Application:	Whitening, freckle removing, antioxidant, anti-wrinkle, anti-aging, anti-acne and etc.
Rec. use level:	0.1 - 1.0% (Refer to local regulations)
Storage:	Store at room temperature. Keep container tightly closed in a dry and well-ventilated place.
Shelf life:	1 year
Package:	1Kg, 10Kg

Items	Specification
Appearance	Straw yellow crystal
Solubility	Can easily soluble in ethanol, Can't soluble in water
Identification	Conforms
Acid value	≤ 2.0
Peroxide value	≤ 1.5 mL
Assay	≥ 2,800,000 I.U./g
Lead	≤ 10 mg/kg
Arsenic	≤ 2 mg/kg
Mercury	≤ 1 mg/kg
Cadmium	≤ 5 mg/kg
Total plate count	≤ 500 cfu/g
Yeast & mould	≤ 100 cfu/g
Escherichia coli	Negative in10g
Staphylococcus aureus	Negative in10g
Pseudomonas aeruginosa	Negative in10g

Product information

Product No.:	**12000403**
Trade name:	SpecKare® VAP100
INCI name:	Retinyl palmitate, Helianthus Annuus (Sunflower) Seed Oil
CAS No.:	79-81-2, 8001-21-6
Application:	Anti-wrinkles, anti-aging, whitening, freckle removing and etc.
Rec. use level:	0.05 - 5.0% (Refer to local regulations)
Storage:	Store at room temperature. Keep container tightly closed in a dry and well-ventilated place. The best temperature for storage in summer is 2-8℃.
Shelf life:	2 year
Package:	1Kg

Items	Specification
Appearance	Yellow, liquid, oily, crystals may be present
Solubility	Virtually insoluble, water
Refractive index (20℃)	1.510 - 1.530
Relative density (20℃)	0.906 - 0.930
Assay (IU/g)	≥ 1,000,000
Lead	≤ 10 mg/kg
Arsenic	≤ 2 mg/kg
Mercury	≤ 1 mg/kg
Cadmium	≤ 5 mg/kg
Total plate count	≤ 500 cfu/g
Yeast & mould	≤ 100 cfu/g
Thermotolerant coliforms	Absent in 1g
Pseudomonas aeruginosa	Absent in 1g
Staphylococcus aureus	Absent in 1g

Product information

Product No.:	**12008800**
Trade name:	SpecKare® HPR
INCI name:	Hydroxypinacolone Retinoate, Polyquaternium-51, Dicaprylyl Carbonate, Octyldodecyl Isostearate, Caprylic/Capric Glycerides, Tocopheryl Acetate
CAS No.:	893412-73-2, 125275-25-4, 1680-31-5, 93803-87-3, 73398-61-5, 7695-91-2
Application:	Anti-aging, anti-wrinkle, whitening/lightening, freckle removing, skin conditioning and etc.
Rec. use level:	0.1 - 3% (Refer to local regulations)
Storage:	Store in cool place. Keep container tightly closed in a dry and well-ventilated place. Keep away from light
Shelf life:	2 year
Package:	1Kg

Items	Specification
Appearance	Yellow transparent oily liquid
HPR Content	9.0 - 11.0%
Specific gravity (20℃)	0.900 - 0.950
Refraction ratio (25℃)	1.300 - 1.600
Acid Value	≤ 2.0 mgKOH/g
Lead	≤ 10 mg/kg
Arsenic	≤ 2 mg/kg
Mercury	≤ 1 mg/kg
Cadmium	≤ 5 mg/kg
Total plate count	≤ 100 CFU/g
Mould & Yeast	≤ 100 CFU/g

Summary of feature

Protects against collagen degradation and increases collagen levels in the skin; improves elastin synthesis

Helps reduce wrinkles, treat hyperpigmentation, and generally lessen signs of skin aging

Decreases melanin content

Treats acne and acne scarring:

Retinoids are able to reduce significantly hyperseborrhea, for their capacity of inhibiting effect on proliferation and differentiation of sebocytes; they also successfully competing with androgen hormones and inhibit hyper-cornification.

Unique product features

Efficacy Test

Increases elastin protein levels (in vitro)

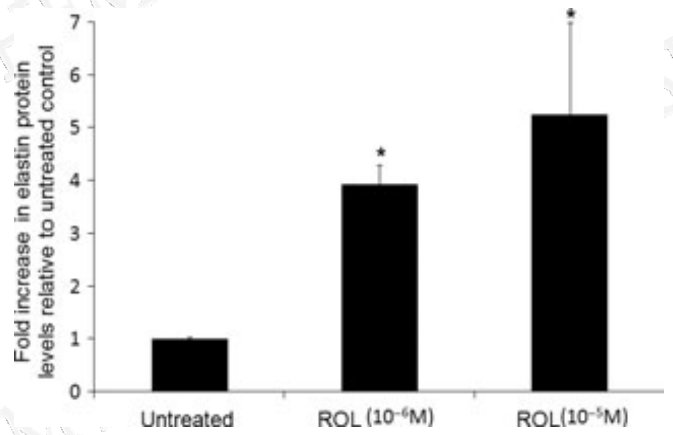


Fig 3. ROL(retinol)increases elastin protein levels in dermal fibroblasts.

Test Method

✓ Normal human adult dermal fibroblasts were treated with retinol at indicated concentrations for 72 h. Cell lysates were examined for elastin protein levels by direct ELISA.

Results

- Retinol increases elastin protein levels in dermal fibroblasts.
- Retinol treatment led to a dose-dependent induction of elastin protein

<A novel anti-ageing mechanism for retinol: induction of dermal elastin synthesis and elastin fibre formation> International Journal of Cosmetic Science, 2010, 1–10

Efficacy Test

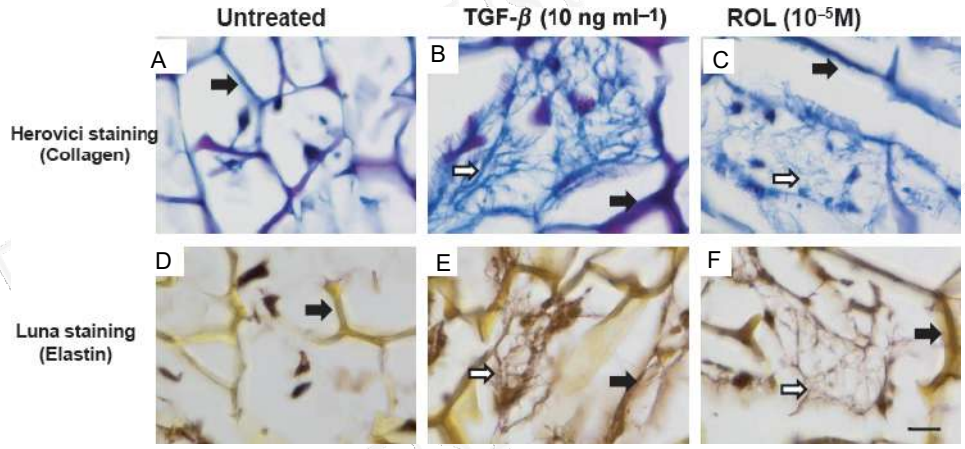


Fig 4. ROL(retinol increases elastin fibre staining in 3D dermal fibroblast cultures

* Herovici-stained (collagen):(A–C) Collagen staining of control (A), TGF-b (B) and ROL-treated sample (C); Luna-stained (elastin): (D–F) Elastin staining of control (D), TGF-b (E) and ROL-treated sample (F)

◆ **Test Method:**

3D dermal fibroblast cultures, established in collagen scaffolds, were treated with TGF-b (10 ng/mL), or with ROL (10^{-5} M), or remained untreated for 2 weeks. Histological staining of the 3D cultures was used to document the induction of collagen synthesis (a known ROL activity, shown by Herovici staining) and the enhancement of elastin fibre formation (shown by Luna staining).

◆ **Results:**

- ROL (Retinol) can induce collagen synthesis and collagen fibre formation, as well as elastin protein synthesis and elastin fibre formation.

<A novel anti-ageing mechanism for retinol: induction of dermal elastin synthesis and elastin fibre formation> International Journal of Cosmetic Science, 2010, 1–10

Efficacy Test

Anti-wrinkles & anti-photoaging (in vivo)

- **Test method:**

  In this eight-week, double-blind, split-face, randomized clinical study, a stabilized 0.1 % retinol-containing moisturizer was tested (36 subjects) against the vehicle (28 subjects) in women with moderate facial photodamage. Each product was applied once daily to the designated half side of the face.

- **Results:**
  - Particularly prominent were the improvements from baseline in mottled pigmentation by 53%, crow's feet lines by 39% (and crow's feet wrinkles by 16%), cheek wrinkles by 20% and overall photodamage by 18% after 8 weeks of Retinol applications.
  - The Retinol treated skin showed significant improvement (P<0.05) against vehicle (*) in all wrinkle parameters, pigmentation and overall photodamage
  - After 8 weeks, there is a visible improvement in the appearance of skin wrinkling.
- **Conclusion:**
  - The stabilized 0.1% retinol moisturizer was efficacious in the improvement of the appearance of photodamage, with very low irritation potentials

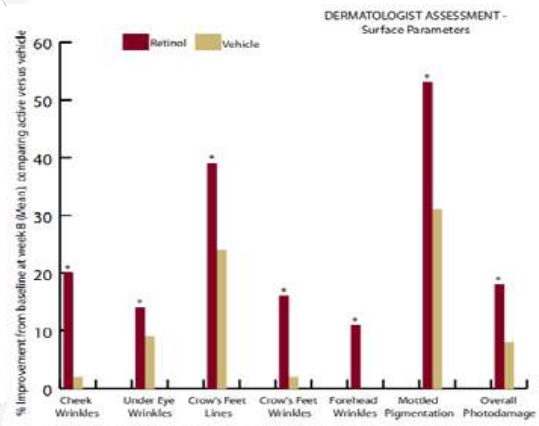


Fig 5. Clinical efficacy parameters: Comparison in surface parameters between 0.1% retinol-containing moisturizer and vehicle

Fig 6. Improvement in wrinkle appearance (Patient using the 0.1% Retinol moisturizer at baseline (left) and at the end of the study (right))

<A stabilized 0.1% retinol facial moisturizer improves the appearance of photodamaged skin in an eight-week, doubleblind, vehicle-controlled study> J Drugs Dermatol, 2009, 8 (10): 932-936

Efficacy Test

Epidermal thickening （In vivo）

Test Subjects: Six healthy adult human volunteers (three males and three females, aged 35–55 years)

Test Duration: 4 weeks

Application: Topically on the forearms, occlusion for 1 day per week

Test Sample: retinoic acid (0.1%), retinol (0.1%), or a base formulation as a vehicle control

Test Method: Skin histology was examined by H&E staining and in vivo confocal microscopy.

Test results: Quantitative measurement of the epidermal layer of the biopsy tissue sections: Treatment with retinol and retinoic acid showed an increase in epidermal thickness over control values of 46.28% and 78.79%, respectively.
The epidermal thickness based on in vivo confocal imaging, measured from the stratum corneum to the top of the dermal papillae, increased following retinol and retinoic acid treatments by 20.03% and 33.68% over control values, respectively.

Conclusions: Topical application of retinol and retinoic acid can increase epidermal thickness.

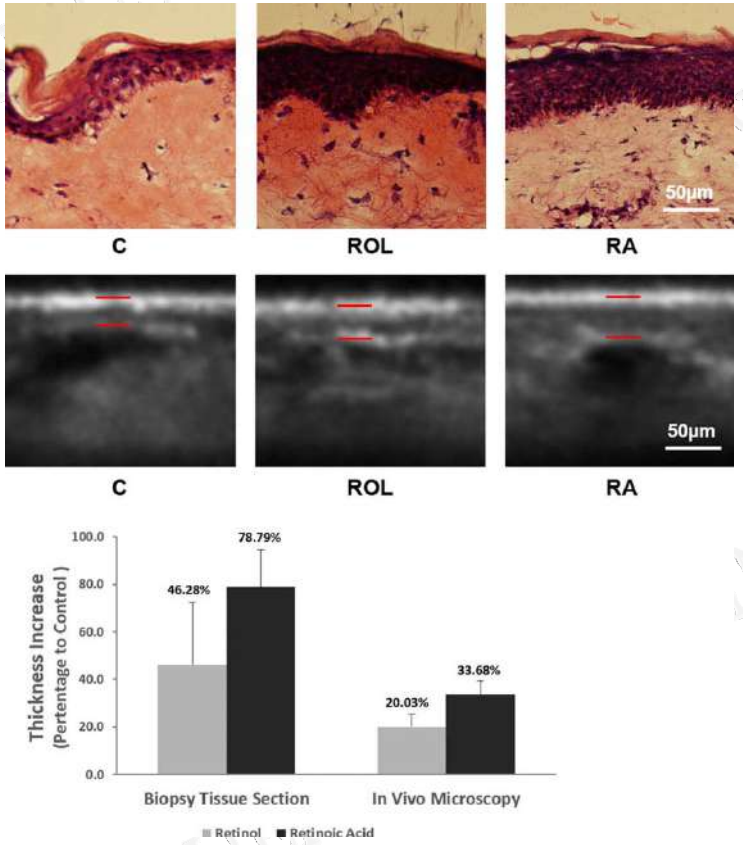


Fig 2 Epidermal thickness measurement, C: vehicle control; ROL: retinol; RA: retinoic acid.

Kong R, Cui Y, Fisher GJ, Wang X, Chen Y, Schneider LM, Majmudar G. A comparative study of the effects of retinol and retinoic acid on histological, molecular, and clinical properties of human skin. J Cosmet Dermatol. 2016 Mar;15(1):49-57

Efficacy Test

Treat mild/moderate acne (In vivo)

Retinoids are able to reduce significantly hyperseborrhea, for their capacity of inhibiting effect on proliferation and differentiation of sebocytes; they also successfully competing with androgen hormones and inhibit hyper-cornification.

Test Subjects:	Twenty subjects (9F/11M) (mean age: 30, range. 18-40 yrs) with mild to moderate acne
Test Duration:	6 weeks
Test Time:	Week 0, Week 6
Test Sample:	0.1% Hydroxypinacolone Retinoate (HPR), and 1.0% Retinol entrapped into Glycospheres Technology, containing Papain, R-NMF (Rebuilt-Natural Moisturizer Factor), tocopherol (Vit. E), glycerol, Treolase, Aloe Barbadenis.
Test Method:	Digital images were obtained with Reveal photo imaging system (Canfield). The subjects were photographed in three facial positions: left 45°, center 0°, right 45°. 10 subjects follicular biopsy have been performed. The samples obtained have been analyzed by electron microscopy or stereomicroscopy in order to evaluate changes in the density of microcomedones and macrocomedones, before and after treatment.

Gabriella Fabbrocini, Evaluation of efficacy and safety of the combinated use of two topic retinoids to treat mild / moderate acne. EJA, Vol. 2, n. 2, 2011

Efficacy Test

Treat mild/moderate acne (In vivo)

Results:

- Most of patients had satisfactory therapeutic response with a reduction of Global Acne Grading System (GAGS) global score of 70%. Digital images confirmed clinical improvement (Figure 1).
- Micro-comedones and macro-comedones showed respectively a reduction of 38% and of 65% (Figure 2). Follicular biopsy proved a reduction about 60% in the density of micro and macro-comedones.
- No patients dropped out the study because of side effects and tolerability was very good in 90% of our sample.

Conclusions:

The double action of retinoids (hydroxypinacolone retinoate + retinol) can have a synergic effect such as:

- To render follicles inhospitable to Propionibacterium acnes.
- To normalize follicular epithelial desquamation.

Fig 1. Before (A) and after (B) treatment

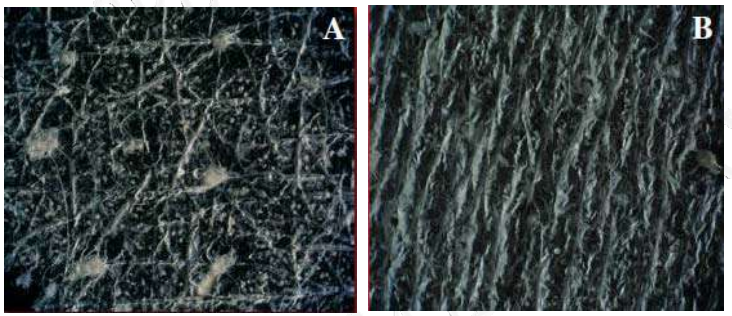


Fig 2. Stereomicroscopy image of follicular biopsy: before (A) and after (B)

Gabriella Fabbrocini, Evaluation of efficacy and safety of the combinated use of two topic retinoids to treat mild / moderate acne. EJA, Vol. 2, n. 2, 2011

Efficacy Test

Treat melasma (In vivo)

Test Subjects: 30 patients with melasma

Test Duration: 3 months

Application: applied on one side of the face and the vehicle on the other, twice daily during 3 months

Test Sample: Hydroxypinacolone Retinoate+ Retinol

Test Method: Standardized photographs were taken using RBX technology on the three visits (basal, at one and a half months and at 3 months). The main variable to determine the efficacy was the improvement of the hemifacial Melasma Area Severity Index (MASI). Other variables were determined such as improvement perceived by the investigator, improvement perceived by the patient, impact on quality of life or side effects.

Test results: The MASI improvement at 3 months of treatment was significant on the treated side vs. the vehicle side, reaching an improvement of 70%, which is comparable to the percentage of improvement described with hydroquinone. No notable side effects were detected.

Conclusions: This new combination of retinoids and depigmenting agents proved to be effective and safe in the treatment of melasma.

Fig 1 Photography with RBX technology before treatment and 3 months after the treatment on the side treated with the new combination of retinoids

Truchuelo MT, Jiménez N, Jaén P. Assessment of the efficacy and tolerance of a new combination of retinoids and depigmenting agents in the treatment of melasma. J Cosmet Dermatol. 2014 Dec;13(4):261-8.

Application Guide

➢ Difficulties

✓ **Unstable**: VA and its derivatives contain 5 conjugated double bonds, which are particularly susceptible to the energy of light waves, causing it to undergo isomerisation, polymerisation, and oxidation and lose its activity. VA and its derivatives are also unusually sensitive to temperature, and thermal degradation of VA esters is consistent with a first-order reaction (R2> 0.99).

✓ **Phototoxicity**: Photoreactions of retinoids can further result in phototoxic or photosensitising reactions.

✓ **Darkening effects**: Daytime use may result in skin darkening.

✓ **Irritation:** Converted to retinoic acid to act on the skin (except HPR). Retinoic acid is an agonist of the specific transient receptor potential channel vanilloid subtype 1 (TRPV1) receptor, which promotes inflammatory responses, leading to pain, burning, and inflammation. This ultimately leads to pain, burning, redness, swelling and hyperpigmentation of the skin. Retinoic acid also causes overexpression of aquaporin 3 in human skin, disrupting intercellular bridges and affecting the expression of barrier-related structural proteins, thereby increasing transdermal water loss and causing dryness and peeling of the skin.

➢ Tips

✓ Retinol is miscible with fats and oils.

✓ Technical properties and handling Retinol is a crystalline solid that is sensitive to oxygen, heat, light and heavy metals. It is therefore dissolved in oils, filled under nitrogen, stabilized with antioxidants and stored in aluminum cans at low temperatures.

✓ Retinol can crystallize out at low temperatures, but the crystals can be redissolved by heating the can to 50℃. Once a can has been opened, the remaining contents should be kept under an inert gas, and used up quickly.

✓ It is recommended to manufacture retinol formulations under an inert atmosphere and to add the retinol together with chelating agents at a temperature not exceeding 40℃. The finished formulation should be filled under an inert atmosphere into aluminum collapsible tubes which should then be kept below 20℃ during storage and transport.

Application Guide

Stability of Retinoids during 6 months of long-term and accelerated stability testing

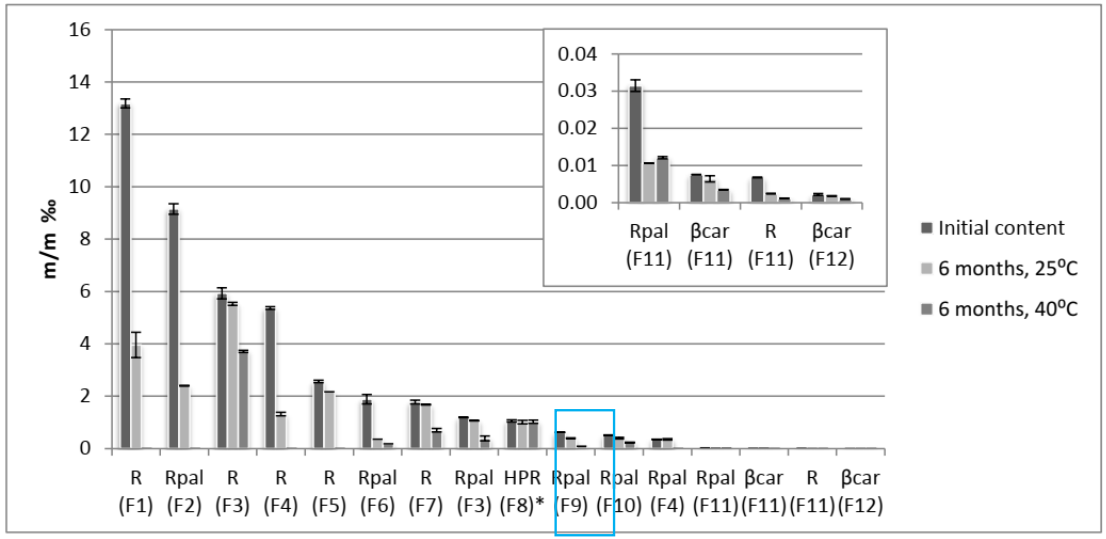


Figure 1. Comparison between the initial content of retinol (R), retinyl palmitate (Rpal), β carotene (βcar), and Hydroxypinacolone retinoate (HPR) in the tested commercial cosmetics formulations (F) and their remaining contents after 6 months at 25 ℃ and 40 ℃. *The presented content for HPR in F8 is the result after 3 months of storage at 40 ℃ because of latter stratification.
All above formulations were commercial products, no detailed info regarding dossage could be provided.

Retinoid stability in commercial cosmetic products in various formulations was evaluated after their opening, during 6 months of storage at room temperature and elevated temperature.

Results:

- The obtained results showed a significant decline of retinoids practically in all tested products (Fig. 1).
- The decline in retinoid contents after 6 months at 25 ℃ ranged from **0 to 80%, 40-100%** at 40 ℃), resulting in total degradation of the retinoids in almost one-third of the tested products.
- HPR was found very stable in the tested formulation at 25 ℃ after 6 months (95% of the initial content remained). High chemical stability was also evident at 40 ℃ (97% of the initial content remained after 3 months).

Among the studied retinoids, the stability of the newer hydroxypinacolone retinoate was the most prominent.

Application Guide

Effect of temperature on retinoid degradation kinetics

Table 1. Effect of temperature on the degradation kinetics of retinoids in commercial cosmetics.

	25 °C			40 °C			Ratio
	k ($month^{-1}$)	R^2	$t_{90\%}$ (days)	k ($month^{-1}$)	R^2	$t_{90\%}$	$k_{40°C}/k_{25°C}$
Rpal (F6)	0.277	1.000	11.6	0.317	0.995	10.1	1.1
R (F4)	0.234	0.973	13.7	1.990	1.000	1.6	8.5
Rpal (F2)	0.218	0.996	14.7	17.15	1.000	0.2	78.7
R (F1)	0.202	0.999	15.9	2.446	0.996	1.3	12.1
Rpal (F11)	0.160	0.928	20.0	0.164	0.997	19.5	1.0
R (F11)	0.150	0.894	21.4	0.292	0.996	11	1.9
βcar (F11)	0.138	0.959	23.2	0.133	0.992	24.1	1.0
Rpal (F9)	0.076	0.998	42.1	0.425	0.993	7.5	5.6
R (F3)	0.048	0.914	67.1	0.079	0.999	40.4	1.7
R (F5)	0.047	0.945	68.7	0.641	0.996	5.0	13.8
Rpal (F10)	0.042	0.999	76.0	0.133	0.998	24.1	3.2
βcar (F12)	0.032	1.000	98.7	0.145	0.996	22.1	4.5
R (F7)	0.024	1.000	133	0.150	0.996	21.4	6.2
Rpal (F3)	0.018	1.000	174	0.193	0.995	16.6	10.5
HPR	0.008	0.998	384	0.017*	0.992	188	2.0
Rpal (F4)	nd	nd	nd	0.623	0.975	5.1	nd

2nd

1st

*stable for 3 months (97%), afterward physical changes (stratification) occurred.

nd – not determined because of its stability (no degradation).

Summary:

- The newest generation retinoid (HPR) was the most stable retinoid among the tested formulation at ambient temperature, with more than two-fold longer shelf-life compared to the second most stable retinoid (Rpal (F3)).
- Excluding the new retinoid (HPR), which significantly deviates from the others, the average shelf-life at 25 ℃ was about 2 months; in one-third of the tested cosmetics, it was < 1 month.
- At elevated temperature (40 ℃), the shelf-lives were significantly shortened to an average of < 14 days.
- The thermal stability of the cosmetic products is formulation dependent.

Application Guide

Retinoid contents at shelf-lives

Table 2. Retinoid contents in tested commercial cosmetics at their shelf-lives

Retinoid (Formulation)	Declared shelf-life after opening (months)	Predicted retinoid remaining at shelf-life (%)	Determined retinoid at shelf-life (%)
Rpal (F6)	12	3.6	19.0*
Rpal (F2)	12	7.0	26.2*
βcar (F11)	defined expiration date	10.6	46.0*
R (F11)	defined expiration date	11.0	17.4*
Rpal (F11)	defined expiration date	12.9	38.4*
R (F4)	6	26.3	24.6
R (F1)	6	29.7	30.0
Rpal (F9)	12	40.4	63.5*
R (F5)	12	56.2	84.6*
βcar (F12)	12	68.1	82.3*
R (F3)	6	73.1	78.1
R (F7)	6	86.6	88.7
Rpal (F3)	6	89.8	89.6
Rpal (F10)	defined expiration date	92.2	77.7*
HPR (F8)	6	95.4	95.2

*retinoid content was not determined, in the case of shelf-life longer than 6 months and therefore determined retinoid (%) after 6 months is presented.

Summary:

- Degradation kinetics was applied to determine the remaining retinoid contents at the shelf-lives of the tested cosmetics, stability data at ambient temperature, simulating their real-life usage, was utilized.
- Less than one-third of the tested cosmetics contained ≥80% of the initial retinoid content at their shelf-lives, while more than half of them contained about or less than half of the retinoid contents.
- HPR-containing cosmetics showed the highest retinoid content at its shelf-lives, indicating its superior stability.

Application Guide

Relation between Retinoids concentrations and their stability

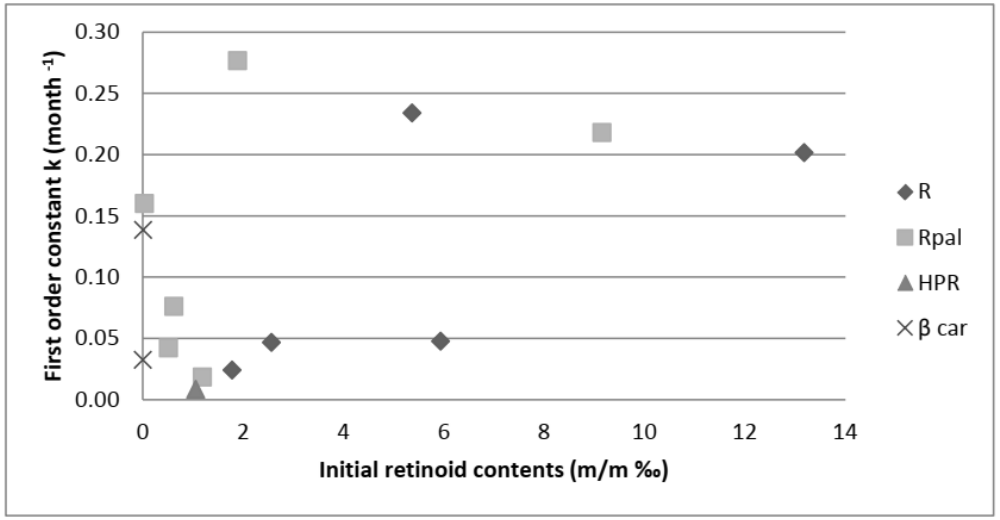


Figure 2. First-order reaction rate constants of retinoids degradation in the tested cosmetics in association with their initial contents.

Summary:

Higher found concentrations did not have a stabilizing effect on the retinoids, although in some of the tested products inversely proportional concentration dependence can be observed (Fig. 2). Interestingly, retinoids present at higher concentrations seem to be more susceptible to degradation. As no evident correlation between retinoid concentrations and their rate constants implied that their stability is formulation dependent, rather than Concentration dependent.

While HPR-containing formula show the lowest first order constant-K, indicating its stability.

Application Guide

Effect of formulation type on retinoid degradation kinetics

Table 3. Effect of the presence of antioxidants and stabilizers on the degradation kinetics of retinoids in tested commercial cosmetics.

	$k_{25\,°C}$ ($month^{-1}$)	Dosage form	Stabilizers in the cosmetics
Rpal (F6)	0.277	Semisolid	Tocopheryl Acetate, Tocopherol, Ascorbyl Palmitate, Ascorbic acid, Citric acid, BHT
R (F4)	0.234	Semisolid	Tetrahexyldecyl Ascorbate, Tocopheryl Acetate, Disodium EDTA
Rpal (F2)	0.218	Semisolid	Tocopheryl Acetate, Tetrahexyldecyl Ascorbate
R (F1)	0.202	Liquid	BHT
Rpal (F11) R (F11) βcar (F11)	0.160 0.150 0.138	Semisolid	Tocopheryl Acetate, Citric Acid, Beta-Carotene, Tocopherol
Rpal (F9)	0.076	Semisolid	Disodium EDTA, Tocopherol
R (F3)	0.048	Semisolid	Tocopheryl Acetate, Ascorbic Acid, Sodium Ascorbyl Phosphate, Disodium EDTA, BHT
R (F5)	0.047	Liquid	BHT, BHA
Rpal (F10)	0.042	Semisolid	Tocopherol, Citric acid
βcar (F12)	0.032	Semisolid	Tocopheryl Acetate, Sodium Ascorbyl Phosphate, Trisodium EDTA, Tocopherol
R (F7)	0.024	Semisolid	Tocopherol, Disodium EDTA
Rpal (F3)	0.018	Semisolid	Tocopheryl Acetate, Ascorbic Acid, Sodium Ascorbyl Phosphate, Disodium EDTA, BHT
HPR (F8)	0.008	Liquid	Disodium EDTA

BHT – butylated hydroxytoluene, BHA - butylate hydroxyanisole

Tocopheryl acetate does not have a stabilizing effect during storage; however, some cosmetic products state its antioxidant activity.

Summary:

The most stable retinoid (HPR) was formulated in liquid dosage form (F8: o/w emulsion), although in general, retinoids are unstable in water-based liquid preparations.

In the remaining two liquid formulations, where retinoids were dissolved in various oils, their stability was comparable to that in semisolid dosage forms and was most likely associated with the type and quality of the oil (especially peroxide content) as well as the added stabilizer.

Almost all cosmetics involved in the stability study contained some stabilizers, including antioxidants (e.g. BHT, vitamin C, E) and chelating agents (e.g. EDTA, citric acid). Their stability in formulations is more likely dependent on the amount of added stabilizer than on the presence of different stabilizers or their larger number.

HPR-containing formulation showed the lowest constant K even by using with EDTA (no other stabilizers-antioxidant and etc.)

Application Guide

Photostability evaluation

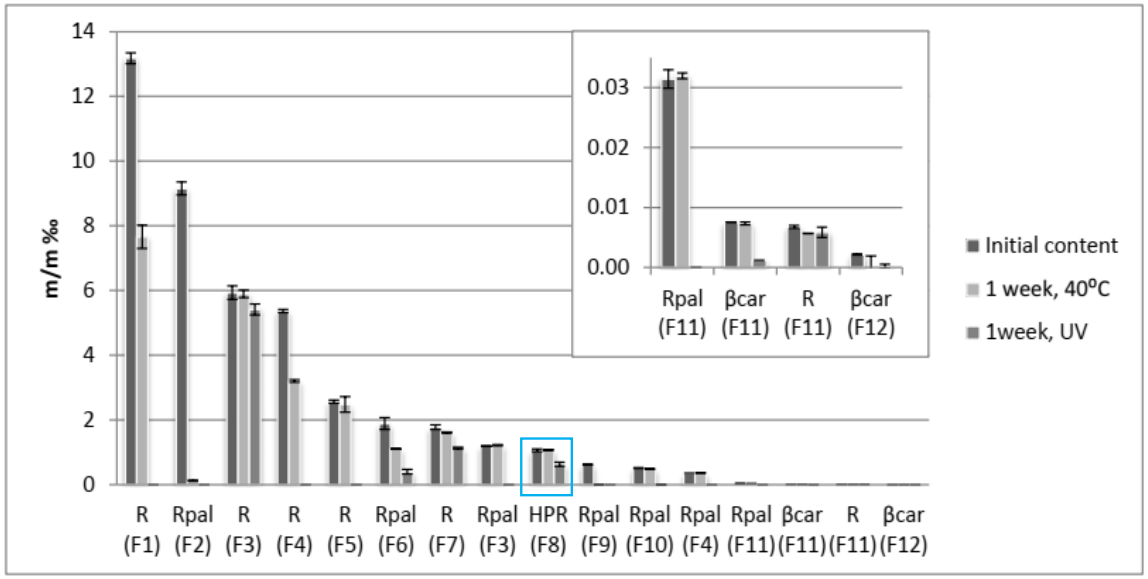


Figure 4. Comparison between the initial content of retinol (R), retinyl palmitate (Rpal), β carotene (βcar) and hydroxypinacolone retinoate (HPR) in the tested cosmetics formulations (F) and their remaining contents after 1 week at 40 ℃and exposure to light.

Summary:

- Performed following the ICH Q1B guidelines
- When comparing different retinoids after the same exposure time to a single factor of instability (elevated temperature and light exposure), light degradation was substantially more pronounced than temperature-induced Degradation.
- All tested retinoids were found overall photosensitive with various degradation rates, including HPR.

To achieve adequate photostability, the addition of UV filters to the cosmetics should be considered, which were not listed in any of the daycare products, subjected to the stability study.

Application Guide

Formulation Example: Vigorous Antioxidant Repairing Cream

	Product Name	INCI Name	w/w%	Function
A	Cetearyl Olivate & Sorbitan Olivate		3.0	Emulsifier
	Cetyl Palmitate & Sorbitan Palmitate & Sorbitan Olivate		1.5	Emulsifier
	SpecSufc® M68	Cetearyl Glucoside & Cetearyl Alcohol	0.5	Emulsifier
	Isopropyl myristate		1.0	Emollient
	SpecKare® GTCC	Caprylic/capric triglyceride	1.0	Emollient
	Dicaprylyl carbonate		3.0	Emollient
	Butyrospermum Parkii (shea butter)		1.0	Emollient
	Dimethicone		2.0	Tactile Enhancers
	SpecThem® C1618	Cetostearyl alcohol	2.0	Emollient
	SpecThem® GMS	Glyceryl Stearate	1.0	Emulsifier
	SpecKare® 3GF	Glyceryl Linoleate, Glyceryl Oleate & Glyceryl Linolenate	3.0	Emollient
B	Glycerin		1.0	Humectant
	SpecThem® XTG200	Xanthan gum	0.15	Stabilizer
	Water		To 100	
	SpecKare® ALLA	Allantoin	0.2	Conditioning Agent
	Disodium EDTA		0.1	Chelating Agent
C	**SpecKare® RRT501**	Retinol, Tocopheryl Acetate	0.5	Anti-aging Agent
	SpecKare® VEA	Tocopheryl Acetate	1.0	Antioxidant
	SpecKare® DPA	Panthenol	1.0	Humectant
D	**SpecPed® AH8P**	Acetyl Hexapeptide-8	0.015	Anti-wrinkle
	PrzvFree® CE85	Caprylyl Glycol & Ethylhexylglycerin	0.5	Preservative
	Fragrance		0.1	

➢ **Procedure:**

1. Mix part A and heat to 80℃, stirring until completely dissolved.
2. Mix part B components and stir well.
3. Add part A into B, and homogenize.
4. Cool to about 40℃, add phases C homogenize again.
5. Then Add part D while stirring until uniform.

➢ **Properties:**

Appearance: Off-white cream

pH : 5.5±0.5

Viscosity : 8,000±500 (25 ℃, 4 #, 30 rpm ,mpa·s)

Market Application

Elizabeth Arden RETINOL+HPR Ceramide Capsules

Ingredients

CYCLOPENTASILOXANE, DIMETHICONE CROSSPOLYMER, C12-15 ALKYL BENZOATE, VINYL DIMETHICONE/METHICONE SILSESQUIOXANE CROSSPOLYMER, DIISOPROPYL ADIPATE, DIMETHICONE/VINYL DIMETHICONE CROSSPOLYMER, DIMETHICONE CROSSPOLYMER, GLYCINE SOJA (SOYBEAN) OIL, TOCOPHERYL ACETATE, SILICA SILYLATE, CERAMIDE NP, BISABOLOL, SORBITAN L AURATE, ***HYDROXYPINACOLONE RETINOATE, RETINOL***, C18-36 ACID GLYCOL ESTER, C18-36 ACID TRIGLYCERIDE, LACTIC ACID, FARNESOL, COLLOIDAL OATMEAL, PHYTOSPHINGOSINE, LIMNANTHES ALBA (MEADOWFOAM) SEED OIL, MACADAMIA INTEGRIFOLIA SEED OIL, PALMITOYL TRIPEPTIDE-1, PALMITOYL TETRAPEPTIDE-7

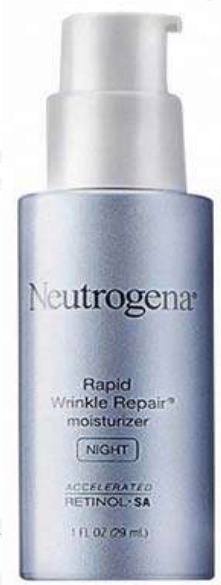
Marketing References

KIEHL'S SINCE 1851 RETINOL SKIN-RENEWING DAILY MICRO-DOSE SERUM

Ingredients

WATER, GLYCERIN,BUTYLENE GLYCOL, PENTYLENE GLYCOL, NIACINAMIOE, CETYLALCOHOL, ISOHEXADECANE, ISONONYL ISONONANOATE, DIISOPROPYL SEBACATE, DICAPRYLYL ETHER, 4-t-BUTYLCYCLOHEXANOL, GLYCINESOJA (SOYBEAN) OIL, BEHENYL ALCOHOL, AMMONIUM POLYACRYLOYLDIMETHYLTAURAT CETEARYL ALCOHOL, PHENOXYETHANOL, LAUROYL LYSINE, SODIUM CHLORIDE, STEARETH-100, CAPRYLYL GLYCOL, CARBOMER, PENTAERYTHRITYLTETRA-DI-I-BUTYL HYDROXYHYDROCINNAMATE, SORBITAN LAURATE,SODIUM HYALURONATE, CHLORPHENESIN, CETEARYL GLUCOSIDE,TRISODIUM ETHYLENEDIAMINE DISUCCINATE, ***RETINOL***,TOCOPHEROL, SODIUM HYDROXIDE,HYDROXYETHYLCELLULOSE, ADENOSINE, OCTYLDODECANOL, ACETYL DIPEPTIDE-1CETYL ESTER, POLYCAPROLACTONE, LECITHIN,PHENETHYL ALCOHOL, 2-OLEAMIDE-1,3-OCTADEACNEDIOL, POLOXAMER188, HYDROXYPALMITOYL SPHINGANINE, HELIANTHUS ANNUUS(SUNFLOWER)SEED OIL,BETA-CAROTENE

Marketing References



Neutrogena Rapid Wrinkle Repair moisturizer

Ingredients

WATER,PENTAERYTHRITYL, TETRAETHYLHEXANOATE, DIMETHICONE, GLYCERIN,PPG-15 STEARYL ETHER, STEARYLALCOHOL,CETEARYL ALCOHOL, BUTYLENE GLYCOL,CETEARETH-20,ISOHEXADECANE, DIMETHICONE, CROSSPOLYMER,TRISILOXANE, PHENOXYETHANOL, CAPRYLYL GLYCOL,CELLULOSE, AMMONIUM ACRYLOYLDIMETHYLTAURATE/VP COPOLYMER, POLYACRLYAMIDE,FRAGRANCR, CHLORPHENESIN, C13-14 ISOPARAFFIN, HYDROLYZED MYRTUS COMMUNIS LEAF EXTRACT, POLYSORBATE 20, BHT, ***RETINOL***, SODIUMHYALURONATE, DISODIUM EDTA, LAURETH-7, ASCORBIC ACID, SODIUMHYDROXIDE, ETHYLHEXYLGLYCERIN, BHA

Marketing References

Market products with Retinyl Acetate

Neostrata
Targeted Clarifying Gel

Kate Ryan
Total Nutrition Night Repair Complex

BioAqua
6x Gentle - A Retinol Serum

Provence Beauty
Vitamin C And Retinol Anti-aging Eye Serum

Marketing References

Market products with Retinyl Palmitate

MADICARE PROFESSIONAL
Retinyl Palmitate, Retinyl Acetate, Retinol

Dr.Alva
Retinol Professional Micro-Capsule Essence (Retinyl Palmitate 0.2%)

Cleanbeauty
Hydrating Facial Oil

Avivie
Intensive Lifting Mask

THANK YOU

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