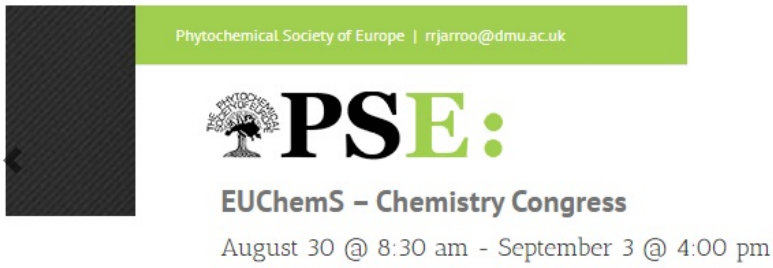

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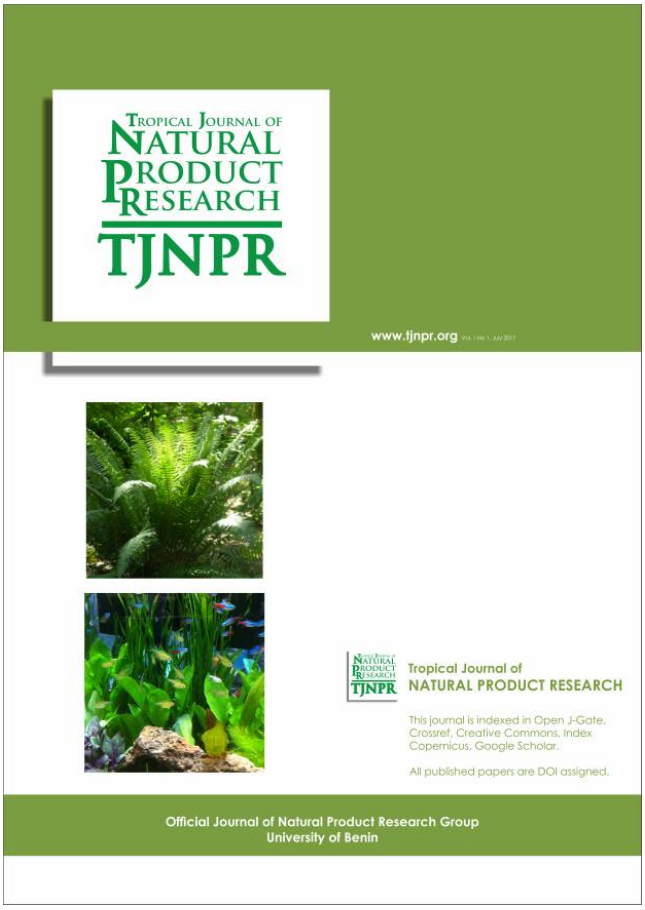

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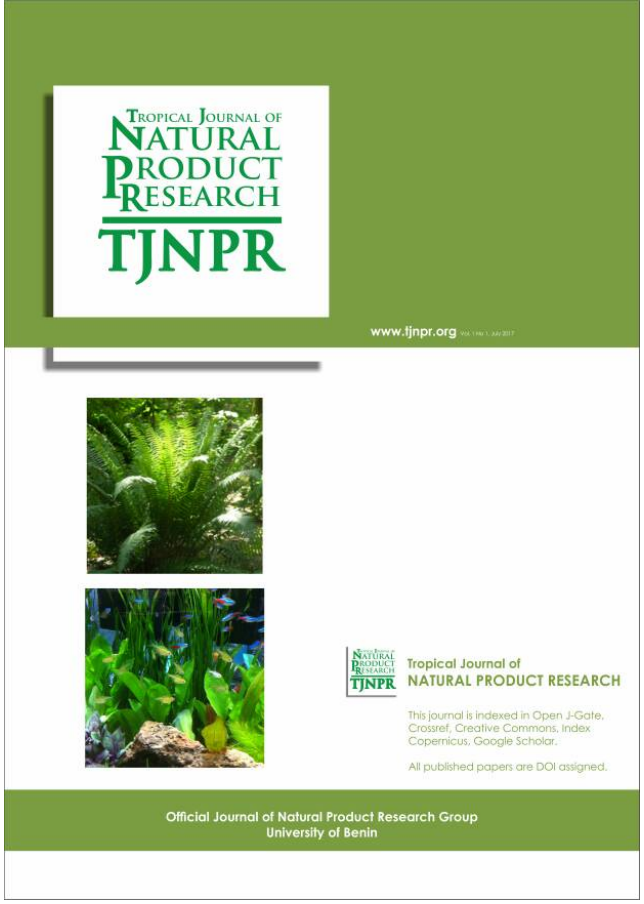

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Review Article

Ubiquinone-Nanostructured Lipid Carriers Hydrogel Mask for Antiaging: the Journey so Far

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ABSTRACT

Aging of the skin become a common problem in the society, especially in women. Sun exposure is a very influential factor in the occurrence of skin aging. One alternative to solve skin aging problem is by using cosmetics with anti-aging activities. Ubiquinone is an enzyme found in almost every cell of the body, especially mitochondria which function as antioxidant which can reduce the production of Reactive Oxygen Species (ROS) and useful for regulating the aging process. However, ubiquinone has some weaknesses in its characteristics; therefore a suitable delivery system such as Nanostructured Lipid Carriers (NLC) is required. Ubiquinone-NLC is suitable for water-insoluble active agent that is able to produce a fairly good environment which can increase the effectiveness of ubiquinone. Unfortunately, in application, Ubiquinone-NLC is less acceptable due to the very oily nature of the preparation and instability on storage. This can be overcome by formulating Ubiquinone-NLC into a Hydrogel base and used during night breaks where the skin's blood vessels can absorb well (sleeping mask). This development of Ubiquinone-NLC hydrogel sleeping mask is greatly influenced by gelling agent, which will trigger changes in the characteristics of the hydrogel. Changing the characteristics of the hydrogel will affect the effectiveness, physical stability, and also affect the irritation to the skin. This review article discusses ubiquinone-NLC in hydrogel sleeping masks and how this preparation can act as an antiaging cosmetic and how the gelling agent affects the effectiveness, physical stability and skin irritation.

Keywords: Ubiquinone-NLC, Hydrogel, Sleeping Mask, Antiaging, Gelling Agent.

Introduction

As the body's largest organ, the skin carries out a number of major functions resulting from the various chemical and physical reactions.[1] Several conditions can appear on human skin, including premature aging that occurs due to the accumulation of intrinsic and extrinsic factor.[2-4] Lifestyle, over exposure to ultraviolet (UV) rays is the main cause of premature aging. This is due mainly to the induction of excessive free radicals. The aging process (premature aging) is the most common process and its characterized by the emergence of wrinkles, depigmentation, rough skin texture, and decreased skin elasticity.[5]

Many efforts have been made to reduce the aging process. By the development of technology in cosmetics, anti-aging compounds that can help reduce the aging process have been found, which usually consists of skin growth factors or antioxidants such as vitamin C, retinoids, vitamin E and Ubiquinone. Ubiquinone is an enzyme that can be found in almost every cell in the body, especially in mitochondria. Ubiquinone is an antioxidant that can reduce the production of Reactive Oxygen Species (ROS) which is useful for regulating the aging process (Figure 1).

Ubiquinone also reduces DNA damage due to UVA radiation on human keratinocytes and helps to reduce UVA stimulated Metaloprotein Matrix (MMP) in skin fibroblasts.[3] Ubiquinone has a role to protect collagen components from degradation in order to protect the skin from wrinkles.[2,6] Since the development of cosmetic formulations, many techniques and methods can be used to increase the effectiveness of ubiquinone, one of the most suitable carriers for ubiquinone is named Nanostructured Lipid Carriers (NLC).[7,8] The combination of Ubiquinone in NLC continues to be developed in order to achieve an adequate level of effectiveness, therefore the combination of Ubiquinone in NLC is also developed which is formulated in a hydrogel sleeping mask. Hydrogel sleeping masks basically depend on the type of gelling agent used in the formula. It is important to choose a gelling agent that is in accordance with the purpose of the formulation in order to achieve the desired preparation quality.[9-12]

This review paper explores how the aging process, the advantages of ubiquinone, NLC and hydrogel, and effect of gelling agents on the quality of preparations including physical stability, effectiveness on skin quality and skin irritation. This review describes how the Ubiquinone-NLC hydrogel sleeping mask can improve skin quality and provide information for the development of antiaging cosmetic formulations with the active agent of Ubiquinone in Nanostructured Lipid Carriers (NLC) combined with the hydrogel system.

Materials and Methods

The review was conducted from the available literature on the internet that discuss about discovery and development of the ubiquinone-NLC and hydrogel sleeping mask. We used the search terms ubiquinone-NLC, hydrogel, gelling agent, antiaging,sleeping mask, on Google Scholar, PubMed, ScienceDirect, directory of Open Access Journal (DOAJ), ResearchGate search engines. From the results generated, articles that have a definite relationship with the subject matter were included in this review, and otherwise were excluded.

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Ubiquinone-NLC

Ubiquinone ($C_{59}H_{90}O_4$) or Coenzym Q10 is a lipophilic antioxidant compound that is present and produced by every human cell.[14] The main function of Ubiquinone is a component of the electron transport chain in the mitochondria by delivering electrons between complexes I, II, and III which are then processed to produce the main cell power, namely Adenosin Triphosphate (ATP) and as an antioxidant which prevents the process of lipid peroxidation due to free radicals.[6,14]

In the process of skin aging especially photoaging, solar radiation (UV) can accelerate the regeneration of ROS. Excessive ROS can cause oxidative damage which will trigger the breakdown of collagen.[15] In addition, ROS is a factor for upregulation of MMP in keratinocytes and fibroblasts. ROS does not only damage membrane lipids and DNA but also the structure of proteins and catalytic proteins which are very important in the process of forming cell energy. This results in disrupted energy metabolism and skin aging. There are two countermeasures against it, keeping cellular energy levels steady to avoid decreasing mitochondrial activity and protecting antioxidants against ROS. Ubiquinone itself in its own antioxidant role acts as a free radical deterrent and protects membrane lipids, proteins and DNA from capturing ROS electrons.[2] Ubiquinone with a concentration of 1% for five months can reduce the presence of wrinkles. Ubiquinone can also inhibit the production of IL-6 which stimulates fibroblasts in the dermis to regulate MMP production.[16]

Ubiquinone formulation through research has proven that Ubiquinone needs to be formulated in a delivery system in order to penetrate into the skin. Similar studies were also proven by the research.[2,14,17]

Hydrogel mask

Hydrogel is a three-dimensional polymer matrix that has the flexibility of a strong molecular structure network and good material capabilities and a reliable profile in moisturizing the skin.[11,18,19] Variations in the concentration, structure and functionality of the monomers and cross-linked used in the gel can change the hydrogel structure. Many forms of new gel ingredients are being studied with various purposes, one of which is as a carrier of active ingredients into the skin.[18,20,21] Hydrogel systems with various groups are easily affected chemically and structurally to external stimuli including temperature, pH, ion concentration, light, magnetic fields, electric fields, and chemicals.[20]

Hydrogels are classified into two categories, natural and synthetic hydrogels. Natural hydrogels include collagen, fibrin, hyaluronic acid, and derivatives of natural agents such as chitosan and alginates. They remain the most physiological of the hydrogels as they are components of the extracellular matrix (ECM) *in vivo*. However, there are two major drawbacks to natural hydrogels that make it difficult for this microstructure to produce reproducible experimental results. First, the fine details of their mechanical properties and their dependence on polymerization or gelation conditions are often poorly understood. Secondly, because of their natural origin their composition can vary from one batch to another.[20]

In contrast, synthetic hydrogels such as poly (ethylene glycol) acrylate, poly (acryl amide), poly (vinyl alcohol) are more reproducible, although their final structure may also depend on polymerization conditions. In general, synthetic hydrogels offer more flexibility. They can also be selected or modified to be hydrolyzed or biodegradable over a period of time.[20]

The hydrogel mask, in this case the hydrogel is intended for masks which are usually used at night (sleeping mask) because it is the right time for skin to regenerate and optimal absorption of active agents due to the dilation of blood vessels when we sleep. This can be achieved by using it in the form of hydrogel sleeping mask periodically between 2-3 times each week. Hydrogel sleeping masks generally contain a strong antioxidant group with the ability to regenerate the skin. The hydrogel sleeping mask is easy to use. Similar to the day cream, the hydrogel sleeping mask can be applied at bed time avoiding the eye area and rinsing with warm water, this way, the hydrogel mask can deliver active agents well into the skin to produce improvements in skin moisture, skin tone, and skin texture.[12,18]

Ubiquinone-NLC hydrogel mask

The important factor in Ubiqunone-NLC which is formulated into the hydrogel base is the interaction between the NLC and the gel constituent base itself. Gelling agent can affect the quality of the hydrogel preparation because of its role in the three main parameters of the porosity properties and the swelling result of the hydrogel itself. The three parameters are the “cross-linked” level, the nature of the polymer (natural/synthetic) and the concentration.[22] The two properties of the hydrogel affect the diffusion kinetics passively of the active substance that it carries in the matrix and this is very decisive in its release function. There are two mechanisms of drug release from hydrogels, namely diffusive release and release by concentration degradation.

The use of single hydrogel is less desirable because it causes problems including large gel pore size and high water content which results in small and water-soluble drugs that will quickly come out and settle from the hydrogel structure which of course will greatly affect the profile of drug release. This also occurs in ubiquinone preparations in a single hydrogel because of the hydrophobic nature of ubiquinone. However, this can be overcome by first combining the ubiquinone into a water insoluble carrier, namely NLC.[22]

Most drug research with the NLC-hydrogel system currently uses gelling agents derived from the polyacrylic acid group which is known as Carbopol.[10] Carbopol is easy to find and quite reliable as well as good delivery character. Apart from the polyacrylate group, there are also groups that are polysaccharides. The advantage of this group is its fairly good biocompatibility.[23,24] Another group that can be used as a gel-forming material is the cellulose group which usually comes from natural plant biopolymers so that in its use it has good biocompatibility and biodegradation properties.[25] The groups of gelling agents greatly influence the final quality of the hydrogel preparation, therefore it needs some considerations to understand the inherent properties to select the suitable type of gelling agents. . Unfortunately, the first research on NLC-Hydrogel is relatively new because it was only introduced around 2004 by Souto *et al*.[26] This makes data on characterization, rheology, and *in vivo* drug release kinetics from hydrogels very scarce.[22]

With the many choices of delivery systems that have been researched to date, it certainly needs to be adjusted to the needs and characteristics of the active agent that will be delivered into the skin itself. Among the several delivery systems available, ubiquinone is the most suitable for NLC-hydrogel delivery. This is due to the nature of ubiquinone itself, which is a lipophilic active agent with log P 19.[4,14] on the other hand NLC itself is a delivery system that is intended for active agent with a relatively large log P or lipophilic compounds, but with the combination of ubiquinone and NLC, which are both lipophilic agents, the penetration of the active agent will certainly be inhibited and will be difficult to help maintain skin moisture. Therefore combination with hydrogel system is highly suggested in the formulation to fill the lack of hydrophilic and moisturizing properties of the skin.[18,22]

Gelling agent is a factor that can affect the yield of the hydrogel. Gelling agents that are often used are relatively varied, including Carbopol and CMC-Na. Both of these gelling agents have the same mechanism of action, namely; forming a gel mass through the "Swelling" mechanism. The difference is the origin of the gelling agent. Carbopol which is a synthetic material, while CMC-Na is semi synthetic. This can affect the ability of each material to form a gel mass and its physical characteristics result in different effectiveness, irritation and physical stability.[10] It is known that high gel viscosity will increase the strength, hardness, and rigidity of the gel.[22,27] This will affect the release of the amount of active agents contained in the matrix and slow down the deposition as a result of the repulsion of hydrophobic molecules from ubiquinone and NLC to their hydrophilic carriers, namely hydrogels.[28,29] This is an advantage to reduce the potential for irritants as a result of avoiding contact with large quantities of materials which can be potentially irritating.[30]

Topical delivery systems for antiaging

The table below shows the physical characteristics and effectivity of topical delivery systems for anti-aging to compare NLC, hydrogel and

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other carriers (Table 1). In Table 2, Physical characteristic of Ubiquinone in SLN, NLC, and Hydrogel are shown.

Effect of gelling agent on In vitro effectiveness, irritation and physical stability

As previously explained, the function of the gelling agent is to increase the viscosity of the hydrogel preparation. Viscosity certainly greatly affects the drug release characteristics, stability and irritability of the final preparation.

Effectivity

The effectiveness of topical preparations is mainly influenced by the ability of the preparations to be able to release the active agent they carry to penetrate into the skin layer. In the aspect of the effectiveness of hydrogel preparations, viscosity is sufficient to affect the release rate of the active agents it carries.[28] This is because the higher the viscosity, the diffusion rate movement of the active ingredient will be more restrained due to the strong bonds of the polymer carboxyl molecules in the hydrogel structure. This is evidenced by the research on the effect of gelling agents on permeation rate.[57] Sakini *et al* examined the effects of different gelling agents on the release profile of the active agents from nanocubosomal gels.[29] Results of this study indicate that the higher the concentration of the gelling agent, the lower the release of the active agent. Table 3 shows the effect of gelling agent on viscosity and release profile.

Skin irritability

Irritation of the skin can occur due to several factors including the nature of the material, the pH incompatibility with the pH of the skin or other factors. Many attempts have been made to overcome the irritation that occurs by formulating the preparation in such a way that the potential for irritation of the ingredients used can be minimized. Previously, we discussed how viscosity can affect the profile and speed of release of active agent by hydrogels. It can be said that this is a form of preventing potential irritation because with the high viscosity that occurs there is the formation of a barrier that blocks the rate of contact of the irritant to the skin. By increasing the viscosity of hydrogel preparations with the use of gelling agents, it will prevent irritants from spreading and direct contact with the skin in large concentrations but according to the concentrations degraded from within the carrier system.[30]

Physical stability

It has been discussed previously that the active agents with hydrophobic properties are formulated in preparations that contain lots of water; there will be rapid deposition as a result of the repulsive properties between the hydrophobic active agent molecules and the carrier molecules which have opposite properties. With the presence of a gelling agent that increases viscosity and forms a network of polymer structures, the deposition rate can be greatly reduced due to the slow diffusion process due to high viscosity and trapping of active ingredient molecules in the polymer gel network.[20,22] In addition, the differences in the types of gelling agents used also affect the strength, hardness and stiffness of the gel.[27] Regarding the strength of the gelling agent that is affected is the ability of the structure to hold water during the gel syneresis process. The increase in gel strength was due to the synergistic effect between the NLC system and the hydrogel which can lead to an increase in gel strength and a decrease in syneresis impact. Decreased gel strength can occur because the strength of the polymer chain bonds in the gel is weakened due to the influence of the amount, type, and position of the sulfate. These phenomenon will have an impact on gel formation because they can produce a soft gel and of course reduce the strength of the gel in inhibiting the syneresis process due to the gelling agent molecules that bind to each other not strong enough to hold water trying to get out of the polymer matrix that has been formed.[27] The type of gelling agent, on the other hand, also affects the rigidity or gel stiffness, where the gel stiffness is influenced by the diffusion process of the small molecules present in the gel structure. Strong gelling agent such as Carbopol produce the greater stiffness at a lower concentration than the cellulose group such as CMC. As we know that the concentration and type of gelling agent can affect the strength, hardness and stiffness of the gel and these three factors will produce various gel stability which is usually indicated by the occurrence of gel syneresis. In storage, the aggregation process continues, therefore with the higher concentration and strength of the type of gelling agent, the gel that is formed will also be harder, denser and coarser, of course in addition to the factors of temperature, humidity, and the concentration of salt and polysaccharides contained in the gel.[62] This will cause the water molecules that were originally stored in the polymer matrix to be pushed out and syneresis occurs. The syneresis process can be controlled from changes in the proportion and concentration of hydrocolloid materials and the addition of a co-gelling agent.[27] Table 4 shows the effect of gelling agent on physical characteristics.

Table 1: Physical Characteristic and Effectivity of Topical Delivery System

No.	Active Agent	Delivery System	Methods	Physical Characteristic	Stability Test	Effectivity Test	Reference
1.	Ubiquinone	SLN	*Phase Inversion Temperature (PIT)*	pH = 4.78-5.10 Mean particles size = 30-49 nm Loading capacity = < 0.7% $^{w}/_{w}$ Mean PI = 0.140-0.323	Stability test was carried out at 37°C for 2 months in a dark room and results were less stable in terms of particle size due to the high temperature producing energy in the system which causes aggregation	*In vitro* penetration test using the stratum corneum of pork skin found that formulation with SLN can significantly increase the distribution of the active agent into the skin layer	31

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2.	Tempe (*Rhizopus Oligosporus*)	*Hydrogel*	*Polymer Crosslinking*	Spreadability = 4.07 ± 0.058 Viscosity = 276.67± 2.887 Particle size = 69.7 ± 0.93 µm	Stable in room temperature storage for 30 days	Results of the antioxidant test found an IC_{50} of 36.752%	32
3.	Ubiquinone	NLC	*Hot High Shear Homogenization*	PI = 0.35 ± 0.05 pH = 4.45 ± 0.006 viscosity = 387 ± 3.55 %EE = 74 ± 0.87 % Spherical shape	Stable in storage for 45 days	Penetration result for 6 hours of CoQ10-NLC was higher than CoQ10 with emulsion	14
4.	Ubiquinone	NLC	*Ultrasonication*	PI = 0.11-0.29 Droplet size = 160.1-171.1 Drug recovery = 88.1-84.7% Zeta potential = -21.1 –(-23.80) mV	Not Observed	Mitochondrial cells incubated for 24 hours with CoQ10 -NLC and irradiated with UVA oxidation showed the results that NLC-CoQ10 could protect cells from loss and restore cell viability to the same as controls	33
5.	Ubiquinone	NLC	*High Shear Homogenization*	Particles size = < 400 nm Viscosity= 186.70 %EE = 58.21±0.09 PI = < 0.400 Spherical shape with smooth surface	Not observed	*In vivo* penetration test using the mouse skin membrane found that results were deeper penetration than the control (lipid ratio 7: 3)	34
6.	Ubiquinone	NLC	*High shear homogenization*	pH = 6.26-6.38 Viscosity = 37.83-88.38 Particles size = 145.27 – 178.3 nm Zeta potential = 10.4-15.4 mV (negative value) %EE = 79.19-95.56% Spherical shape with smooth surface	Not observed	*In vivo* penetration test using the skin of the stomach of male Wistar rats and the fluorescence method found that the penetration rate of ubiquinone formulated in NLC increased significantly compared to the control	35
7.	Terbinafine & Citral	Hydrogel – Nanoemulsion	*Emulsification*	pH = 6.9 Droplet Size Distribution = 15.53 (Nanoscale)	Stable on heating and centrifugation to 12.000 rpm for 30 minutes	Formulation with NE in hydrogel did not show any irritation during use. The deposition of active agent in the epidermis / dermis increased	36

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8.	Pentyl Gallate	Hydrogel-Nanomulsion	*Polymer Crosslinking*	PI = 0.33±0.04 Droplet size = 297.0±8.6 Zeta potential = 52.6 ± 0.1 %EE = 94.4 ± 4.8%	Stable on storage for 90 days with a temperature of 8.0 ^{o}C and centrifugation test	*In vitro* testing for 24 hours on pork skin did not produce a significant difference between the active ingredients in nanoemulsion alone or in nanoemulsion-hydrogel	37
9.	α -Tocopheryl acetate	Hydrogel-Emulsion	*Melt emulsification*	pH = 5.58-5.82 Viscosity = 4.50-7.11 Spreadiblity = 23.0-27.9 Extrudability = 18.58 – 24.58 Drug content = 97.8-98.5%	Stable in 3 month storage.	Antiaging activity test with observations of skin moisture resistance, transepidermal water loss, and skin elasticity, it was found that the formulation of α-Tocopheryl acetate in hydrogel can improve skin quality	38
10.	Rice Bran Extract (*Oriza sativa L.*)	*Hydrogel*	*Ionic Interaction*	Not Observed	Stable, on the freeze thaw method for 12 weeks	Growth of fibroblasts was stimulated and increased hydration, pigmentation, and skin thickness in 30 volunteers after 28 days of use	39
11.	Faloak Trunk Bark (*Sterculia quadrifida R.Br.*)	*Hydrogel*	*Polymer Crosslinking*	Meet the organoleptic requirements, spreadability, pH, viscosity after and after the accelerated test	Stable in *accelerated* methods	Results of the antioxidant effectiveness test using spectrophotometry found antioxidant activity with an IC50 value of 17.04 µg / L	40
12.	Hyaluronic Acid	*Hydrogel*	*High shear homogenizer*	Particles Size = <50 µm	Not observed	Changes in particle size and flow rate fraction can increase the flexibility of the hydrogel itself	41
13.	Red Pidada leaf extract (*Sonneratia caseolaris* L)	Nanoemulgel	*Melt-emulsification and Low-temperature Solidification, Ultrasonication*	Characteristic odor, transparent color, good homogeneity. Viscosity = 2.21± 0.32-5.83±0.12	Stable, at 40 ^{o}C for 30 days.	Not observed	42

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Table 2: Physical Characteristic of Ubiquinone in SLN, NLC, and Hydrogel

No.	Delivery System	Methods	*Gelling agent*	Physical Characteristic	Reference
1.	SLN-Hydrogel	*High Shear Homogenization*	Carbopol 940P	Particle size = 142.4 nm % EE = 89% Zeta potential = -18.6 ± 1.2 – (-13.7 ± 1.3) mV Spherical shape	[43]
2.	SLN-*Hydrogel*	*Ionic interaciton*	Soybean oil, suppocire NL, lipoid s75	particle size = 52 ± 2 PI = 0.12 ± 0.01 Zeta potential = -6.8 ± 0.5	[23]
3.	NLC	*Melt-emulsification and Low-temperature Solidification, High Shear Homogenization*	Cetyl Palmitate, Olive Oil	Particle size = 69.7 ± 0.93 µm PI = 0.35 ± 0.05 pH = 4.45 ± 0.006 Viscosity = 387 ± 3.55 %EE = 74 ± 0.87 % Spherical shape	[44]
4.	NLC	*Solvent diffusion, hot homogenization*	Glyceryl distearate & behenate, glyceryl triacetate	PI = 0.312 ± 0.055 Zeta potential = -35.3 ± 2.1 %EE = 67.91 Drug Loading = 52.79% Spherical shape with smooth surface	[45]
5.	NLC	*Hot high pressure homogenization*	Glyceryl monostearate, glyceride	Particle size = 101.6 ± 1.1 PI = 0.139 ± 0.016 Zeta potential = 60.9 ± 1.6 mV AFM Micrograph shows non spherical shape	[46]
6.	NLC	*Hot high pressure homogenization*	Soybean lecithin, octyl decyl acid triglyceride.	Droplet size = ± 65 nm Homogenous spherical shape	[47]
7.	NLC	*Hot high pressure homogenization*	Cetyl palmitate, Miglyol 812	Particles size = <441 nm Microparticulate droplet range = 1-10 µm Melting point = 47.5 ^{o}C (onset 43 ^{o}C)	[48]
8.	NLC	*Hot High Pressure Homogenization*	Cetyl Palmitate, capric triacylglycerols	Particle size range = 180-240 nm PI = < 0.200 Zeta Potential = -40 – (-50) mV % EE = 100% (Deduced) SEM test found anisometric shape with sizes ranging from 200 nm due to changes in lipid characters when drying the test sample	[49]
9.	NLC	*High Shear homogenization and ultrasound*	Glyceryl palmito-stearate. Medium chain fatty acid triglycerides	Particles size = 86.9 ± 4.3 PI = 0.21 ± 0.04 Zeta Potential = -29.6 ± 1.7 %EE = 99.4 ± 0.8	[50]
10.	NLC	*Hot High Shear Homogenization*	Cetyl Palmitate, Olive Oil	Particle size = 69.7 ± 0.93 PI = 0.35 ± 0.05 pH = 4.45 ± 0.006 Viscosity = 387 ± 3.55 %EE = 74 ± 0.87 % Spherical shape in TEM evaluation	[44]

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11.	NLC	*Phase inversion temperature (PIT)*	Glyceryl Oleate, methylisothiazolinone,	Particle size = 28.78 ± 0.90 PI = 0.235 ± 0.030 Zeta Potential = -2.00 ± 0.24 Spherical shape in TEM evaluation	[51]
12.	Ultra-Small NLC	*Hot High Pressure Homogenization*	Cetyl palmitate, polyglyceryl-3 methylglucose distearate	Zeta potential = -34.5 PI = 0.132 Particle size = 81 nm	[52]
13.	Ultra-small NLC	*Hot High Shear Homogenization*	Cetyl palmitate, dioctylether	Particle size = 84 nm PI = 0.145 Zeta Potential = -35 mV TEM test revealed a shrouded spherical core	[53]
14.	NLC-Based Gel	*Hot High Shear Homogenization*	Carbopol	Particle size = < 200 nm Zeta potential = -29.1 ± 1.96 mV Drug loading = 7.945 ± 0.035% % EE = > 96% $^{w}/_{w}$ Spherical shape	[54]
15.	NLC-Based Gel	*High-pressure Microfluidics*	Cetyl palmitate, MCT, carbomer	Particle size = 151.7 ± 2.31 PI = 0.144 Zeta Potential = -44.1 ± 1.68 Drug Loading = 2.65 ± 0.91 %EE = 100% TEM test found that the spherical shape was around 100 nm in size	[55]
16.	*Hydrogel*	*Chemical crosslinking*	Xanthan gum	Particle size = 180-250 nm PI = 0.450 Zeta potential = -40 – (-55) mV	[56]

Table 3: Gelling agent effect on Viscosity and Release Profile

Active Agent	DDS	Gelling agent	Viscosity	Release Profile	Reference
Caffein	Gel	Carbopol 934 & HPMC K4M	The optimal formula has the following results: pH = 7.2 – 7.4 Viscosity = 65000 – 76000 cps Spreadability = 276.21 gm/2.54 cm Drug content = 99.00%	Franz diffusion cell release method was used with the yield of up to 96.89%	[58]
Andaliman Fruits (*Zanthoxylum acanthopodium DC.*)	Gel	Carbomer & HPMC	Carbomer = 28.3 ± 0.5 cps HPMC = 6.26 ± 0.161 cps	Not observed	[59]
Tender coconut water, aloevera extract, grape seed extract. Vitamin E, jojoba oil phytosomes	Gel	*Carbopol 940*	The optimal formula has the following results: Viscosity = 2499.534 ± 4.3 cps Spreadability = 23.4 ± 1.25 g/sc pH = 6.13 ± 0.15 Extrudability = 92.5 ± 0.88	Not observed	[60]

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Table 4: Effect of gelling agent on gel physical characteristics

Active Agent	DDS	*Gelling agent*	Stability	Gel Hardness/Rigidity	Reference
Sugar-free Guava Preserves	Gel	Locust bean gum Carrageenan Low methoxyl pectin	Not observed	The results of the analysis using a texture analyzer in the Mean Square ± F ratio data: Hardness: LBG = 3,54 N ± 7,56 LMP = 1,44 N ± 3,07 CAR = 9,19 N ± 19,61 Strenght : LBG = 0,02 ± 42,30 LMP = 0,00 ± 0,14 CAR = 3,64 ± 1,37 Rigidity : LBG = 0,18 ± 2,22 LMP = 0,22 ± 2,78 CAR = 1,37 ± 17,24	62
Liposomes	Hydrogel	Semi refined Carrageenan & Glucomannan	Stable at 40 ^{o}C for 4 weeks	Hardness: Carbopol = 306.4 ± 9,7 LMW Chitosan = 44,6 ± 0,5 Poloxamer = 753,2 ± 11,0 Rigidity : Carbopol = 3240,4 ± 82,0 LMW Chitosan = 100,1 ± 0,5 Poloxamer = 8571,6 ± 335,9 Strenght : Carbopol = 267,00 ± 109,6 LMW Chitosan = 83,43 ± 0,7 Poloxamer = -5862,08 ± 471,5	63
Astaxanthin oleoresin	Lipogel	Carbopol 974P	Storage at two different temperatures (25 ± 0.1 ^{o}C and 4 ± 0.1 ^{o}C) showed stable results for 3 months.	The results of Lipogel analysis using a texture analyzer tool obtained the following data: Hardness = 23,69 ± 0,001 Strenght = 32,75 ± 0,002 Rigidity = 0,95 ± 0,001	64

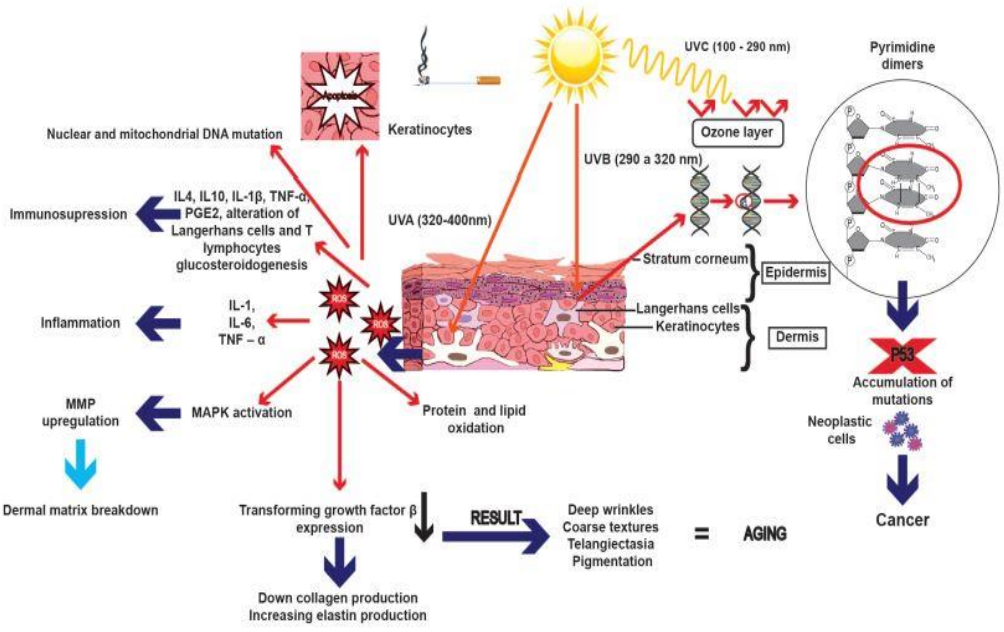

Figure 1: Skin Aging Process [13]

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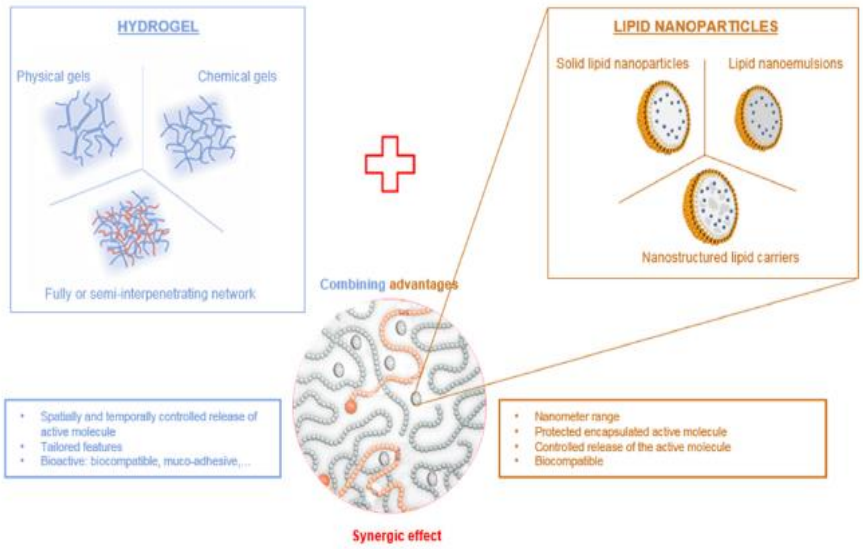

Figure 2: NLC-Hydrogel Combination as Carriers [22]

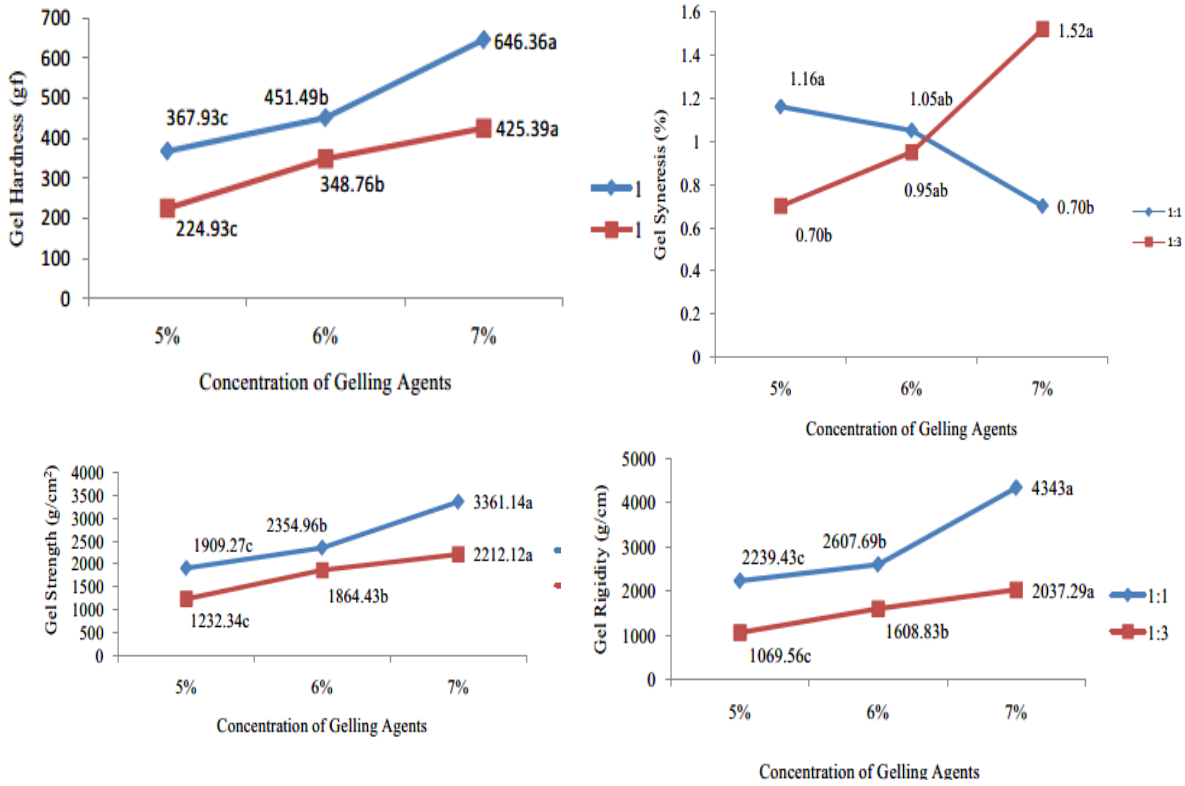

Figure 3: Effect of Gelling agent concentration on Hardness **(a)**, Strenght **(b)**, Rigidity **(c)**, Syneresis Phenomenon **(d)** [27]

Conclusion

Ubiquinone-NLC in the hydrogel sleeping mask is a formulation technology development by combining ubiquinone which has been formulated into NLC into the hydrogel matrix system to reach maximum absorption of active agent. The main function of ubiquinone-NLC in the hydrogel sleeping mask as an anti-aging agent is by acting as an endogenous antioxidant against the skin and inhibiting ROS. On the other hand, ubiquinone which has been formulated in NLC can help stimulate collagen formation due to the function of ubiquinone, which is an electron transporter; therefore, the production of hyaluronic acid in the skin also increases. By formulating in the hydrogel system, it can increase penetration into the skin which is triggered by the moisturizing effect of the hydrogel to expand the structure of the stratum corneum and make penetration easier. This is greatly influenced by the selection of the gelling agent that makes up the hydrogel system in which different types of gelling agents will certainly produce different viscosity which will affect the hardness, rigidity and elasticity of the hydrogel structure. This further affects the effectiveness, irritability and physical stability of the final ubiquinone-NLC preparation in the hydrogel sleeping mask.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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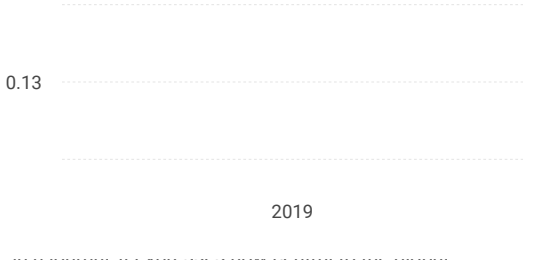

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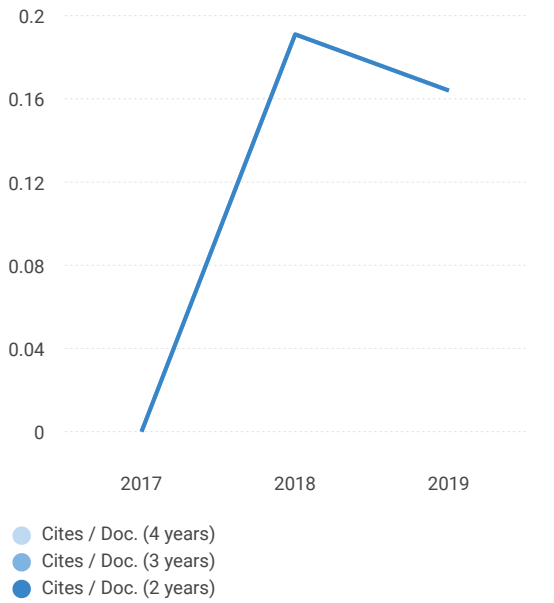

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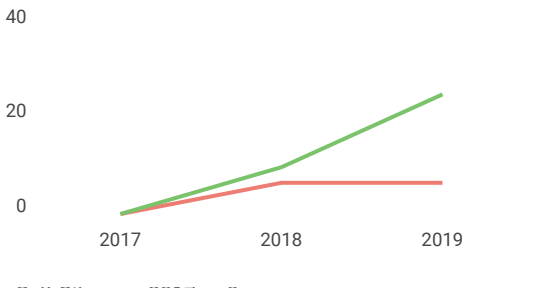

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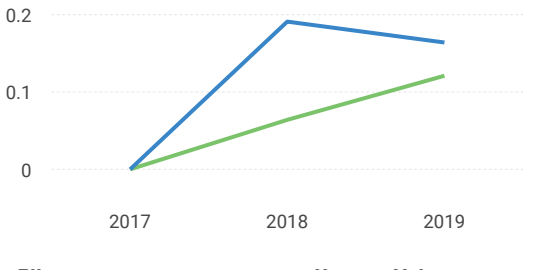

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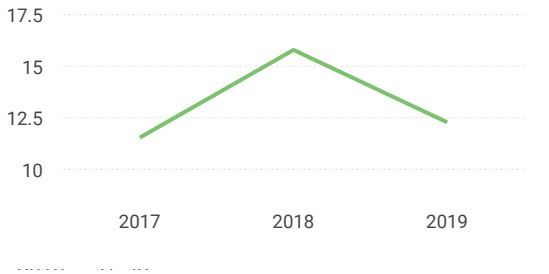

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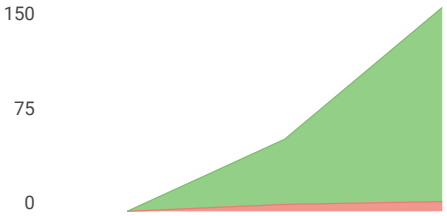

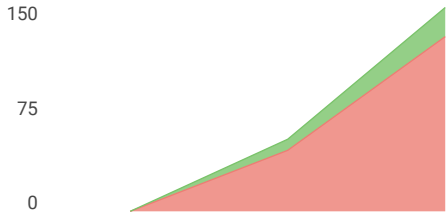

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