Reserch and Development Report

Regional Consortium Project

Reserch of new Brightening & Whitening product

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Summary

Chapter 1
Outline of research and development

1 － 1
Background, research purpose, and target of research and development

As for the demand of people who wish that is white and beautifully, does not know stopping very high.
Especially, isn't the wish of the woman international and common?
The development of cosmetics which have a white effect to increase the scale every year, and to answer it is always important the theme for domestic and foreign cosmetics maker etc. in the skin whiting market probably because of, and a lot of time is poured into the search for an effect high, new beauty white material.
In the effect of the skin whiting, that ″ Hydroquinone ″ is high so, it is paid attention from old, and the effectiveness has already won high support as use by the purpose of the bristletail and the bruise treatment etc. among specialists. However, this it was not possible to avoid was a big problem as for manufacturing medicine deterioration, which happened because of a very unstable character of hydroquinone.
The impossible is that simply requesting that in a general market need not say in the much more.
The instability of hydroquinone which is about even to give up a wide, general use because it has not evaded the fault on the character up to now by the research and development in this project though the high effect of the skin whiting is admitted is improved. It aims at the practical use to develop a beauty white product with high safety by which hope is given to people who not only answer needs of a consumer who is strongly interesting to the skin whiting but also worry as a disease because of various calm coloring matters.

1 － 2
Outline of result

The following results could be achieved by this research and development.
The molecular complex array decision was clarified by an X-ray, structural analysis and the existence of the doing molecule was clarified.
It was clarified that obtained hydroquinone molecular complex was extremely steady compared with heat, oxygen, and light compared with single purpose hydroquinone by the physical, chemical examination experiment, and enabled the thing that hydroquinone was able to be treated as a material which had high stability by making the molecule complex with

the surfactant under various conditions.
Moreover, the safety evaluation to the human body of not only the material stability but also the safety evaluation of this molecular complex was examined in testing the patch to an ordinary man Takeshi and each specific person doing, and unifying the examination experiments of the skin stimulation examination which used a small animal, the acute toxicity examination, the chronic toxicity examination, and the skin feeling work examination (allergic examination), etc.
As a result, it could be confirmed to have obtained hydroquinone molecular complex that safety which was not the exaggeration to say the big low stimulation occasionally stressed to the skin is high.
In addition, when It administered that to the patient who has an observation of the increase and decrease of the melanin coloring matter which uses the skin cell model as an evaluation of the the skin whiting action of Surfactant/Hydroquinone molecular complex and a coloring matter calm disease under the cooperation of the specialist; The melanin synthesis control was able to be confirmed to hydroquinone molecular complex, and the diseased part recovery of the patient was able to be admitted furthermore. It might be able to be said that a new skin whiting product by the new technique introduction, which won't exist in the research and development of this project up to now at all, could be obtained from the bove-mentioned thing.

1 — 3
Work turned to making to three businesses

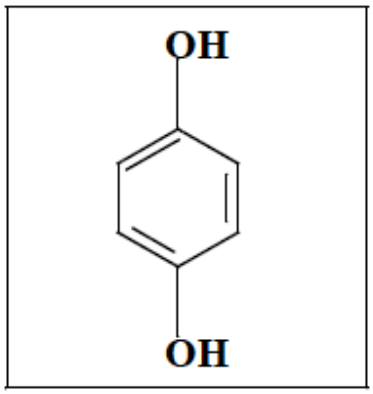
The homepage in the Internet is used as a means of public relations.
The enterprise, which requires buying here, is picked up.
The sales development is done for the enterprise, which demands information with the purchase purpose because this business is caught to the end as the skin whiting cosmetics raw material supply.
It can be forecast that they are the following two classifications as a customer classification.
First of all, that is a customer as the first classification who sells hydroquinone complex as an element raw material such as cosmetics makers.
A lot of cosmetics makers mix hydroquinone complex, and have the cream radical material to sell that as a product.
Hydroquinone complex is offered by an important location of the additional value of Kazunari amount by which the effect of the skin whiting is improved therefore to give that.
As the second classification, it is a medicine manufacture maker who does not have the cosmetics raw material, and it is customers of the import cosmetics sales industry and the hospital relation, etc.
The cream, which mixes hydroquinone complex with the above-mentioned type of business, is sold.

It offers that as a state that the supply destination can be immediately sold as a private brand. It is scheduled to manufacture, and to sell that to adjust to the record two classifications further.
In this report, a mechanism of calm coloring matter and current white medicine of beauty is brought together concisely describing the outline of the research and development, the background, and the purpose, etc. in Chapter 1, showing a physical chemical character of hydroquinone with a high effect of skin whiting in detail hereafter in Chapter 2, showing the instability of hydroquinone by using the photograph data etc, and continuously.
It is shown as the explanation of Chapter 3 of a new technology which uses the surface-active agent of the improvement of instability of hydroquinone which becomes a main purpose of this research and development to have assumed a molecular array of a molecular complex to which takes and is generated with the technology to be clear by an X-ray, structural analysis.
Moreover, the synthetic method is described about the development of a new surface-active agent.

Chapter 4 can apply to the human body among molecular complex obtained in Chapter 3 and reports on the result of examining the selection of suitable molecular complex and the stability of the molecular complex to making to the product.

Chapter 5 shows the result of doing the safety evaluation examination of molecular complex, which seems that suitable to making to the product in a small animal and the homo patch test, and the safety evaluation
Examination of the passing skin absorption of molecular complex is done at the cell level, and the melanin synthesis control is examined at the same time in Chapter 6. In addition, the effectiveness examination of molecular complex is done by the cooperation of the dermatology specialist and the coloring matter calm type contact dermatitis patient and it reports on the passage of the diseased part recovery.
This project research and development is summarized in Chapter 7.

Chapter 2
Main discourse(1)



2 － 1

The skin whiting element: Hydroquinone which pays attention to hydroquinone as the skin whiting element is best at this time.

Structure of Hydroquinone (HQ)

- Externals: Colorless needle shape or pillar-shaped crystal
- Melting point: 173.8- 174.8℃
- sublimes without decomposing at 285℃.
- Boiling point: 285℃ (730mmHg).
- sublimes without decomposing at 285℃.
- Specific gravity: D 1.332 15
- Solubility:6g (15℃) melts to the water 100g.It is 7 in the water 100g G (25℃) melts.9g (2 8 ℃) melts to the water 100g.It is melts easily in ethanol and geetilatel that melts easily. It is small dissolution in benzene. That melts little.
- Solution has weak sweetness. That is oxidized, and that becomes brown when leaving them in air.

(S cheme2-1、)

- Usage: It is used as a medium, an oxidation, a polymerization prevention medicine, and an anti-ozone medicine agricultural chemistry materials of the photograph development medicine and dyestuff and the medicine synthesis. Moreover, it is used as a reagent for the analysis of phosphorus, the arsenic, and the Kei acid.

2 － 1 － 1

About a structural change with the oxygen of hydroquinone

Quinhydrone: C H O (molecular weight 218.21).
Molecular compound which can be done by mixing quinhydrone 1 molecule and hydroquinone 1 molecule.
Infiltration in pharmacology and the medicine area is hardly known as long as the report, which shallowly affects hydroquinone is seen though a structural change by the oxidation of hydroquinone was found for about 30 years ago.
It is doubted very much therefore, not having been found yet is a current state in an appropriate method as for coloring according to the oxidation of hydroquinone though various devices are performed.
When there is a problem like the above-mentioned even if it is effective to the bristletail hydroquinone treatment, It comes, and the effectiveness is lost the include amount decrease in the principal ingredient hydroquinone in the product. It is necessary to improve this immediately. This project accomplishment, the thing to know the character of hydroquinone enough as shown in Chapter 2 is a necessity and indispensable.

2 － 2
About the skin whiting and the skin whiting medicine

It is said that bristletail ephelides etc. are quite a lot of bristletail ephelides and the woman who is dark-skinned and worries, and begin to appear in one's teens, and become in her fifties if early until most people have the bristletail.

The purpose of the skin whiting is to suppress the production life of an excessive melanin. The skin whiting medicine is the one to be proud more than flesh-colored and to return flesh-colored an advanced calm coloring matter. Help the recovery to earlier more flesh-colored in usual sunburn, and as an action on the bristletail part. It is the one which always proudly for changeless, tries to suppress an advanced melanin synthesis, and bring that close to flesh-colored unlimitedly.
The following materials are enumerated typical the skin whiting.

2 － 3
Bristletail generation mechanism and cause

① Skin structure
The skin covers the whole body and does the role to protect the living body from various stimulation, the troubles or dryness from the outside.
The skin is roughly sequentially divided from the surface into three layers (bark, the corium, and the hypodermic organization).

【 epidermis 】
Epidermis is sequentially divided from deep into a base layer, stratum spinosum, stratum granulosum, and astratum corneum layer.
Melanocyte coloring matter cell, which synthesizes the melanin coloring matter, exists in the base layer. It is said that this is scattered at one rate per ten base cells in the cell with a dendritic projection.

② Melanocyte and melanin synthesis

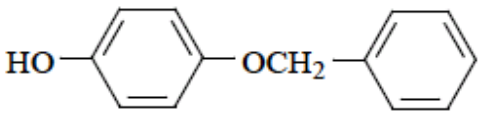
Melanocyte exists in the base layer of bark. It is known as melanocyte that bark is located in interiors most, and is a cell, which generates the melanin assumed to be a big factor to decide the person the color etc. of the skin, and proliferates by the ultraviolet rays irradiation. Melanocyte is a cell, which synthesizes the melanin, and supplies the melanin to surrounding keratinocyte through the projection extended like branch of tree. The synthesis of the melanin is synthesized in small granule, which is called melanosome, which can be made in melanocyte.

③ Cause and the generation of bristletail and ephelides
Ultra violet rays are a big threat for the living body. As for the ultraviolet rays irradiated to the skin, the melanin which melanocyte produces plays a defense of the ultraviolet rays which penetrates in the skin the most important role though the part is first scattered by detailed irregularity of the surfactant. It is said that the skin which receives ultraviolet rays keeps being said that the division of bark melanocyte promotes, and the melanin synthesis ability in an increase of melanosome and melanocyte has been improved, and being made the melanin coloring matter from this excessively. The bristletail causes as the above-mentioned, and indicates the calmness state of to the bark all layers by the melanin in the limited part of the skin. Ephelides is also similar for the bristletail it is partially said that an inherited element is related to this; too by the melanin coloring matter though the one, which can be done production.
The cause of the appearance such as bristletails
○ Ultra violet rays
○ Proliferation of melanosome in melanocyte
○ Activation of tyrosinase ferment
If these can be controlled, the bristletail etc. can be controlled, and be treated.

④ Kind such as bristletails
A)
Bark elderly human character coloring matter spots

It appears while aging from 30 years old, and the outline is made clear the elderly person character coloring matter spotted in comparatively thick brown. It is a bristletail seen best.
B)
Spots of petal coloring matter
C)
Seborrheic dermatitis
Seborrheic dermatitis is the one in the state which rises by over forming horny by the resin seborrhea-making syndrome or the elderly person character verruca skin's aging like verruca is said.
D)
After the inflammation, the coloring matter is calm.
After the inflammation, the coloring matter of a calm coloring matter, which can be made after the inflammations such as wounds and the burns, is calm.
E)
Corium Oota nevus mole
F)
Doing sticky mortar brown, which symmetrically extends on the cheekbone and amount and the gills indicates seeing by liver spot.
G)
There are the corium one a lot of the one youth bark a lot ephelides delaying. The one that a lot of brown, small maculas exist on both cheeks and noses is said.
H)
The Oota nevus is brown birthmark. It is said that the nature ahead is.

It is thought that hydroquinone treated by this project is effective to the bristletail shown in the above-mentioned. However, the following things are thought as a reason why hydroquinone does not come into the market easily.
○ It is unstable compared with oxygen and light and causes a structural change.
○ Because it had been recognized as similar goods by some specialists etc. Because it was similar to the hydroquinone monobengelatel a structure assumed to be dangerous, a similar treatment was performed.
The thing of two points is given above as the big problem.



Hydroquinone monobengelatel

It seems that the thing to be born the skin whiting product which can be used trying to improve the stability of hydroquinone in this project, and at ease becomes a chance by which wrong recognition to hydroquinone which not only answers an interesting market trend to mere the skin whiting but also has taken root deeply is renewed. The meaning of this research and development is large in such a respect.

Chapter 3
Main discourse(2)

3 — 1
Technology for stability improvement of hydroquinone

3 — 1 — 1 Molecular complex making with surfactant

There is ″Elucidation of the crystal structure and physical properties of crystalline molecular complex generated between an aroma family compound and various surfactants″.
They are very effective for discharge stabilization little by little methods of an aroma family compound, which contains the medicine and the spices, etc., and a variety of aroma family compounds by a molecular complex formation with the surfactant. In most cases, because it is a crystal, handling becomes very easy as for molecular complex, which could be generated. The structure of a molecular complex was elucidated by succeeding in the acquisition of good quality monocrystalline and using an X-ray, structural analysis, and it was clarified to the structure of interaction which worked between the surface-active agent and the aroma family compound two and those molecular complex that common pattern (Ｃｏｍｍｏｎ　ｐａｃｋｉｎｇ　ｐａｔｔｅｒｎ) was seen. Moreover, the aroma family compound from which the molecule is made complex by the surfactant can be stabilized if it is controlled, and it is unstable if a character different from it is shown, and a water solution is increased, and it is easy to evaporate if it is a hard solution compared with oxygen and light. In addition, it was clarified that had the advantage that changing the kind and the length of the alkyl chain of the surfactant could control them used.
The success in an X-ray, structural analysis of molecular complex can explain various physical properties which molecular complex shows at a molecular level, and both researchers can say that proposed surfactant molecular complex based on chemical grounds. This project is a work by which the content of this research is assumed to be technological seeds, it tries to improve hydroquinone which cannot be achieved by now stability, and it aims at the achievement of the hydroquinone content product with high effect of the skin whiting.
When the technique of molecular complex making with the surfactant is introduced and hydroquinone molecular complex is generated with the surfactant

(1)It is necessary to form steady complex in heat with hydroquinone, and search for the surfactant to which a structural change does not take place because of light and oxygen.
(2)When an enough effect cannot be expected in a surfactant on the market, a molecular design which changes length of the alkyl chain and an ion part is done, and those syntheses are attempted.
It seems that the thing of two points is important.
About (1)Item, that drank and when researching up to now of Imura and experiencing that, the following ion surfactant attempted the molecular complex generation which used them by being thought that a cation surfactant was especially powerful.
A molecular array was decided when monocrystalline which was able to analyze X rays and the structure of obtained molecular complex was obtained and the existence of molecular complex was clarified.
It seems that glucide surfactant is very effective when thinking from respect only of safety though the reason is that it is forecast to obtain molecular complex, which has high stability as a reason to select an ion surface-active agent.
Molecular complex generation was attempted with glucide surfactant, the stability was examined, and it made that to the thing to select surfactant, which had both the comparison and stability and safety with molecular complex obtained by an ion surfactant and hydroquinone molecular complex as a candidate of the product development. It is describes that about these 3-2.

3 － 1 － 2
About the surfactant these3-2

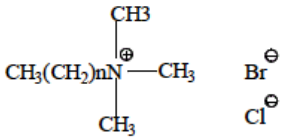
It touches a little here about the surfactant.
Surfactant has the part, that is, the canal part where the harmony of the part, that is, hydrophilic which harmonizes with water and is high and water is low in the structure the molecule, and the surface tension of water is decreased remarkably with the surface-active agent because of a small amount of addition. It is said amphiphile from the possession of two stuffs such as water and oil with different character and the characters it to be easy become familiar.
It has washing, moist, infiltrating, distributing, emulsifying, making to the melt ability, and sterilization, lubrication, and rust prevention, etc. as a characteristic of the surfactant.
The role of the surfactant in the cosmetics manufacturing is used as washing, emulsification, decentralization, and a medicine of making to the melt ability, and the development is still active. Moreover, It does not stop in a basic type with only strong washing power and emulsification power, and the surface-active agent to aim at infiltration and continuation is developed.

The surfactant can use even by the purpose of skin care, and defends skinning from dryness. It is a material thought to be showing the barrier function to stimulation from the external world, and important as the ultraviolet rays interception medicine which causes the skin aging of the bristletail, ephelides, and the wrinkle, etc.

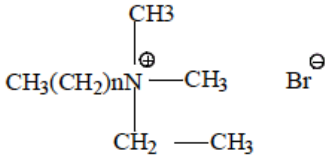
3 － 2
Surfactant／ Hydroquinone molecule complex generation

3 － 2 － 1
Selection of surfactant

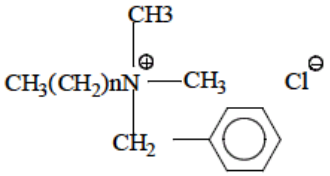
It is necessary to select a suitable surfactant from among the surfactant, which exists variously to generate molecular complex between hydroquinone molecule complex generation and the surfactant for this project achievement. It is necessary to clear can the application of the final result thing to the human body. Therefore, the selection of the surfactant at the molecular complex generation stage has a very important meaning. The selection was tried from a surfactant from which use had been first permitted as a method on the market.
The selected surfactant and the abbreviation name is shown by
Scheme 3-1.



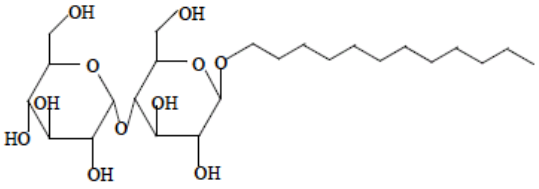
n=17 Octadecyltrimethylammonium bromide ,chloride (STAB, STAC)
n=15 Hexadecyltrimethylammonium bromide ,chloride (CTAB, CTAC)
n=13 Tetradecyltrimethylammonium bromide ,chloride (MTAB, MTAC)
n=11 Dodecyltrimethylammonium bromide ,chloride (LTAB, LTAC)
n= 9 Decyltrimethylammonium bromide ,chloride (DTAB, DTAC)



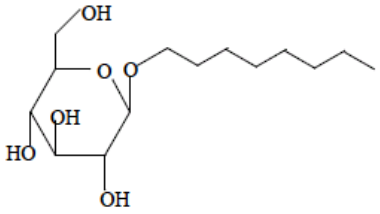
n=15 Hexadecyldimethylethylammonium bromide (CDEAB)



n=17 Octadecyldimethylbenzylammonium chloride (BSDAC)
n=15 Hexadecyldimethylbenzylammonium chloride (BCDAC)
n=13 Tetradecyldimethylbenzylammonium chloride (BZCl)
n=11 Dodecyldimethylbenzylammonium chloride (BLDAC)
n= 9 Decyldimethylbenzylammonium chloride (BDDAC)



n-Dodecyl- -D-maltoside (DM)



n-Octyl- -D-glucoside (OG)

( ) 内は略名を示す。

( ) The abbreviation name is shown.

Scheme 3 － 1

Chemical structure of surfactant

3 － 2 － 2

Making of molecular complex of Surfactant and Hydroquinone

When the solution is done making to the melt ability usually under the nitrogen current of air adding hydroquinone to the surfactant solution, made to a uniform solution, and is cooled and left, molecular complex generated as a precipitation thing between the surfactant and hydroquinone can be obtained with the crystal.

Moreover, the solution is cooled, left after the surfactant and hydroquinone are warmed to the methanol or the ethanol as another method under the nitrogen current of air, it dissolves, and a uniform solution is obtained, and a molecular complex crystal is obtained.

3 － 2 － 3
Confirmation method of molecular complex of surfactant and hydroquinone

Crystalline molecular complex obtained from the solution of making to the melt ability etc. was decided, and the dry sample was made a methanol solution after it washed that by cold water several times of according to the furnace, the existence of the additive in complex was confirmed with visible outside purple spectrum brightness meter (U V - 1 6 0 A, Sh i m a d z u), and the mole composition ratio was decided.
When a good quality crystal is obtained, the monocrystalline X-rays and structure analyses become powerful means of a molecular complex confirmation though molecular complex generated between the surfactant and hydroquinone is often extracted as a minute crystal.
About obtained molecular complex is shown by Table 3 -1 .

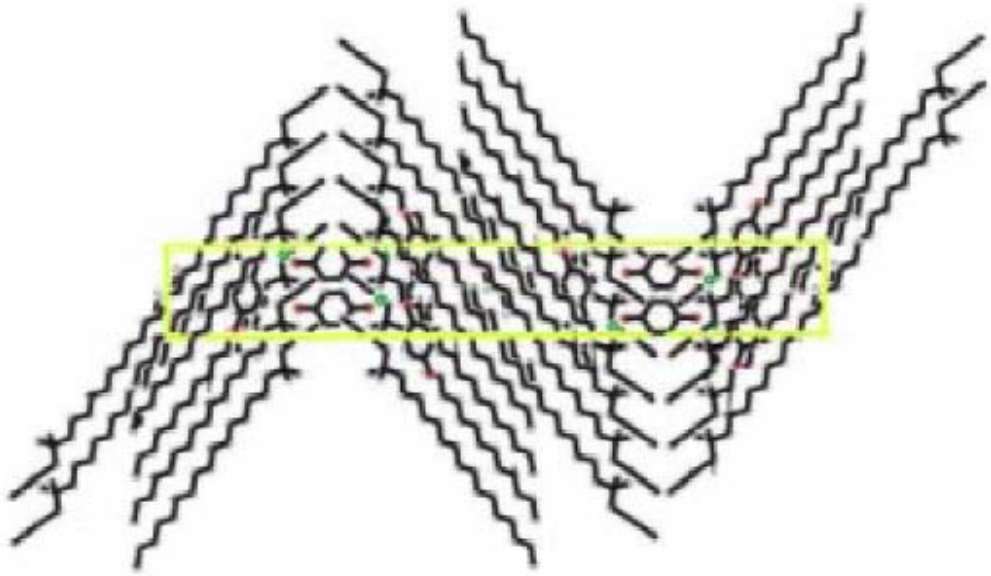
Table 3 -1
Molecular complex and generation mole ratio obtained by this project

The ○ sign is molecular complex in which an X-ray, structural analysis succeeds.

3 － 2 － 4
Surfactant / Crystal photograph of Hydroquinone molecule complex
Crystal photograph of BCDAC/HQ　　Crystal photograph of CDEAB/HQ

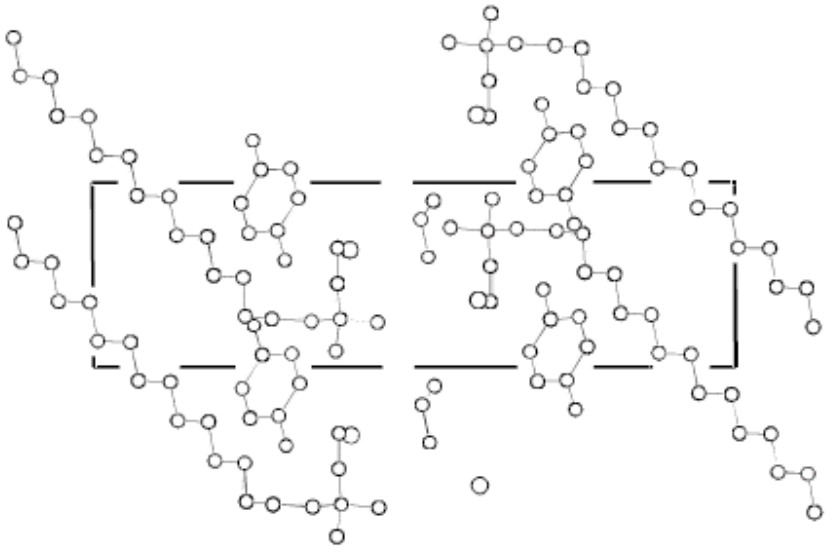
3 － 2 － 5
X-ray, structural analysis of molecular complex, which consists of surfactant, and hydroquinone molecule complex

Diffraction strength was measured by using the Mok-ray, or the Cuk-ray line under the room temperature with imaging plate monocrystalline X-rays and automatic structure and analysis devices (RAPID-L, Rigaku).
The following Figure 3-2, 3-3 was that the structure of the crystal was made precise by assuming w( ) to be minimum by using program SHELXS-97 of the method directly and using a full matrix by SHELXS-97 of solving and the least square method program.
The structure of the Fo-Fc 2 CDEAB/HQ crystal was made precise by assuming w( ) to be minimum by using directly, solving program SIR-92 of the method, and using a full matrix by SHELXL- 9 7 of the least square method program.
Figure 3- 2 and 3 -2 two examples of a crystal structural chart for three - are shown.
Moreover, the crystallography data is shown in Table 3-2.



An axis projection chart

Figure 3 -2 Crystal structure of BCDAC/ Hydroquinone



A axis projection chart

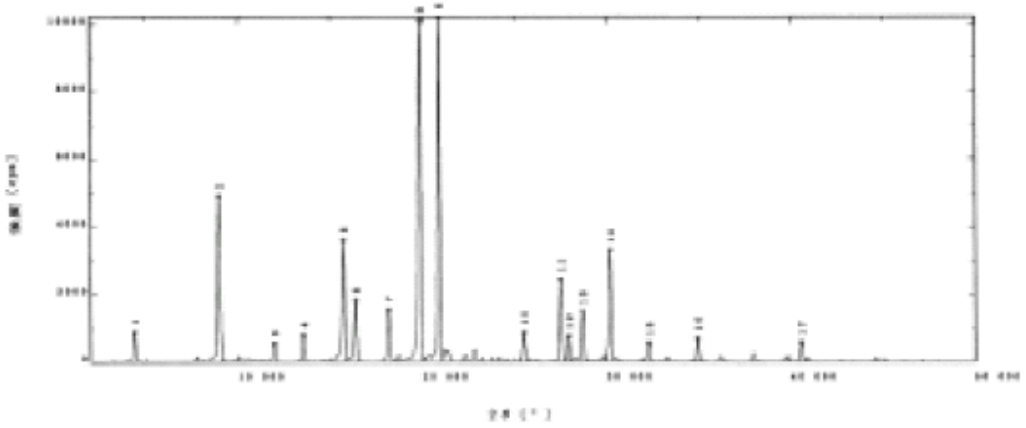
Figure 3 -3 Crystal structure of CDEAB/ Hydroquinone

Table 3 -2 Crystallography data

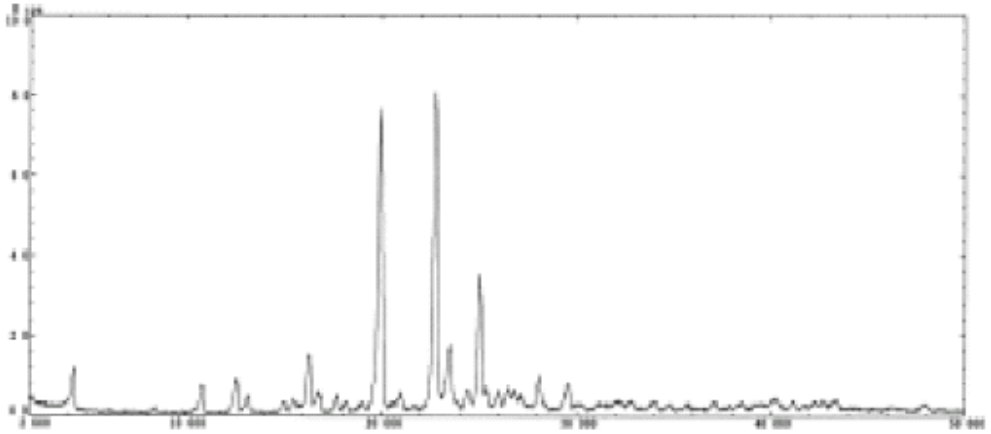
complex	BCDAC/HQ	CDEAB/HQ
Formula	$C_{19}H_{42}NCl/1.5C_6H_6O_2$	$C_{20}H_{44}NBr$ $/C_6H_6O_2$ $/C_2H_6O$
Mol.Weight	506.19	534.644
Crystal system	monoclinic	triclinic
Space group	C2/c	$P\bar{1}$
a(Å)	18.3719(5)	9.8615(26)
b(Å)	7.0309(2)	23.5466(20)
c(Å)	50.6482(13)	7.125(25)
(°)		93.857(25)
(°)	91.1170(10)	110.7247(20)
(°)		80.091(24)
Z	8	2
R factor	0.0725	0.0535

It has been understood that the (common packing pattern) exists also in the crystal structure of BCDAC/HQ and CDEAB/HQ.
It comes the slide of the alkyl chain of the surfactant, which lines up in the opposite direction, is taken hydroquinone into the gap, which can be done by uniting hydrogen, and is CH. This crystal structure is stabilized partly because of the interaction. Moreover, hydroquinone queued up near for the hydrophilic group of the surface-active agent like the column, and the hydrogen uniting could be confirmed there about BCDAC/HQ complex.
The solvent ethanol used when complex was molecule generated entered in CDEAB/HQ complex, and anion bromide, which was the ion of the surfactant and hydrogen, united through the solvent.
It was molecular complex with an ion surfactant to be able to obtain the crystal which was able to be the monocrystalline X-rays and structure analyses though glucide surfactant was used for molecular complex generation at this time.
There is a powdery, X-ray diffraction measurement in other molecular complex confirmation methods.
As for us, when the surfactant forms an aroma family compound and molecular complex with a current research, the powdery, X-ray diffraction pattern obtains the result in which shifting to the difference low corner side with the pattern of the surfactant unit.
For instance, the thing is shown in Figure 3-4.
It is not understood that the diffraction peak, which it is neither hydroquinone unit, is nor the BCDAC unit either appears on the low corner side in the powdery, X-ray diffraction pattern of BCDAC/HQ in Figure 3-4.

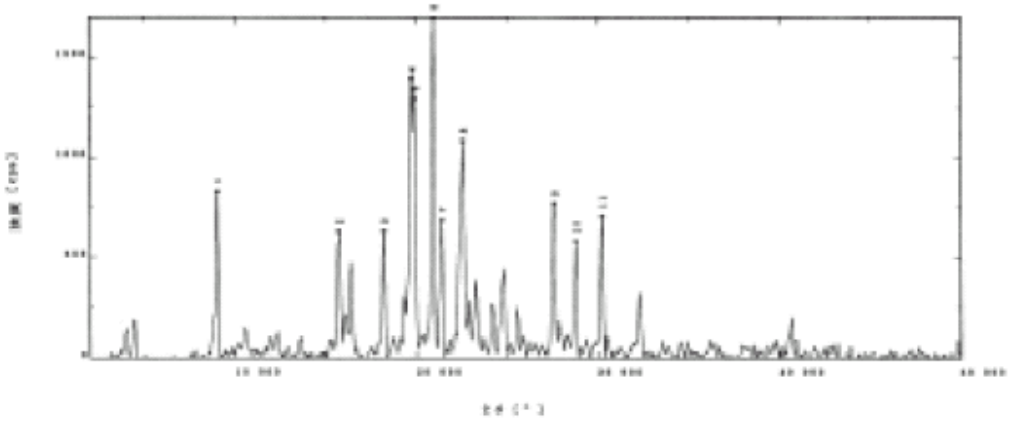
This peak suggests a molecular complex formation.



Powdery, X-ray diffraction pattern of hydroquinone unit



Powdery, X-ray diffraction pattern of CDBAC unit



Powdery, X-ray diffraction pattern of CDBAC/HQ molecular complex

Figure 3 -4

Comparison of powdery, X-ray diffraction patterns of unit and molecular

complex

About molecular complex of glucide surfactant and hydroquinone molecule, the above-mentioned judgment method was introduced because monocrystalline could not be obtained and the confirmation was done. Figure 3-5 shows the result.

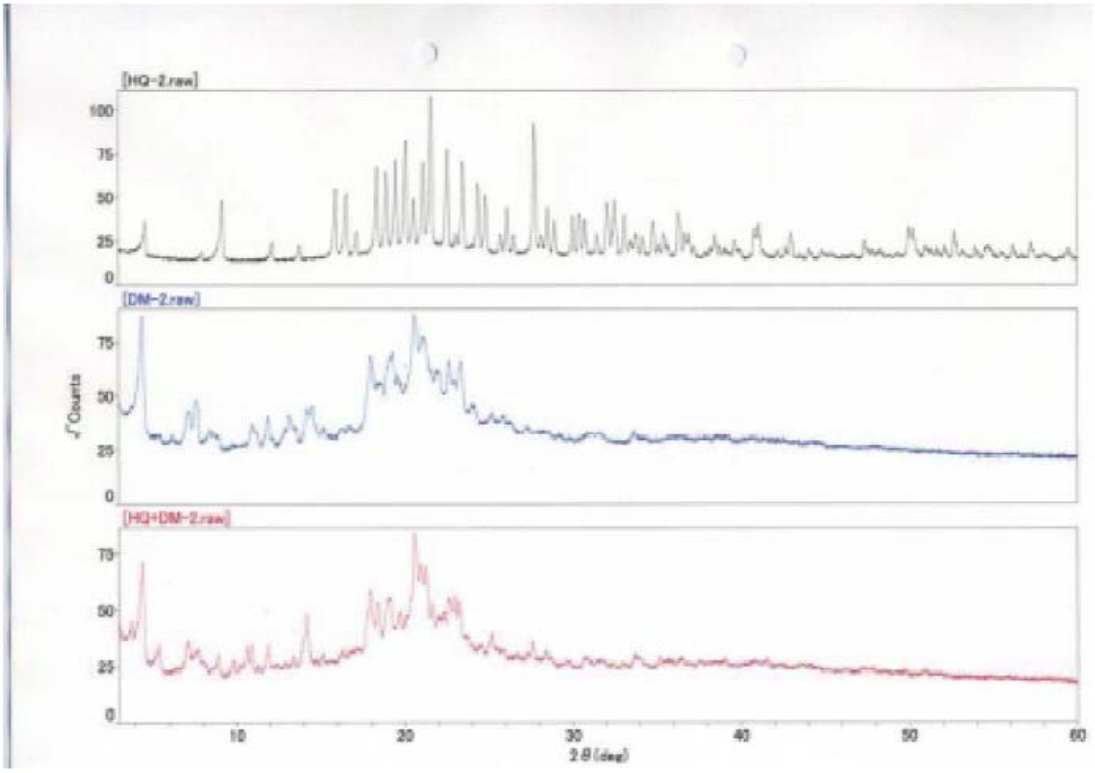


Figure 3- 5
Confirmation of molecular complex formation of glucide surfactant and hydroquinone

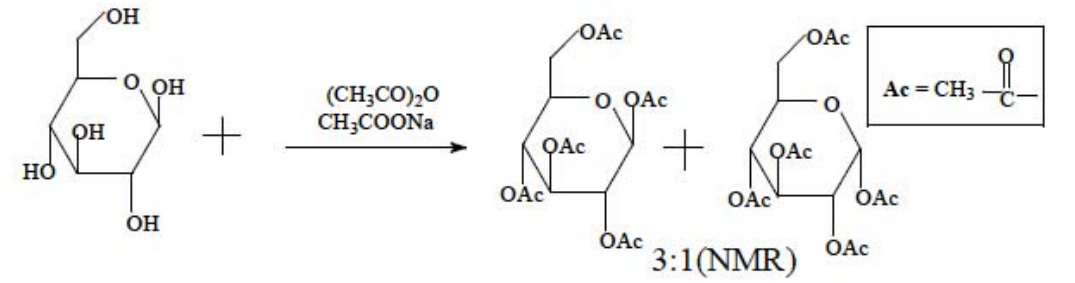
To the upper row of Figure 3-5 though the powdery, X-ray diffraction pattern of n-Dodecyl--D-malt side (DM)/HQ molecule complex was shown in the powdery, X-ray diffraction pattern of the n-Dodecyl malt side (DM) unit and the lower in a powdery, X-ray diffraction pattern of the hydroquinone unit and inside steps; A new peak which appears leftmost of the powdery, X-ray diffraction pattern of n-Dodecyl- -D-malt side (DM)/HQ molecule complex can be judged the origin from molecular complex generation, and the thing that glucide surfactant and hydroquinone molecular complex can be obtained has been understood. However, it seems that it is guessed that poor yield of obtained molecular complex becomes a problem in making to the product and some measures of this are necessary.
The photograph of monocrystalline X-rays and structure and analysis the devices and a

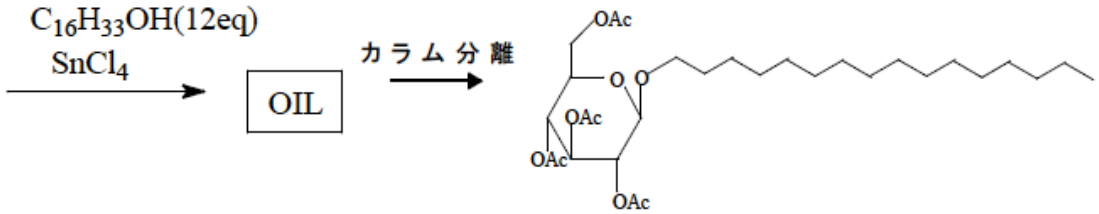
powdery, X-ray diffraction devices used at this time is shown below.

Imaging plate monocrystalline X rays and automatic structure and analysis devices (RAPID-L, Rigaku)
Powdery, X-ray diffraction device (Rigaku)

3 － 3
Synthesis of glucide surfactant

Structural elucidation is considered in molecular complex generated with glucide surfactant by the low degree of yield and stability and poor crystalline, and the matter of difficulty becomes a problem and it can be considered that it is not from a current experiment result to making to the product even though it is suitable though the safety of glucide surfactant is widely admitted.
However, molecular complex with the surfactant which had the length chain in the result of the research of a current project planned and executed the synthesis of the following surfactant by thinking whether the above-mentioned problem was able to be evaded if a molecular complex which used the glucide surfactant artificially synthesized in consideration of the (-OHreduction) of the result in which showing high stability and the radical was formed.





1-*O*-n-hexadecyl- -D-glucopyranoside 2,3,4,6-tetraacetate

Column separation
==========➔

Making glucose acetyl happens when D glucose, the acetic acid sodium, and the no water acetic acid are stirred for four hours at 100℃ as shown in the above-mentioned reactive type under the nitrogen current of air, and α and β are obtained in a ratio of 1:3.

The thing confirmed with nuclear, magnetic resonance device (N M R) can have been done about this. An oily generation thing can be obtained by making it react for four hours in the room temperature <under the nitrogen current of air> under SnCl and the gecrorometan coexistence cetyl alcoholic the generation thing. It separated in the column and the shown record final compound could be obtained.

Chapter 4
Main discourse(3)

4 － 1
Selection of surfactant/ hydroquinone molecular complex turned to making to product

The generated molecular complex has the thing of showing very high stability to heat, oxygen, and light by using an ion surfactant, especially a cation surfactant for the result of the research of this project. It was possible to look for that still in surfactant/ hydroquinone molecular complex, which had been obtained because of the research and development at this time. It was confirmed that hydroquinone molecular complex with glucide surfactant by which only safety was valued was admitted coloring at preserved at the room temperature a difficult, for instance considerably early stage, and chipped to durability for humidity. Yield not requires considerable time for the synthesis of the glucide surfactant designed to improve the stability, and is so good at the present stage either.
To accomplish this project smoothly, the selection of suitable molecular complex is demanded of making to the product in an early stage.
The thing to advance development thought suitability as a target of molecular complex with an ion surfactant therefore this project.
It publishes from molecular complex obtained by this project based on the above-mentioned thing in making to the product and suitable molecular complex is published in ″Cosmetics type permission standard″.
It was judged that it was molecular complex with chloridization (*hekisadeshilgemetilbengelammonium*) (BCDAC).
This molecular complex succeeds in an X-ray, structural analysis, and is complex which elucidates the molecular array.

4 － 2

Stability examination of surfactant/ hydroquinone molecular complex

The examination of the following stabilities was evaluated by doing four examinations centering on BCDAC/ HQ molecular complex.

(1) Heatproof examination
(2) Oxidized examination
(3) Optical examination
(4) Stability examination to various ointment radical medicine by mixing

4 － 2 － 1
Heatproof examination

Obtained molecular complex was examined and stability was examined to heat by the thing to observe the loss in weight of hydroquinone according to the temperature rise with that

It has been understood that it is understood to be able to suppress the loss in weight of hydroquinone according to the temperature rise by making the molecule complex with the surfactant even in a considerable high temperature area in a heatproof examination compared with the unit, and has considerable durability for heat by molecular complex generated between surfactant BCDAC and hydroquinone.

4 － 2 － 2
Oxidized examination

Deterioration to the oxygen of hydroquinone was observed by leaving in the constant temperature tank where obtained molecular complex was kept 37℃ while opened after the particle diameter was arranged with 48-80 meshes, being sample for a fixed time, and measuring the specrto photometer of the specific wavelength of hydroquinone with the UV/Vis Recording Spectrophotometer.

The molecular complex generated between surfactant BCDAC and hydroquinone while deterioration in about 30% a day was accompanied by hydroquinone unit escaped it, and was able to obtain being able the expectation of a long series of oxidation-proof of an oxidation of the expectation of the obtains in oxidized examination. The result, that is, result.

4 － 2 － 3
Optical examination

After the particle diameter is arranged with 48-80 meshes, obtained molecular complex is put in the bag made of polyethylene. The escape nature was done enough, the sample which did the sealing up seal with vacuum Sealer was observed, and after an optical irradiation had been done during the fixed time in 25 degrees C with a xenon lamp (optical amount:　3 0 mW/cm), deterioration to the light of hydroquinone was observed by measuring the measuring in the specific wave length of hydroquinone with a visible outside purple spectrum brightness meter.
Figure 4 shows the result.

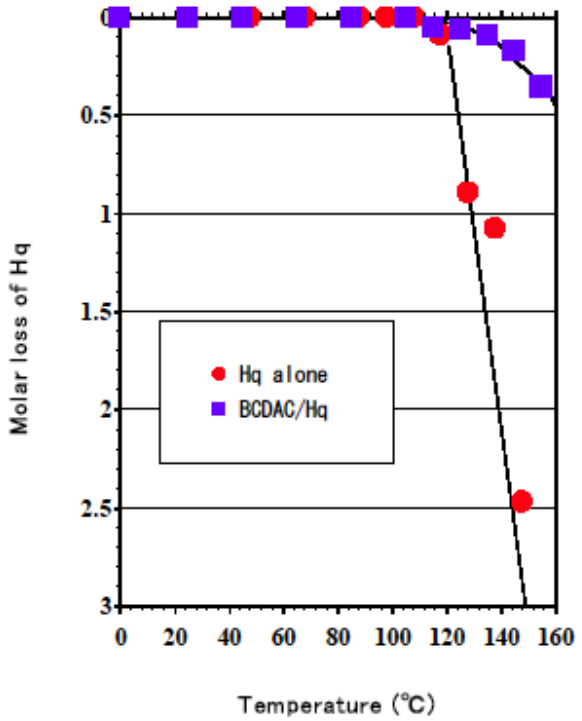


Figure 4-1 Heatproof examination results

It has been understood that it is understood to be able to suppress the loss in weight of hydroquinone according to the temperature rise by the moleculecomplex making with the surfactant even in a considerable high temperature area in a heatproof examination compared with the unit, and has considerable durability for heat by molecular complex making generated between surfactant BCDAC and Hydroquinone.

4 － 2 － 2
Oxidized examination

Deterioration to the oxygen of hydroquinone was observed by leaving in the constant temperature tank where obtained molecular complex making was kept 37℃ while opened after the particle diameter was arranged with 48-80 meshes, Being sample for a fixed time, and measuring the specrto photometer of the specific wavelength of hydroquinone with a visible outside purple spectrum brightness meter.
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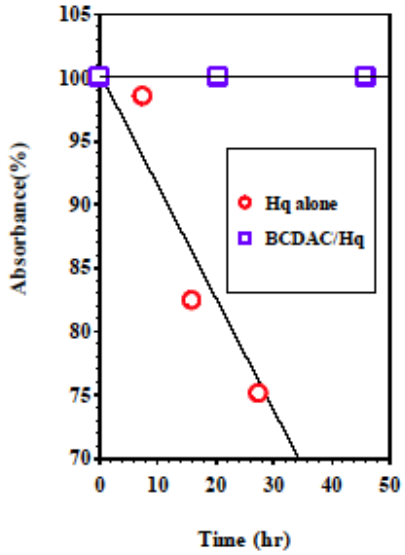

Figure 4-2 Oxidized examination result

Molecular complex making generated between surfactant BCDAC and hydroquinone while deterioration in about 30% a day was accompanied by hydroquinone unit escaped it, and was able to obtain being able the expectation of a long series of oxidation-proof of an oxidation of the expectation of it the obtains in oxidized examination. The result, that is, result.

4 － 2 － 3
Optical examination

After the particle diameter is arranged with 48-80 meshes, obtained molecular complex making is put in the bag made of polyethylene.
The escape nature was done enough, the sample which did the sealing up seal with vacuum

Sealer was observed, and after an optical irradiation had been done during the fixed time in 25 degrees C with a xenon lamp (optical amount:　3 0 mW/cm), deterioration to the light of hydroquinone was observed by measuring the in the specific wave length of hydroquinone with a visible outside purple spectrum brightness meter.

4 － 2 － 4
Stability examination to various ointment radical medicines by mixing

That stability examination to various ointment radical medicines by mixing of BCDAC/HQ molecular complex making and coloring by the oxidation of deep and hydroquinone was observed.

HO: Hydrophilc Ointment
HP: Hydrophilic Vaseline
WP: White Vaseline
PB: prastibas
ZSO: Zinc base ointment
Comp: Ointment of mixed complex
HQ: Ointment of hydroquinone alone

The ointment which kneaded molecular complex making kept radical medicine and what states which did not change even though passed two months though was obviously admitted coloring as for the one (photograph HO HQ) to knead the Hydroquinone drinking to Hydrophilic ointment (HO) two months later.　The improvement of stability by molecular complex making with the surfactant could be admitted from this experiment result.

4 － 3
Stability of existing hydroquinone cream

Hydroquinone cream is widely used, and is products in Europe and America, which are done marketing and obtained simply.
They are done the import sales, and are mechanism in Japan over user's hand through the Internet etc.
The change cream, the color of the gel had thickened by coloring cream was seen two months later as shown in photograph 4—2 when the quality change of the cream according to coloring was observed.
This seems a phenomenon, which happens because of a structural change by the oxidation of hydroquinone.
I think that it can have done the thing to propose the technology which improves the

instability which hydroquinone originally has from there is no change seen with existing cream in hydroquinone which we propose by this project from which the molecule is made complex.

Chapter 5
Main discourse(4)

5 － 1
Safety examination of surfactant/hydroquinone molecular complex making

Chapter 4 has stated the stability of surfactant/hydroquinone molecular complex making. Especially, it was proven that it attached to molecular complex which seemed that suitable, durability was examined to heat, oxygen, and light to making to the product, and the molecular complex making with the BCDAC/HQ surfactant improved the stability of hydroquinone.
However, it is not significant in goods, which is lack to safety even if only the stability of the material has been reinforced when making the product.
Then, Chapter 5 describes the result about the safety of BCDAC/HQ because it examined the first skin stimulated examination and the acute toxicity examination.
Moreover, it is necessary to examine the stimulation when repeating and using it and toxicity only of the stimulation immediately caused after it is used because cosmetics etc. are usually the one used for the skin for a long time.
This was examined through the skin effect examination, the chronic toxicity examination. The result is also described in Chapter 5.

5 － 1 － 1
The first skin stimulated examination

The first skin-stimulated examination did the thing to forecast the level of the skin reaction to generate the effect material in the human skin by the thing to apply single times to the purpose.
By using male hearesrat as an examination method and blockage of the rat for 24 hours is pasted Vaseline the mixing the BCDA C/HQ molecule complex making (The hydroquinone content rate was assumed to be 4%).
The administering part was observed in the naked eye 24, 48, and 72 hours later after the medicine had been pasted.
The judgment followed Table 5-1 ICDRG (International Contact Dermatitis Research Group).

Table 5 -1 ICDRG judgment standard

Isn't there reaction====➔ Red, edema, and bleb
It could be judged that the skin reaction was not admitted, and was gloomy in the ICDRG standard in the observation of the passage of all time.

5 — 1 — 2
Acute toxicity examination

The examination assumes a fatal action to be an evaluation index, and is an examination method to understand strength 500 of acute toxicity of the effect material by obtaining LD and the LDL value as for the death density of the rat to which it was exposed.

It makes to the BCDAC/HQ HQ solution which dissolves each of seeing BCDAC, a molecular complex making as the examination medicine, and drinking to the physiology brine solution by using male hearesrat (one crowd5) which gives jugular conjuration as an experiment method, an intravenous injection administering is done with tslus versatility injection machine, and the result of calculating the LDL value from the average value at the death time and dosage as a density is shown in Table 5-2.

Moreover, in was done by the following experiment methods about an oral administering.
Examination animal: hearesrat (male) (One crowd Three)
Examination medicine: Only BCDAC, BCDAC/HQ molecular complex, Respectively only of HQ makes to the solution which dissolves to 10%HCl content physiology brine solution, and 0.1g/2ml is administered.

Hydroquinone was set about the density based on the document value by which the oral was administered to the rat

Table 5-2 Acute toxicity examination result
Examination animal (Rat, hearresrat, Guinea pig, Mouse, Dog)
Administering method (Oral, quietly injects, In belly empty)

Measurement data of this time. Another indicates the document value.

The surfactant shown in the table is a material being used for cosmetics etc. now. Hydroquinone molecular complex making stands out especially and does not show acute toxicity compared with them. Therefore, it was judged that molecular complex making, which was paid attention as a result by this research and development and selected, was not a material with high risk of had the stop of use at once.

5 － 1 － 3
Skin effect examination

Skin effect examination is touched to the skin repeatedly with the thing of the peculiar skin reaction by which the change such as erythemas and edemas that the is generated in the thing for single times to touch afterwards is assumed to be an index is said.
Skin effect examination is an examination done to forecast the presence of the skin reaction cause by the inducement of the peculiar immunity system caused by the thing, which the human applies to the skin repeating the effect material and the result and the extent.

Adjuvant and Patch Test were executed by the examination method which used more typical, Adjuvant (immunity reinforcement medicine) and Patch Test method by using the passing skin administering method from the product development research it which seemed that the case spread on the human skin was a lot of overwhelmingly at this time though the examination method included administering in the skin and the passing skin administering method.

Examination animal: hearesrat (male) (one crowd5 use)
Examination group: Only Freund 's Complete Adjuvant (FCA) is administered.
○ BCDAC/ HQ molecular complex making (Adjuvant)
○ BCDAC/ HQ molecular complex making (No Adjuvant)
Sample: BCDAC/HQ molecular complex The hydroquione content rate was assumed to be 4%) is kneaded to the Vaseline, It does not come, and it uses that.
Administering method: skin effect examination of the first time treatment
Blockage affixation after cervix part backside skin is injected in FCA skin for 24 hours of medicine

It seems to inject the cervix part backside skin in the FCA skin.
Skin effect examination of the second times treatment.
This part it after one week skin effect examination of the first time treatment and pasted medicine for 48 hours
< Cause treatment >

Spreading of open of medicine after two weeks skin effect examination of the second times treatment on this part

Observation: The naked eye of the administering part was observed in the 24th hour and 48 hours after it had pasted.
Judgment: It judged according to the skin reaction judgment table in the document (skin and 23 Adjuvant and Patch Test of 1 9 8 1) by which the experiment by which the Adjuvant and Patch Test method was introduced was discussed, and skin effect examination rate and the

average evaluation points were calculated.

Skin effect examination rate and the average evaluation rate were shown in Table 5—3 and the judgment table of the skin reaction (erythematic and edema) was shown in Table 5—4.

The average evaluation rate was obtained by the next expression by using the judgment table of the skin reaction.

$$\text{Mean Response} = \frac{\sum^{n}\{(1)+(2)\}}{\text{Total number of animals}}$$

Table 5—3
Skin effect examination and average evaluation rate

	Pos./Total	Mean Response
BCDAC ／ HQ	0/5	0

Table 5-4 Judgment table of skin reaction (erythematic and edema)

<Erythema formation>	
No erythema	0
Very slight erythema	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema	4
<Edema formation>	
No edema	0
slight edema	1
Moderate edema	2
Severe erythema	3
Overall maximum score	7

Any skin reactions were not clearly admitted .

The average evaluation rating more over: though skin effect examination occupies it large

<the indication of a large value>. It could be judged that the late contact hypersensitivity reaction was not admitted from 0 the value in BCDAC/HQ molecular complex.

5 － 1 － 4
Chronic toxicity examination

It is an examination method examined to examine a whole body influence, which happens when the examination material is continuously applied for a long term. In the examination, observing changing amount by which food is taken of the weight under the examination and food and a general state did it. To obtain the evaluation result of the chronic toxicity from the research and development of concentrated type as the experiment method this project for a short time surely, the infiltration pressure pump was buried in the hypodermic, and the method of making it compulsorily absorb that was used and executed.

Infiltration pressure pump chronic toxicity examination method
Examination animal: Rat (male) Lewis　(1 three crowd or 4)
Examination medicine: 1 0 % H C l fills in the content physiology brine solution and BCDAC/HQ complex, the BCDAC unit, and the solution which dissolves each hydroquione unit are filled to the infiltration pressure pump.
(Experimented in the density where the extraction of the medicine was not admitted at 37℃)
Administering route: The infiltration pressure pump to the hypodermic is buried by the operation and the medicine is absorbed.
Average administering speed: 2.60 l/hr
Administering period: 28 days

It was died for the administering period about the rat of which medicine, neither a rapid weight change nor the decrease in amount by which food is taken, etc. were seen completely, and a special change in the state was not seen. A special change in the rat was not seen though 28 days were ended.

5 － 1 － 5
Patch test by human

It is difficult to evaluate by the animal examination and to forecast sense stimulation such as twitch and itchy though it seems that it is possible to forecast some skin reaction from the examination result, which has been described by now about surfactant/hydroquione molecular complex making.
Moreover, the patch test in the human actually becomes important from becoming the

material applied to the human. The patch test is a handy foresight examination method by which it is confirmed that dermatitis does not happen when the raw material and the product are used development.
It drank and pettiest was executed for both the normal skin and a specific skin (human where the skin reaction was caused for the medicine etc. comparatively sensitively) under the cooperation of the dermatology specialist with the following patch testers this time.

Experiment method
Taste: Adult 12 examples
Administering route: Passing skin
Administering method: It mixes Vaseline and sample, and affixes dorsal or the above hummer's blockage. (For 48 hours)
Administering frequency: One time

Observation: It is waited that the transitory erythematic caused when removing it after affixation is removed disappears and observes the skin reaction after 48 hours and 72 hours.
Judgment and evaluation: The level of the erythematic and the edema is I judgment and is evaluated based on the ICDRG judgment standard.
It has aimed to observe the skin stimulation of the skin reaction of the delay (allergic reaction) in the observation after 72 hours in observe after 48 hours.

The sample used to test the patch is as follows.
1. BCDAC/HQ complex
2. BSDAC/HQ complex
3. Only BCDAC
4. Only BSDAC
5. Control (Only the patch bonds :)

A gloomy judgment was able to be obtained about them about skin stimulation and both allergic reaction though the patch test in a healthy person always did mainly BCDAC/HQ to which paid attention in this project. Therefore, BCDAC/HQ molecular complex making can have done the thing guessed to be a material, which had considerably high safety of application to the human body.
Next, the execution condition and the result of the patch test in a specific human are shown.
Experiment method
Taste: Adult one example (adult woman who has judge specific human from dermatology specialist)
Administering route: Passing skin
Administering method: Vaseline sample mixes, and affixes dorsal the above blockage. (For 48 hours)
Administering frequency: One time

Observation: It is waited that the transitory erythematic caused when removing after affixation is removed disappears and observes the following skin reaction on the tenth after 48 hours and 72 hours later.
Judgment and evaluation: The level of the erythematic and the edema is judged and evaluated based on the ICDRG judgment standard.

When the patch of various samples was requested to be tested, approval could be obtained in this also because being given at the chance that was able to meet the person judged to be a specific person was rare.

It is a valuable splendid chance that proof that not only the ordinary man Takeshi but also a specific person can use molecular complex making obtained in this research and development can be done to execute this patch test and we wish to express our gratitude.

Table 5-5 shows the patch test execution sample and the list of the judgment result.

The ointment radical medicine and HQ HO show the hydrophilic ointment which contains the hydroquione unit which has been used up to now among the dermatology specialists about inspection material in Table 1-5.
Moreover, VC in the table shows the ascorbic acid of an anti-oxidant. Control, that is, the 50th table inside is only patch test bonds.
A specific person did not react to an ointment radical medicine alone when judged from the table.

Only the length of the alkyl chain understands it has been understood that using BCDAC, which has long length of the chain, is high safety with surfactant BCDAC and B Z C L though it is a different structure.

This was an agreement well for the example of reporting on the skin stimulation of a lot of surfactant, which had been reported up to now.
The thing, which even a specific person was able to use, was clarified to a molecular complex making with hydroquione, which used BCDAC, which had number 16 of carbons from judgment result.
Moreover, the result in which not being admitted that it was skin stimulation, and an allergy to use the parent hydrophilic ointment which used BCDAC/HQ when the parent water ointments which contained the parent water ointment which used the unit of hydroquione which had prepared congressional up to now by the prescription of the dermatologist and BCDAC/HQ were compared was able to be obtained.
It has been understood that stability high BCDAC/HQ molecular complex making developed in this research has the safety, which a specific human can also use.

Chapter 6
Main discourse(5)

Passing skin absorption experiment of surfactant/Hydroquinone molecular complex

The medicine movement when absorbed to inside the body cannot be forecast though stimulation to the skin of BCDAC/HQ and the allergy were examined in Chapter 5 by the examination which has been done in Chapter 5. For instance, if the attenuation of the medicine might be accumulated in inside the body for a long term late, the thing to offer the market the product, which can be used connecting, and at ease is toxic of the product is difficult.

6 － 1 － 1

The inside the body movement of hydroquione in complex of hydroquione molecular complex making and surface-active agent/BCDAC/HQ was examined in Chapter 6 through the passing skin absorption experiment. 6-1-1 hydroquione is necessary and indispensable to knowing the inside the body movement of the hydroquione unit it quietly knows the inside the body movement of the medicine by the passing skin absorption of inside the body movement measurement BCDAC/HQ molecule complex making by the injection administering first of all.

The inside the body movement measurement examination of the hydroquinone<under the following examination conditions> unit was done. The Hydroquinone unit is made the solution of the physiology brine solution which contains 10% HCl by using hearesrat for the examination animal and 10 mg/kg is collected blood to the target at the time of passing after quietness note is administered to shift the medicine in blood surely. The hydroquinone the blood inside density was detected by a high-speed, liquid chromatography by using 0.1M phosphorus acid buffer liquid, which had contained 12% methanol in the movement aspect after having removed the protein.

Figure 6-1 shows the result.
Figure 6 -1 Inside the body medicine movement of hydroquione

It has been understood that hydroquinone hardly exists from Figure 6-1 in inside the body in about ten minutes. That is, an early material the disappearance speed of the medicine, and no material accumulated in inside the body for a long term was clarified by the actual examination.

6 － 1 － 2
Measurement of density in blood of hydroquinone by passing skin absorption

As for the inside the body movement of the hydroquinone unit, the thing confirmed from the above-mentioned examination result can have been done. However, to actually become a product, which did the spreading use to the skin as for molecular complex making the product at which, it aimed by this project. Therefore, it is interested in the medicine inside the body movement by the passing skin absorption.

It was removed in the Vaseline here in dorsal of hearesrat the cervix, and blood was collected, and the protein was removed to the target at the time of passing afterwards doing blockage affixation mixing BCDAC/HQ complex (4 %). And, the hydroquinone the blood inside density was detected by a high-speed, liquid chromatography by using 0.1M phosphorus acid buffer liquids, which contained 12% methanol in the movement aspect.
Figure 6-2 shows the result.

After the medicine had been pasted, the detection of hydroquinone could be confirmed at once though it was a result, very a small amount. However, confirming the peak which seemed that hydroquione to the inspection material which had been collected blood ten minutes later became possible.

It can be guessed that the inside the body disappearance of hydroquinone happened in ten minutes because of this, and is looked the disappearance speed in inside the body fast as well as the deflecting unit as for hydroquione, which makes the molecule complex making. When the result of this experiment result and the patch test is also considered, the surfactant and hydroquione from which the molecule is made complex are materials thought to be low stimulation and low toxicity for the skin.

6 － 1 － 3
Observation of melanin synthesis control which uses human skin three dimension mode

The melanin synthesis control was confirmed by observing an actual melanin formation by <effect of the skin whiting of BCDAC/HQ> using the normal human bark corner making cell. By the way, various animals are used to evaluate the safety of a chemical material intended for the human such as cosmetics, and reliability is assumed to be a high method very much. However, this method is reviewed from the idea of the animal protection etc. in recent years. Then, the safety evaluation examination method, which does not use the animal, has been

developed. There is a method of using the person skin three-dimension model as one of the animal substitution evaluation methods. That is, this method can be evaluated to the skin stimulation and toxicity at the same time as being able to examine the effect of the skin whiting. In that case, it becomes in vitro examination by which the cell existence rate caused by the effect material's touching with the cell etc. is assumed to be an index. When the melanin formation was observed, the existence of the cell decided to be observed together in the actual examination this time.

Examination method.

Human skin three dimension model: Normal person bark corner making cell (MEL-300 and Kurabo), which contains normal person bark melanin cell

Examination group:

○Only Dulbecco PBS (DPBS) (Only the buffer liquid :)
○BCDAC/Hydroquinone complex
○Only BCDAC
○Only hydroquione

Administering density: Critical missal density of surfactant 4.4×10-3 mol/l. Two kinds of the back and forth are prepared on the boundary of (cmc). (The forth: Low density, the back :It is expressed that it is high density.)

UV irradiation:365nm UV is irradiated for 20 minutes on the first day , the third day, the fifth day, he seventh day.

A part of the model cell, which gave DPBS, prepared the one not irradiated at all.

After the examination ends, The model cell was put with DPBS which contained the rinse doing and 10% formal in at a night, fixed once with DPBS, taken a picture of the microscope (x175) from the basale, and the presence of the melanin formation was done by the thing to observe the projection of a black tree in the photograph or the generation of the macula.

This experiment can be thought that toxicity to the cell of the medicine is low because the cell was able to finish not becoming extinct on the way.

A considerable melanin formation can be observed by especially irradiating UV from the Skin whitening evaluation examination of a molecular complex making, which used the person skin model cell only in the buffer liquid in one week. If UV was not irradiated moreover oppositely, it was possible to control during the melanin formation and it was possible to confirm it from the actual examination.

Moreover, it is understood that the progress of the melanin formation is obviously controlled though the UV irradiation was given compared with the cell only of the buffer liquid from this experiment result in the cell, which is the contact of molecular complex making. Hydroquinone molecular complex making generated from seem the effective action because of the cell that is the contact of the hydroquinone unit by this research and development is thought to be a

material, which stabilizes and is safe without ruining the effect of the skin whitening of original hydroquione.

6 － 1 － 4
Effect of molecular complex making on chromatosis type contact dermatitis patient

There was a case to administer the hydroquinone unit to the patient who had kneading deep and a variety of chromatosis diseases in a suitable ointment radical medicine by the treatment purpose from of old among the dermatology specialists. However, it is necessary to stop using by the tint by the stimulation of the hydroquione ointment. The BCDAC/HQ content ointment was applied to chromatosis dermatitis patient who had increased red by administering hydroquione single purpose ointment under the cooperation of the agreement of the patient and the dermatology specialist and the recovery passage of the diseased part was observed this time.
Effect of molecular complex making on chromatosis type contact dermatitis patient

When the use stop of the ointment was done because red has been increased after they use it, red has been pulled at the age of 69 though a start hydroquinone single purpose ointment is used, treated to chromatosis dermatitis patient. Therefore, this red can be judged to be a symptom, which happens for the hydroquinone single purpose ointment use. It was possible to look not showing the application of hydroquione molecular complex making developed by this patient at this time, especially red, and nor the gradual recovery of a calm coloring matter from which the recovery had not been seen easily furthermore either up to now on April 16, 2002. The effectiveness of molecular complex making of hydroquione is suggested from these.

6 － 1 － 5
Examination of cosmetics radical medicine prescription

The cosmetics radical medicine, which functioned molecular complex making stabilizing, was examined in this research. The examination of the radical medicine is important so that the principal ingredient in the product may work furthermore functionally stabilizing and safely. A wide examination was necessary in the future, and about this content, a molecular complex making was shown by examining for the research and development period, and using the radical medicine which seemed even though it was suitable and the product which kneaded and did though it was thought that it was necessary to keep researching spending time a little more.

Chapter 7
Summary

The research in this project improves by making the character of hydroquinone from which use is assumed to be difficult with a high effect of the skin whitening because of the unstable physical properties molecular complex mixing with the surfactant, and aims at the development of a steady, safe, new the skin whiting product.

Then, the generation of suitable molecular complex making was attempted to making to the product, and the examination of stability to heat, oxygen, and light were done. Moreover, that aimed at the generality of the hydroquinone content skin whitening product which had been assumed that it was difficult to put out to the market up to now by doing the safety evaluation examination by capitalizing on a small animal and the cell.
Suitable molecular complex making was decided to making to the product as a result of this research and development, an X-ray, structural analysis, and the interaction, which worked between the surfactant, clarified the molecular array and hydroquinone was elucidated. And, the improvement of instability of hydroquinone was achieved by molecular complex making with surfactant by the proof of the hydroquinone molecular complex making of an extremely steady material it to heat, oxygen, and light compared with single purpose hydroquinone.
The one that there is a problem in safety even if the stability of hydroquinone is improved is not in making to the product even though is the best. Therefore, the evaluation examination was done by a variety of examination methods by capitalizing on a small animal and the skin model cell of safety. A lot of findings, which could be judged to be low stimulation and result low toxicity, could be obtained. In addition, it is evaluated by administering to the patient who had the skin model cell and the skin disease of the examination of the medicine inside the body movement of hydroquinone molecular complex making and the effect of the skin whitening and the effectiveness of hydroquinone molecular complex making was able to be confirmed. Low stimulated a new product which has high stability which was born by this project research and development can be expected to infiltrate inside and outside the country widely for the enterprise with the purchase purpose especially and the hospital, etc. It seems that the prospect of this product is extremely high compared with a large-scale the skin whitening market.