J Skin Stem Cell. 2016 September; 3(3):e65815. doi: 10.5812/jssc.65815.

Published online 2016 June 20. **Review Article**

Liposomes in Cosmetics

Hamid Reza Ahmadi Ashtiani,[1,*] Parisa Bishe,[1] Naser-Aldin Lashgari,[1] Mohammad Ali Nilforoushzadeh,[2] and Sona Zare[2,3]

[1]Department of Basic Sciences, Faculty of Pharmacy, Pharmaceutical Sciences Branch, Islamic Azad University (IAUPS), Tehran, IR Iran
[2]Skin and Stem Cell Research Center, Tehran University of Medical Science, Tehran, IR Iran
[3]Department of Biology, Faculty of Basic Science, Islamic Azad University, Hamedan Branch, Hamedan, IR Iran

[*]*Corresponding author*: Hamid Reza Ahmadi Ashtiani, Department of Basic Sciences, Faculty of Pharmacy, Pharmaceutical Sciences Branch, Islamic Azad University (IAUPS), Tehran, IR Iran. E-mail: ahmadi@iaups.ac.ir

Received 2016 April 30; **Revised** 2016 May 27; **Accepted** 2016 June 14.

Abstract

Context: In this article we are going to clarify the importance and practical role of liposomes in cosmetics.
Evidence Acquisition: In pharmaceutics, we have a vast area for designing different dosage forms in order to deliver the active pharmaceutical ingredient to its site of action. However, in cosmetics, since skin is the first defensive barrier against external factors and prevents many substances from entering the underlying layers or systemic circulation, there are some limitations to deliver the active ingredient to the target site.
Results: Therefore, we investigated the role of liposomes in cosmetics, and reviewed references in which the properties and applications of liposomes in cosmetics have been studied.
Conclusions: This article explains the constituents of liposomes, how they have been discovered and entered the cosmetic field, as well as their definition. Subsequently, it introduces different types of cosmetic liposomes that can be utilized in various cosmetic formulations depending on their specific properties and finally, the benefits of application of liposomes in cosmetics are taken into consideration. By using liposomes, we are able to overcome some restrictions such as low penetration, solubility, stability, duration of effect and high side effects or costs, and improve some other characteristics.

Keywords: Liposome, Cosmetics, Types Of Liposomes, Applications

1. Context

1.1. Composition

Although in the manufacture of liposomes a wide variety of amphiphilic molecules are employed, which may have uncharged positively, negatively or 2 oppositely charged polar heads, the membrane of liposomes is essentially formed by natural or synthetic phospholipids in which adding cholesterol will increase their stability. The properties of liposomes depend on the characteristics of the used structural phospholipids. Phospholipids often used in liposomes are lecithins, which are mostly extracted from natural sources such as egg, soya bean, or synthesized. Lecithins are mixtures of glycerophospholipids, which phosphatidylcholine is the most common. Another commonly compound that is used in liposomal membranes is cholesterol. Cholesterol itself does not cause a double-layered structure, though when added to the compound, enable liposome to keep the entrapped substance inside for a longer time. Based on sophistication, other stabilizers may play a role as well (1-3).

2. Evidence Acquisition

2.1. History

The possibility of forming vesicular structures from amphiphilic molecules in aquatic systems was initially speculated by Bernard (1947) during microscopic observations of myelin bodies formed with ammonium oleate in water. Bangham and Horne (1992), via electron microscopy, observed the disparity of phosphatidylcholine (lecithin) or its combination with cholesterol in water by performing negative staining using 2% sodium phosphotungstate and ammonium molybdates. Conclusions showed that a decent number of vesicles of diverse sizes were formed after shaking or sonication. Later, Wizeman dubbed these vesicles, Liposomes, which consists of Lipos (fat) + soma (body) (4).

Until early 1980s liposomes were just used as a synthetic model of bio membranes and then as a vehicle for delivery of drug molecules. Mezei and Gulasekharam reported the efficacy of liposomes for exploitation in delivery of drugs with topical approach (5).

The first liposomal cosmetic product introduced into the commercial market was the Capture anti-aging cream by firm Christian Dior in 1986, which has been followed by many other products.

In field of skin care also Laboratories RoC launched 2 products in 1987 and 1990 that were Myosphere, the first emulsion with inclusion of liposomes and the first liposomal facial cream for men. For body care, the first liposomal formulation was introduced in 1987 and many other products, which the majority of them that claimed to be effective for slimming were manufactured after that. In 1988 and later, other skin protectives such as sunscreens or self-tanning products were also turned out.

Liposomal products in cosmetics are not limited to skin care and for hair care, in 1989 a liposomal formulation was prepared. However, not many other liposomal products applicable for hair came to the market since then.

The first product containing liposomes for make-up was a powder produced in 1988 followed by mascara and different foundations (6).

2.2. Definition

Liposomes are spherical vesicles in which their central aqueous section is surrounded by one or more of a bilayer membrane (Lamella) that is frequently enclosed by aquatic environments. These vesicles are formed when amphiphilic lipids confront with aqueous milieu. They can vary in size from 15 nm to several microns. In the last 30 years, the application of liposome has been expanded from drug delivery to the cosmetic field and it is the most widely known cosmetic delivery system nowadays. Owing to their unique structure, liposomes can be utilized as a delivery system, carrying hydrophilic agents through their enclosed aqueous section, and lipophilic substances via the nonpolar tails of the bilayer section (7-9).

3. Results

3.1. Types of Cosmetic Liposomes

Based on composition and indications, cosmetic liposomes divide to different types. Depending on the features we want our cosmetic product possess, we can use one of these types.

Transferosomes: Transfrosomes are highly deformable, reactive, and efficient liposomes applied until now for direct transdermal drug delivery. In regards to their small dimension (300 - 200 nm), they can easily penetrate the skin and pass across the skin's stratum corneum by using intracellular or transcellular route with the help of 2 elongated elastic layers on their surface. These species of liposomes are made of phospholipids, cholesterol with addition of some surfactants like sodium cholate (cholic acid salt) (8, 9).

Niosomes: Niosomes are small vesicles composed of non-ionic surfactants from alkyl or dialkyl polyglycerol ether class. In cosmetics and skin care, the use of niosomes is very useful due to the fact that it can improve the product effectiveness and increases its penetration, increases bioavailability of poorly absorbed ingredients, and enhances the stability of drugs (3, 8, 9).

Novasomes: Novasomes are non-phospholipid oligolamellar lipid vesicles of 0.1 - 1.0 microns that are a variety of liposomes or modified niosomes synthesized by combining polyoxyethylene fatty acids' monoester, cholesterol, and free fatty acids with a ratio of 74/22/4. They offer further superiority for being used in cosmetic preparations by providing the ability to cleave to skin or hair shafts. This also enables sustained release and enhances the effectiveness and texture of these cosmetics (10).

Marinosomes: These types are made from marine lipid extracts that contain a high rate of Eicosapentaenoic acid and Docosahexaenoic acid that are omega-3 polyunsaturated fatty acids. Metabolized by the skin's epidermal enzymes, they change to their anti-inflammatory and anti-proliferative metabolites, which helps in healing many of the skin's inflammatory problems. The toxicity studies shows that this category of liposomes is safe for skin and eye contact (3, 9).

Ultrasomes: Ultrasomes are a unique category of liposomes that are formed by entrapment of the endonuclease extracted from Micrococcus luteus. They help detect ultraviolet radiation harm to the skin and increase the speed of treatment by up to 4 times. Ultrasomes also act as immunity system protectives by eliminating the destructive effect of ultraviolet radiation to the DNA and inhibiting the expression of some cytokines including the tumor necrosis factor alpha and interleukin 1, 6, and 8 as well as diminish the risk of skin cancer (9).

Photosomes: photosomes act by releasing photolysis enzymes extracted from the marine plant Anacystinidulans. They are extensively used in sunscreens, which prevents light from damaging the cell's DNA, therefore preventing the suppression of the immune system and reducing the risk of cancer induction (9).

Ethosomes: These varieties of liposomes are soft and flexible multilayer vesicles composed of phospholipid phosphatidylcholine, water, and 20% - 50% ethanol. Ethosomes are non-invasive carriers that enable the component penetrate deeply into the skin layers or enter systemic circulation. High concentrations of ethanol make ethosomes unique. Since ethanol is known to cause an imbalance in the arrangement of the skin's two-lipid layer, it can penetrate the horny layer when mixed with a vesicle. Com-

pared with conventional liposomes, they offer better features for efficient delivery of cosmetics to the skin in terms of both quantity and depth (9).

Asymmetric oxygen carrier system (AOCS) liposomes: this system is designed for skin oxygenation. The oxygen carrier vesicles have a perfluorocarbon nucleus and a phospholipid layer enfolded by a dual-layer membrane. Perfluorocarbons are able to dissolve great amounts of different gases including oxygen, however, they have a hydrophobic structure making them immiscible with water. Hence, by placement of them in the center of a liposomal vesicle, we can design suitable systems for transporting oxygen to the skin (3, 9).

Yeast based liposomes: These are derived from yeast cells and provide vitamin C for skin that help in repairing, soothing, and oxygenating the skin. They stimulate skin fibroblasts in their liposomal form, which makes the skin feel healthier. When the liposome is used as a carrier, cellular vitamin C intake increases significantly (3, 9).

Phytosome: they are advanced herbal preparation of liposomes developed by mixing phospholipids and botanical extracts such as flavonoids, glycosides, and terpenoids. Phytosomes improve skin absorption of phytoconstituents and are broadly used in cosmetics for their high lipid profile and enhanced skin penetration (11).

Sphingosome: Sphingosomes are liposomes constituted of ceramides for the aim of normalizing the damaged or dehydrated skin with respect to the fact that ceramides or other analogous molecules can compensate the water deficiency and rehabilitate the skin's barrier function (1).

Nanosome: Nanosomes are very small liposomes formed from highly pure phosphatidylcholine in a low nanometer size range. They are applied as anti-aging serum for enhanced performance designed to upgrade skin to a healthy and youthful looking stage (12).

Glycerosome: glycerosomes are modified liposomes containing glycerol in addition to phospholipids. Their special features include the ability to deliver cosmeceutical active ingredients to the skin with high performance, healing, beautification properties. Lately, unilamellar glycerosomes containing quercetin were designed with the size of 80 - 110 nm, which showed to improve skin defensive activity. The future prospect is using them for manufacture of antioxidant skin creams (13).

Oleosome: oleosomes are natural liposomes and a reservoir of oils, vitamins, and pigments. They are found in a variety of oil bearing plant seeds or fruits and proven to be efficacious delivery systems in personal care. Oleosomes made up of seabuckthorn fruit flesh demonstrated high stability and antioxidant properties (14).

Catezome: catezomes are novel non-phospholipid vesicles with a cationic surface charge prepared from fatty acid salts of quaternary amines that are amphipathic molecules. These liposomes with hydrophilic or hydrophobic cosmeceutical payloads have the ability to be preserved by both hair and skin and are ideal delivery systems, especially when penetration is not of acceptance or when we expect manageable penetration (15).

Invasome: Invasomes are the liposomal vesicles comprising small amounts of ethanol plus terpenes or terpene mixtures, which act as potent carriers with elevated skin penetration properties. Invasomes are soft liposomal vesicles with great membrane fluidity. The attendance of ethanol and terpenes gives the invasome specific features, which cause to get the simultaneous benefit of liposomes as potential carriers and trepenes, which promote the skin permeability and cutaneous delivery by altering the order of stratum corneum packing (16).

4. Discussion

4.1. Cosmetic Application of Liposomes

Liposomes can play the role as both vehicles of cosmeceutical materials and as active agents themselves. When skin is affected by eczema or damaged due to lack of moisture, empty liposomes can highly interact with skin lipids, proteins, and carbohydrates helping in this way the skin to return to normal state and making the stratum corneum perform its defensive function properly (1).

When they are used as carriers for delivery of active ingredients they have multi-function meaning, where besides the ingredients' own effect, they may enhance the penetration, solubility or stability, cause longevity of effect and separation of substance from environment, targeting the ingredient to desired site of action, reduce toxicity, increase control over pharmacokinetics and pharmacodynamics, and make the product cost effective.

4.1.1. Facilitate the Penetration

The skin is the most extensive organ covering the entire body surface and has a significant role in protecting the body. Human skin is made up of 3 layers: the epidermis (the outermost layer of the skin), the dermis (contains connective tissue, sweat glands, and hair follicles), and the hypodermis (constituted of adipose and connective tissue). The epidermis is divided into multitude of layers and its outermost layer, the stratum corneum due to its high profile lipophilicity and high cellular cohesion, act as skin barriers, which is a major task of skin (1).

In order to penetrate easily the stratum corneum, a molecule should possess certain physicochemical properties as it must be low weight, water and oil soluble

with intermediate distribution-coefficient, and have a low melting point (17). Only a few substances match these ideal characteristics and others almost entirely fail to pass through the skin barrier and the adequate concentration of active ingredient does not reach the action site. As a consequence, the intended topical or systemic effect will not be realized.

To overcome this restriction, exploitation of liposomes as carriers for active cosmeceutical and dermatological ingredient may be effective and could assist crossing the skin (1).

Liposomes, with their small size and similarity of structure with skin respecting their lipid composition, provide ease to the penetration inside the horny layer to a great degree compared to conventional dosage forms (9).

4.1.2. Overcome solubility limitations

Liposomes have a biphasic nature, which help them to keep hydrophilic, amphiphilic, and lipophilic molecules in their structure that the substance solubility character will specify where it is located. General, lipophilic, and amphiphilic substances are settled in the lipid bilayer of the liposome and hydrophilic agents are embedded in the aqueous center or in the external aquatic phase. This positioning minimizes the loss of materials when stored (18).

Liposome are mostly used in aqueous systems and from this feature we utilize to carry hydrophobic substances in aqueous formulations.

We have 4 fat soluble vitamins: vitamin A, vitamin D, vitamin K, and vitamin E, which all play an important role in the health and beauty of the skin, while their deficiency cause various skin disorders. As a sample, vitamin E is one of the stable fat soluble compounds that is commonly used in cosmeceuticals for skin protection properties such as antiwrinkle, enhanced skin moisturizing, and prevention of skin disease (13).

Or vitamin K1 (VK1) is a very lipophilic and photosensitive molecule that recently has been proposed for different cosmeceutical applications including antioxidant effect, suppressing skin pigmentation, preventing vascular events due to aging, and resolution of bruising like solving the problems caused by irradiation of laser beams (19).

According to the point that they are insoluble in water, to formulate a cosmetic product of these vitamins we have to use fatty basis such as fat-based ointments. Compared to water-based products, oil-based products have poor compliance due to their unfavorable or unnatural greasy feeling. Liposome particles that dispersed in water are affinative for the skin, thus, encapsulating fat-soluble vitamins in liposomes enables issues due to the lipophilicity to be overcome (19).

As in the previous case we can utilize liposomes as a water-based lip care cosmetic to improve lip condition. The amount of water that evaporates from the lip surface is almost 3 times more than that from other skin surface areas. Wrinkles or lines on the lips are far deeper, and lip movements are more frequent than those of other facial parts, therefore the use of effective lip care is of great importance (20).

In order to achieve whitening effects on hyperpigmented skin, a low water soluble compound, such as linoleic acid (LA) is advised. Liposomal formulations act as boosters for linoleic acid's skin whitening effect. Skin whitening formulations may include liposomes containing vitamin E or retinoic acid, which may reduce the oxidation rate of ascorbic acid (21).

4.1.3. Increase Stability

Many substances are prone to oxidation, degradation, or loss of performance against environmental threats. By using liposomes, we can shield the enclosed ingredient from destructive factors.

An endogenous antioxidant system protects the skin from the damaging properties of free radicals. However, exposure of skin to ultraviolet radiation leads to the amount of pro-oxidants to overtake antioxidants resulting in oxidative stress and photoaging of skin. The utilization of topical antioxidant supplementation is an approach adopted by cosmetic industries for the purpose of quenching free radicals. However, many bioactive substances are prone to change due to light exposure or storage methods. One plan for overwhelming this effect on the skin is the preparation of liposomes that allow the encapsulation of the antioxidant substances (22).

Vitamin C is a vitamin abundant in plants and has lots of roles in the body's health care. It plays a crucial role in the metabolism of collagen and has been further proven as an anti-inflammatory agent. Vitamin C promptly undergoes breakdown when encountering UV radiation or harsh environments. Nanoliposomes of vitamin C enhanced stability and antioxidant activity compared to ordinary liposomes after 60 days of storage (13).

4.1.4. Cause Longer Effect

Today, efforts in cosmetics aimed to develop new nanoparticulate systems to make them control released to skin. Among lots of molcules, liposomes are of course the best known systems. As liposome structure and composition bear a close resemblance to the stratum corneum, percutaneous administration of this vehicle leads to the lipidic components to be deposited from which liposome load can be slowly release and result in prolonged effect of

the ingredient. The majority liposomes that are used topically onto the skin will accumulate more as a reservoir providing a more long action effect in the upper layers of the stratum corneum (23).

The vital function of our breathing reveals the importance of desirable scent in the working area. By using odor pollution masks, the desire to work in such fragrant environments is greater. However, the problem is that the odor does not remain for a long time, therefore, fresheners should be used permanently, which may be harmful for ones health as well as costly. For this purpose, liposome microcapsules encapsulating fragrances such as limonene from citrus species has been manufactured. Liposomes release the capsulated material slowly, inducing a retarded effect, in comparison with the one containing retarding agents, making them an appropriate substitution to products on commercial level. Limonene, because of its favorable odor and flavorings, is widely used in cosmetics as well as food ingredients (24).

4.1.5. Separating Component From External Milieu

Most of the materials, after reacting with other materials, may provide a different function.

The pigment melanin is responsible for the variability in our skin color. Melanocyte, a type of cells deep within the skin, converts tyrosine into melanin using tyrosinase enzyme to achieve this. These pigments are then taken to the higher layers of the skin where they are deposited. The more melanin produced, the darker the skin gets. Liposomal Vitamin C inhibits the enzyme tyrosinase, which is responsible for the formation of melanin; therefore, less melanin pigments are produced (25). Vitamin c has also antioxidant activity, metabolized when encountered with pro-oxidants so we cannot see the skin whitening effects of it. By entrapping vitamin C in liposome bilayer we can prevent encountering the oxidant and antioxidant together.

4.1.6. Target Selectively

Cells react to other cells by specific signaling. By changing the charge of the membrane, or adding specific proteins, antibodies, or immunoglobulins we can increase the specific cells affinity to the liposomes. Other techniques that have been experimented are creating liposomes that react to specific pH's or temperatures before releasing the drug. Liposomes can be made to interact with specific organisms. In an attempt to lower toxicity, liposomes are certain rare cases made to avoid different kind of areas as site-avoidance-therapy (2).

4.1.7. Reduce Toxicity and Side Effects

When we use liposomes as cosmetic carriers we have an envelope for the component, therefore, we have a border that does not let the direct connection between the enclosed material and external substances. In other words the interactions are in our order and as a result they have the least effect on non-target cells.

In addition, when we separate the material, the attraction of it, with the outer environment, will be minimized. Many substances are not intrinsically toxic, however, once they interact with other substances they become toxic.

From another point of view, as liposomes provide high efficacy and targeted delivery of ingredients, the minimum dosage and the risk of intoxication from a high dose of the product is reduced by their utilization (9). Any substance that enters the body more than the amount needed acts as a toxin. We do not let this to happen by applying liposomes containing the least amount of active ingredient. Also, the controlled release of active ingredients from liposomes prevents it from reaching the toxic level.

4.1.8. Improvement of Pharmacokinetics and Pharmacodynamics

Many substances, when applied to skin, require regular doses when given without a delivery system because of the low permeability of skin. Liposomes can increase the pharmacokinetics of cosmetic products such as cause therapeutic index doses being longer and increases specificity of targeting while decreasing toxicity. Liposomes can be formulated with long circulating time and keeping constant of ingredients levels longer (2).

4.1.9. Make the Product Economic

When we use liposomes we try to use small amounts of materials in small package. This results in lower raw materials needed from one side and in another side. By miniaturization of the substance and its carrier we increase the surface-to-volume ratio, which leads to higher efficacy. The more efficient the product is, the more economical it is. Furthermore, controlling over kinetic, dynamic, and targeted delivery help the product to be cost effective.

References

1. Nastruzzi C, Esposito E, Menegatti E, Walde P. Use ano stability of liposomes in dermatological preparations. *J Appl Cosmetol*. 1993;**11**:77–91.
2. Scholtz JC. *Liposomes as drug delivery system*. 2010.
3. Patravale VB, Mandawgade SD. Novel cosmetic delivery systems: an application update. *Int J Cosmet Sci*. 2008;**30**(1):19–33. doi: 10.1111/j.1468-2494.2008.00416.x. [PubMed: 18377627].
4. Bangham AD. Liposomes: realizing their promise. *Hosp Pract (Off Ed)*. 1992;**27**(12):51–6. 61-2. [PubMed: 1452605].
5. Lohani A, Verma A, Joshi H, Yadav N, Karki N. Nanotechnology-based cosmeceuticals. *ISRN Dermatol*. 2014;**2014**.
6. Braun-Falco O, Korting HC, Maibach HI. *Liposome Dermatics: Griesbach Conference*. Springer Science and Business Media; 2012.

7. Laouini A, Jaafar-Maalej C, Limayem-Blouza I, Sfar S, Charcosset C, Fessi H. Preparation, characterization and applications of liposomes: state of the art. *J Colloid Sci Biotechnol*. 2012;**1**(2):147–68.
8. Kurapati S. The current role of nanomaterials in cosmetics. *J Chem Pharm Res*. 2016;**8**(5):906–14.
9. Reva T, Vaseem AA, Satyaprakash S, Md.khalid JA. Liposomes: The novel approach in cosmaceuticals. *World J Pharm Pharm Sci*. 2015;**4**(6):1616–40.
10. Singh A, Malviya R, Sharma PK. Novasome-a breakthrough in pharmaceutical technology a review article. *Adv Biol Res*. 2011;**5**:184–9.
11. Karimi N, Ghanbarzadeh B, Hamishehkar H, KEYVANI F, Pezeshki A, Gholian MM. Phytosome and liposome: the beneficial encapsulation systems in drug delivery and food application. *J Appl Food Biotechnol*. 2015;**2**(3):17–26.
12. Tapas KP, Oli M. Prospect of nanotechnology in cosmetics: benefit and risk assessment. *World J Pharm Res*. 2014;**3**(2):1909–19.
13. Ganesan P, Choi DK. Current application of phytocompound-based nanocosmeceuticals for beauty and skin therapy. *Int J Nanomedicine*. 2016;**11**:1987–2007. doi: 10.2147/IJN.S104701. [PubMed: 27274231].
14. Socaciu C. New techonolgies to synthesize. Extract and encapsulate natural food colorants. *Bull Univ Agric Sci Vet Med Cluj-Napoca Animal Sci Biotechnol*. 2009;**64**(1-2).
15. Nounou MI, El-Khordagui LK, Khalafallah NA, Khalil SA. Liposomal formulation for dermal and transdermal drug delivery: past, present and future. *Recent Pat Drug Deliv Formul*. 2008;**2**(1):9–18. [PubMed: 19075893].
16. Lakshmi PK, Kalpana B, Prasanthi D. Invasomes-novel Vesicular Carriers for Enhanced Skin Permeation. *System Rev Pharm*. 2013;**4**(1):26. doi: 10.4103/0975-8453.135837.
17. Dragicevic N, Maibach HI. *Percutaneous Penetration Enhancers Physical Methods in Penetration Enhancement*. Springer; 2017.
18. Wu X, Guy RH. Applications of nanoparticles in topical drug delivery and in cosmetics. *J Drug Deliver Sci Technol*. 2009;**19**(6):371–84. doi: 10.1016/s1773-2247(09)50080-9.
19. Campani V, Marchese D, Pitaro MT, Pitaro M, Grieco P, De Rosa G. Development of a liposome-based formulation for vitamin K1 nebulization on the skin. *Int J Nanomedicine*. 2014;**9**:1823–32. doi: 10.2147/IJN.S58365. [PubMed: 24748792].
20. Makino K, Isayama R, Hisamitsu I, Hayamizu K, Tsuji T, Shibata M. Preparation of Liposome Film With Pleasant Texture and High Water-Loss Suppression for Lip Care. *J Jpn Soc Colour Mater*. 2013;**86**(7):243–6.
21. Rieger M, Rhein LD. *Surfactants in cosmetics*. **68**. CRC Press; 1997.
22. Vinardell MP, Mitjans M. Nanocarriers for delivery of antioxidants on the skin. *Cosmetics*. 2015;**2**(4):342–54.
23. Hua S. Lipid-based nano-delivery systems for skin delivery of drugs and bioactives. *Frontiers Pharmacol*. 2015;**6**. doi: 10.3389/fphar.2015.00219.
24. SariisIk AM. Disposable Mask Design for Odor Pollution in the Work Environment. *Tekstil ve Muhendis*. 2015;**22**(97):31–6. doi: 10.7216/130075992015229705.
25. Pillaiyar T, Manickam M, Namasivayam V. Skin whitening agents: medicinal chemistry perspective of tyrosinase inhibitors. *J Enzyme Inhib Med Chem*. 2017;**32**(1):403–25. doi: 10.1080/14756366.2016.1256882. [PubMed: 28097901].