Convergence of Natural Trend and Capsulation technology
Biogenics' stabilized active material
BioGenic Gentinol-200 (Stabilized Pure Retinol)

Biogenics, Inc.

1. Biogenic Gentinol-200 (hereinafter called " BG Gentinol-200): Stabilized Retinol

1-1. Retinol (Vitamin A alcohol)

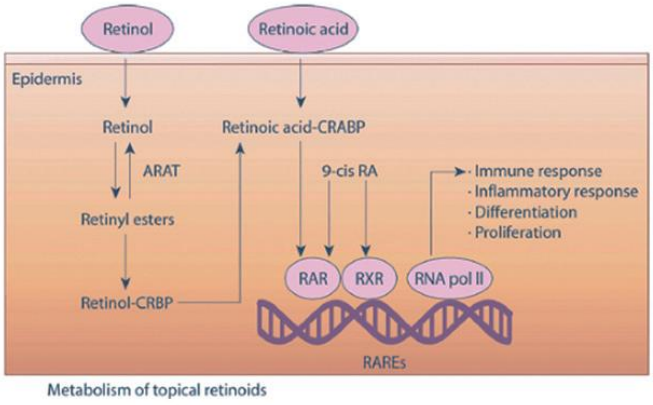
Retinol is one kind of vitamin A which is a kind of fat-soluble vitamin. Vitamin A includes Retinol (Vitamin A alcohol), Retinal (Vitamin A aldehyde), Retinyl acetate, Retinyl propionate, Retinyl palmitate, Retinyl linoleate (types of retinol ester). Among these, Retinol (Vitamin A) was known as a representative wrinkle improving ingredient. Vitamin A is an essential vitamin involved in eye health by improving night blindness and bone growth, immune enhancement and skin health, which was first synthesized in 1947 and has been used as a major ingredient in health functional foods and cosmetics. This component which is abundant in green-yellow plants in natural condition is developed as each derivative depending on its activity and is applied to the food or cosmetic industry. Generally called 'retinoid' by generic name of vitamin A and vitamin derivatives, Retinoic acid which is applied to the drug with an effect on acne skin disease and Retinol & Retinaldehyde which are major ingredient of cosmetics belong to Retinoid family components.

1-2. Skin effect of Retinol

Retinol has been known to be effective in improving wrinkles and enhancing skin elasticity since the late 1990s, and has been dramatically getting popularity as a retinol cosmetic line.

Picture1. Retinol product
(Source: Webpage of each product)

In fact, Retinol has an excellent effect on skin health. Retinol has less direct effect than retinoic acid applied as a medicinal ingredient, but it is made up of pro-fluoric molecules, which make it relatively smooth and less irritating as it is friendlier to the lipid layer of the skin. Retinol that has penetrated the skin is activated to Retinoic acid and maintains epidermal homeostasis by promoting cell differentiation in skin cells and helps improvement of wrinkles by increasing skin elasticity with synthesis of collagen and elastin.



<Picture 2. Topical metabolism of Retinol>
(Source:https://plasticsurgerykey.com/topical-retinoids-in-ethnic-skin)

In addition, it works and has effects on factors that cause skin aging such as skin irritation and pigmentation. The Ministry of Food and Drug Safety has designated retinol-based ingredients with excellent efficacy as a raw material for functional improvement of wrinkles, and the contents are shown in 'Table 1'.

Table 1 raw material for functional improvement of wrinkles designated by MSDS

Materials	Concentration
Retinol	2,500 IU/g
retinyl palmitate	10,000 IU/g
Polyethoxylated Retinamide	0.05%~0.2% or more
Adenosine	0.04%

(Source: raw material for functional improvement of wrinkles at MSDS site)

Three of the four types of wrinkle-improving raw materials of the Ministry of Food and Drug Safety are Retinoid-based ingredients. Retinyl palmitate is a form of retinol combined with palmitic acid, which has a higher stability than retinol, but has a low effect, and thus requires more amount than retinol. In addition, polyethoxylated retinamide is the combination of retinol and polyethylene glycol, and has the highest penetration and stability among the three retinol raw materials.

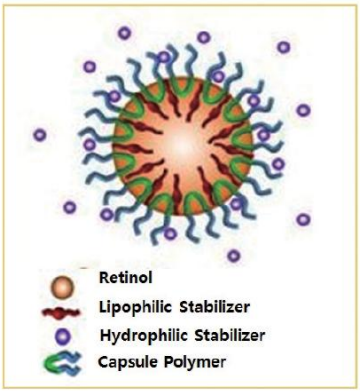
1-3. Limitations of Retinol in cosmetic applications

Even if the efficacy of retinol has been verified as described above, it is not easy to expect actual efficacy through retinol cosmetics. In general, more than 0.0756% of retinol must be included in order for the retinol ingredient to be recognized as a wrinkle improvement function as announced by the Ministry of Food and Drug Safety. Some reports suggest that retinol should be present in at least 0.1% to 1% for a meaningful effect. However, retinol is not only expensive for raw materials itself, but also the problem is the instability of raw materials. When retinol cosmetics are gaining popularity, one of consumer groups has obtained commercially available retinol cosmetics and analyzed the content of retinol in the product and reported it. The results reported that 75% or more cosmetics had no retinol content or lower content than indication. This was a result of the fact that retinol content in some cases was low, but most of the cases is that the retinol which is weak to light and heat, is oxidized and does not functionalize as retinol. Retinol is very unstable to heat, light, temperature,

moisture, oxygen, and elapsed time, so it is easily oxidized when exposed to the atmosphere or water solution. Due to this, the titer of the raw material depreciates and huge problem in stability such as discoloration and odor occurs. To this end, the industry has made many attempts to stabilize it. The raw materials were developed and applied to products through stabilization methods such as micelles and liposomes, and attention was paid to retinol stabilization formulations, utilization of containers that can block contact with light and air, and usage. However, it is also true that there is a limit to overcome the stability issue of retinol which is sensitive to various external conditions in the formulation.

1-4. Stabilized Retinol Ingredient : Biogenic Gentinol-200

BG Gentinol-200, one of the representative active ingredients of Biogenics, is a stabilized Retinol that encapsulated retinol using amphiphilic block copolymer and natural green tea catechin, a patented technology of Biogenics. Biogenic Gentinol-200 contains high content of Retinol which is equivalent to 8-10% pure retinol



<Picture 3. Structure of Biogenic Gentinol-200>

As shown in Picture 3, the high content of retinol stabilized by the multi stabilizing system has remarkable stability of the retinol component itself under various formulation conditions. The results of stability analysis on retinol of Biogenic Gentinol-200 are as follows.

1-4-1. Stability of Biogenic Gentinol-200 at high temperature

To confirm the stability of Biogenic Gentinol-200 at high temperature, the following analysis was performed. The content of retinol was measured while storing Biogenic Gentinol-200 of 10% stabilized retinol at 25 ° C and 40 ° C for 20 weeks (5 months).

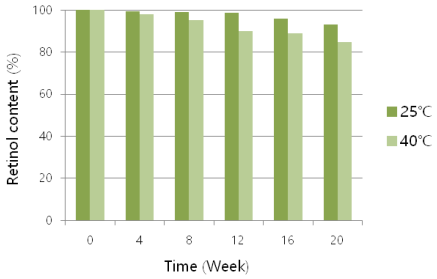
The raw materials were stored in normal glass vials (airless containers were not used), and the content of retinol was measured by HPLC analysis. Graph A of Table 2 shows the stability analysis results for retinol of the Biogenic Gentin ol-200. Retinol retained the content of 95% or more from room temperature (25 ℃) to 16 weeks (4 months), and it shows the retention of the content of 93% or more after 20 weeks (5 months). The more encouraging result was the Retinol content at high temperature (40 ° C), after 20 weeks (5months). The retinol content contained in Biogenic Gentinol-200 was maintained to about 80% or more at high temperature (40 ° C).

1-4-2. Stability of Biogenic Gentinol-200 in cosmetic formulation

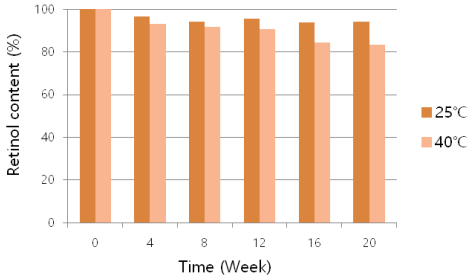
The stability of Biogenic Gentinol-200 in O/W (pH5.5) cream formulation was analyzed as follows. After post- adding 1.1% of Gentinol-200 (0.11% as retinol) to the O/W (pH5.5) cream formulation, place it in a normal glass vial (without using an airless container) and analyzed the stability of it at 25 ° C and 40 ° C respectively for 24 weeks (6 months). And the results are shown in Graph B in Table 2. After 24 weeks (6 months), the retinol content of Biogenic Gentinol-200 in the O / W formulation was 91.8% at 25 ° C and 74.2% at 40 ° C, and it Was confirmed that the retinol content was stably maintained even in the cream formulation.

Table 2. Stability analysis results of Biogenic Gentinol-200

A. Gentinol-200



B. Gentinol-200 in Formulation



A. The Stability of Biogenic Gentinol-200 [Raw material itself]
B. The stability of Biogenic Gentinol-200 [In O/W formulation]

1-4-3. Stability comparison of Biogenic Gentinol-200 *vs* Commercial Retinol

Finally, in order to more objectively analyze the retinol stability of Biogenic Gentinol-200, comparative test and analysis of retinol stability was performed with stabilized retinol which is commercially available in market . A total of two raw materials were applied as a comparison group. Comparative sample A was 4.5% stabilized retinol and Comparative Sample B was 3.5% stabilized retinol. These two comparative samples were applied to the analysis.

All three test groups including Biogenic Gentinol-200 were post-added to the O/W cream (pH5.5) as the pure retinol content , 0.11% in the formulation. And the stability was confirmed for 20 weeks (5 months) at 25 ℃ and 40 ℃. The test method was the same as the test method of above stability analysis . Table 3 shows each test group's results of retinol content . At 25 ° C (at room temper ature), Biogenic Gentinol-200 showed over 90% retinol content. On the other hand, samples A and B from the comparison group were found to have a retinol content of about 70 to 50% compared to the initial concentration, and thus it was confirmed that the retinol content was somewhat very lower than the stability of Biogenic Gentinol-200.

It can be seen that the difference is widened at a high temperature (40 ° C.) stability test. The content of Biogenic Gentinol-200 was maintained with 75% or more, but the comparative group samples A and B were confirmed less than 50% to 40% as retinol content with the remarkably lowered stability.

1-5. Benefits of Biogenic Gentinol-200 and Value of use

Biogenic Gentinol-200, which was stabilized with high content of 10% retinol, is a developed product by Biogenics for 3 year of R&D for aiming to commercialize retinol as a cosmetic ingredient. Biogenic Gentinol-200 has very high value to commercially available ingredient which has improved skin irritation with not only improving thermal stability but also the easy application to formulation by simple mixing / maximizing effectiveness of retinol. Retinol cosmetics, whose popularity has temporarily faltered due to stability issues of retinol raw materials, have recently come to the pore, and are gaining attention from the industry. AMORE PACIFIC has launched a new product of Retinol, and global companies are also interested in product planning. Along with this trend, inquiries about Biogenic Gentinol-200, which has confirmed the stability of raw materials, are also rapidly increasing at home and abroad.

BG Gentinol 200 has already been verified as a raw material by entering the overseas market (Figure 4), and above all, it is possible to apply both US and EU who are very demanding to raw material data.

<Figure 4. Launching product BG Gentinol 200 applied>

The reference material below is an analysis report of an external testing organization (KDRI) for skin irritation test (CNU) and in vitro skin penetration of Biogenic Gentinol-200. In addition, clinical trials for Efficacy was carried out in cosmetic formulation and efficacy data for Biogenic Gentinol-200 is as follows.

[Skin Irritation Assessment of Biogenic Gentinol-200]

KDRI-S-150930-0648-I

Summary of Test Result

<table>
<tr><td>TITLE</td><td colspan="4">Human skin compatibility Evaluation Test of “Gentinol-200”</td></tr>
<tr><td>INSTITUTE</td><td>KDRI Co., Ltd.</td><td>PERIOD</td><td colspan="2">Sep. 30. 2015 ~
Nov. 06. 2015</td></tr>
<tr><td rowspan="4">TEST METHOD</td><td>Sample</td><td colspan="3">1. Cream formulation
2. Gentinol-200 in cream (2,500 IU of retinol)
3. Gentinol-200 in cream (5.000 IU of retinol)</td></tr>
<tr><td>Test Period</td><td>Oct. 27. 2015 ~
Oct. 30. 2015</td><td>Number of Test Personnel</td><td>32</td></tr>
<tr><td>Treatment</td><td colspan="3">24 Hours occlusive patch</td></tr>
<tr><td>Detail on Test Method</td><td colspan="3">1. Subject Selection
: 32 subjects who met the selection criteria and not included in exemption criteria were selected
2. Application Method
: Single application 24hr occluded patch test
3. Evaluation Method
: Skin reactions were classified according to International Contact Dermatitis Research Group (ICDRG) and Personal Care Products Council (PCPC) guideline.</td></tr>
<tr><td>TEST RESULT</td><td colspan="4">The irritation index of “Gentinol-200” was “0”. The tested sample may be considered to have no irritancy to human skin.

KDRI KOREA DERMATOLOGY RESEARCH INSTITUTE</td></tr>
</table>

[In-vitro Skin Penetration of Gentinol-200]

Summary of Test Result

TITLE	Skin Penetration Test of "Gentinol-200"		
INSTITUTE	CNU	PERIOD	June. 22. 2016 ~ June. 29. 2016
TEST METHOD	Sample	1. Retinol (50% retinol dissolved in surfactant) 2. BioGenic Gentinol-200	
	Treatment	Franz diffusion cells[1] with human skin model[2] ([1]Labfine, Korea, [2]Tego science, Korea)	
	Detail on Test Method	• The reconstituted human skin model was mounted on the Franz diffusion cell, with the stratum corneum facing the donor compartment. • Retinol and BioGenic Gentinol-200 were applied on the reconstituted human skin surface in the donor compartment. After application of the test formulation, sample in receptor compartment was taken at 8h, respectively. • The resulting solution was centrifuged and analyzed by HPLC.	
TEST RESULT	• Skin permeability study showed that permeated amount of BioGenic Gentinol-200 similar to Retinol. • Gentinol-200 has same skin permeability compared to Retinol. CNU CHUNGNAM NATIONAL UNIVERSITY		

[Result]

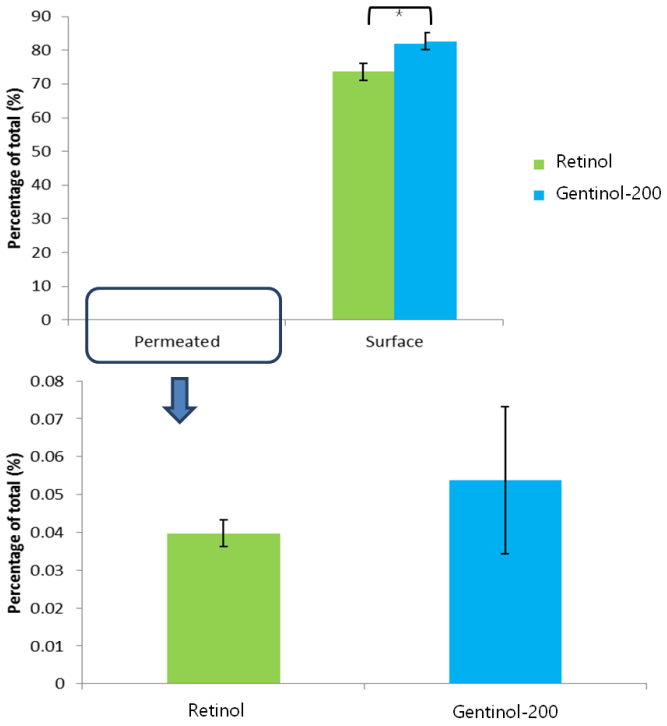


Fig. 1.Skin permeation profiles of retinol and Gentinol-200 after 8 h.*p<0.05

Table 1. Skin permeation profiles of retinol and Gentinol-200 after 8 h.

Sample	Permeated (%)	Surface (%)
Retinol	0.0397 ± 0.0035	73.61 ±2.53
Gentinol-200	0.0538± 0.0195	82.69±2.58

The result of the permeation study was shown in Fig. 1 and Table 1. The percentage of total in permeated skin of retinol (0.0397 ± 0.0035%) and Gentinol-200 (0.0538 ±0.195%) showed the similar values. For retinol at 8 h, 73.61± 2.53% was detected on the skin surface. In contrast, when applying Gentinol-200 at 8h, 82.69± 2.58% remained on the skin surface. The skin permeability study showed that permeated amount of Gentinol-200 is similar to retinol. According to this study, Gentinol-200 has same skin permeability compared to retinol.

[**In-vivo Assessment Anti-Wrinkle Effect**]

KDRI-2020-086

Summary of Test Result

<table>
<tr><td>TITLE</td><td colspan="4">Assessment Anti-Wrinkle Effect of “Gentinol-200” vs “Retinol”</td></tr>
<tr><td>INSTITUTE</td><td>KDRI Co., Ltd.</td><td>PERIOD</td><td colspan="2">Jan. 15. 2020 ~ Apr. 01. 2020</td></tr>
<tr><td rowspan="4">TEST METHOD</td><td>Sample</td><td colspan="3">1. Gentinol-200 1% in cream (3333 IU of retinol, 0.1%)
2. Retinol 0.1% in cream (3333 IU of retinol, 0.1%)</td></tr>
<tr><td>Test Period</td><td>Jan. 23. 2020 ~ Mar. 19. 2020</td><td>Number of Test Personnel</td><td>19</td></tr>
<tr><td>Treatment</td><td colspan="3">Once a day(at night) for 8weeks</td></tr>
<tr><td>Detail on Test Method</td><td colspan="3">1. Subject Selection
: 19 subjects (30~60years old women) who met the selection criteria and not included in exemption criteria were selected.
2. Application Method
: BioGenic Gentinol-200 and Retinol emulsion were applied once a day(at night) for 8weeks by subjects.
3. Evaluation Method
: Measure wrinkle depth using Antera 3D equipment (0, 2, 4, 8weeks). A p value <0.05 was considered significant.</td></tr>
<tr><td>TEST RESULT</td><td colspan="4">BioGenic Gentinol-200 showed significant anti-wrinkle efficacy compared to the Retinol emulsion in Korean female subjects after 8 weeks’ treatment.
KDRI KOREA DERMATOLOGY RESEARCH INSTITUTE</td></tr>
</table>

Result

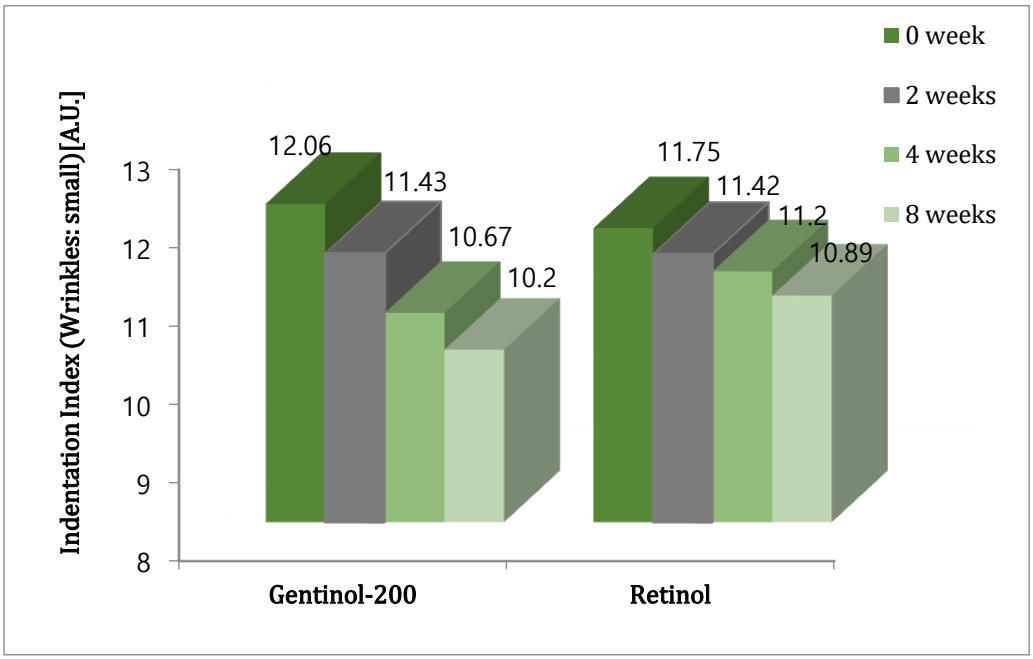


Fig 2. Indentation index, Wrinkles: small

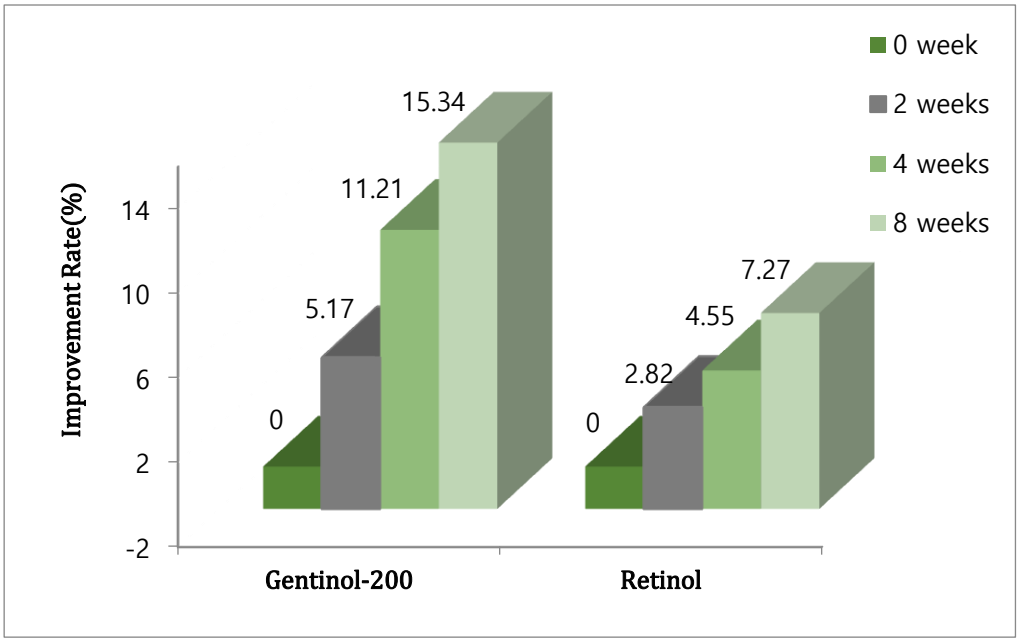
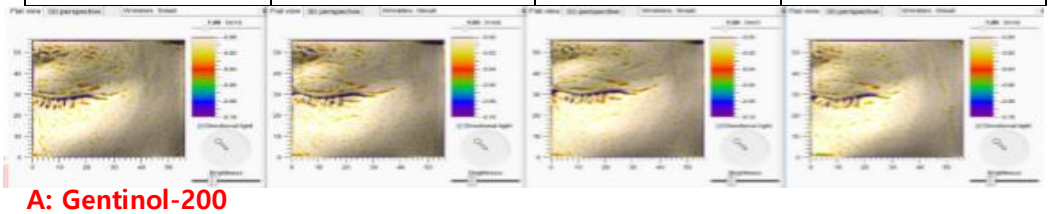


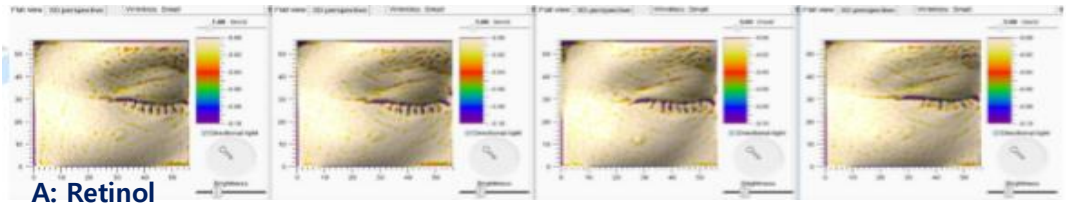
Fig 3. Improvement Rate

BioGenic Gentinol-200 showed more than **twice** the anti-wrinkle efficacy compared to the Retinol emulsion in Korean female subjects after 8 weeks' treatment. It means that only half recommend dosage of Gentinol-200 is equal to pure Retinol for same wrinkle efficacy and it is very cost effective.

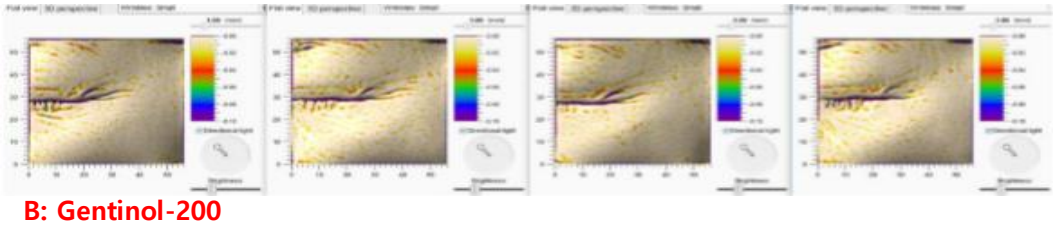
0 week	2weeks	4weeks	8weeks



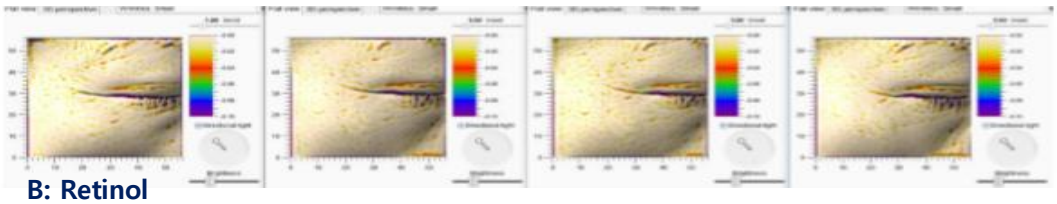
A: Gentinol-200



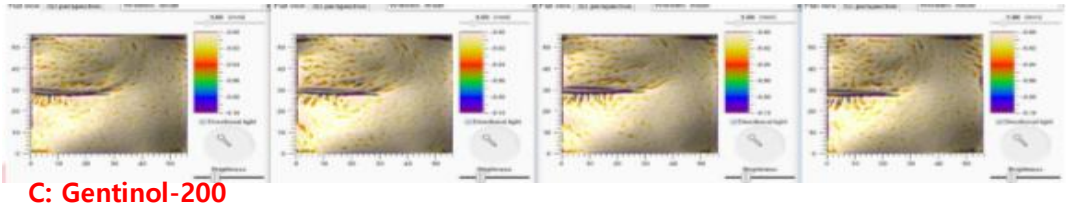
A: Retinol



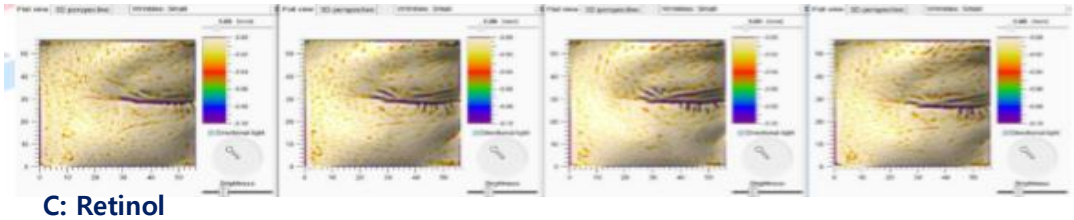
B: Gentinol-200



B: Retinol



C: Gentinol-200



C: Retinol

Product Information

Patent (Domestic and PCT) : Stabilized retinol emulsion compositions using catechin and manufacturing method thereof (PCT/KR2015/001986)