Journal of Drug Delivery Science and Technology 60 (2020) 101984

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

Background and different treatment modalities for melasma: Conventional and nanotechnology-based approaches

Shymaa Hatem [a], Nada M. El Hoffy [a], Reham S. Elezaby [b], Maha Nasr [b,*], Amany O. Kamel [b], Seham A. Elkheshen [c]

[a] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences and Pharmaceutical Industries, Future University in Egypt, Cairo, Egypt
[b] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt
[c] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, Egypt

ARTICLE INFO

Keywords:
Hyperpigmentation
Melanin
Melasma
Tyrosinase
Hypopigmenting agents
Nanocarriers

ABSTRACT

Extensive melanin production and accumulation inside the skin may result in a number of disorders, among which is acquired hyperpigmentation, such as melasma. Skin hyperpigmentation is attributed to either the increase in the number of melanocytes or the hyperactivity of melanogenic enzymes. Genetic susceptibility, ultraviolet radiation, hormonal remedies as well as the abnormal release of the α-melanocyte stimulating hormone (α-MSH) represent the provoking factors contributing to such disorder. On the account of their prominent localization in skin-exposed areas, hyperpigmentation may possess cosmetic and psychosocial relevance, and subsequently many efforts have been exerted to help rectify this skin disorder. The current review presents the approaches adopted to treat melasma. It also reviews the active molecules counteracting the melanogenesis process and the diverse nanotechnology-based delivery systems, which showed successful topical delivery of hypopigmenting agents for the treatment of melasma.

1. Introduction

Skin possesses epidermal elements which are responsible for the production and distribution of melanin; a process named melanogenesis. These elements consist of melanocytes encompassed by keratinocytes and maintained by a paracrine system [1]. Melanocytes; the cells synthesizing melanin pigment, produce a specified lysosomal organelle analogue termed melanosomes. Inside each melanosome, melanin biopolymers are produced which are responsible for the color of skin, hair and other tissues. The synthesis of melanin is a binary process where the endoplasmic reticulum exports the structural proteins that amalgamate with melanosome-specific regulatory glycoproteins and are extricated from the Golgi apparatus as coated vesicles. Melanin production takes place subsequently after relocating and sorting of such proteins to the melanosomes [2]. Each melanocyte is located in the epidermal basal epithelial layer and, owing to its dendrites, it interrelates with nearly thirty-six keratinocytes in order to transport melanosomes, as well as prevent photo-induced skin carcinogenesis. Moreover, the type and amount of pigment formed and delivered to keratinocytes is then incorporated, aggregated and degraded influencing skin color [3]. Hyperpigmentary skin disorders as melasma can result from epidermal melanocytes hyperactivity, which in turn may cause the increased production and accumulation of melanin in the skin [4].

Tyrosinase is the rate-limiting enzyme in the pathway of melanogenesis. It is a glycoprotein carrying copper of nearly 60–70 kDa and is considered the main target for many active molecules in order to diminish skin hyperpigmentation [5]. Melanin is biosynthesized in two vital forms, brown/black eumelanin and red/yellow pheomelanin, which is catalyzed originally by the enzyme tyrosinase. The enzyme catalyzes monophenol L-tyrosine hydroxylation to O-diphenol 3,4-dihydroxyphenylalanine (DOPA), and DOPA oxidation to O-quinone DOP-Aquinone [6,7]. A variety of hypopigmenting agents aim at modulating cutaneous pigmentation by affecting the activity and transcription of tyrosinase enzyme in addition to the related melanogenesis enzymes as tyrosinase related protein-1 (TYRP-1), tyrosinase related protein-2 (TYRP-2) and/or peroxidase [8].

Melasma (or chloasma) as demonstrated in Fig. (1) is an acquired, benign and highly ubiquitous skin disorder with chronic hypermelanosis, characterized by symmetrical patches and macules

* Corresponding author. Ain Shams University, Faculty of Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Monazamet El Wehda El Afrikia St., El Abbassia, 11566, Cairo, Egypt.
E-mail address: drmahanasr@pharma.asu.edu.eg (M. Nasr).

https://doi.org/10.1016/j.jddst.2020.101984
Received 17 April 2020; Received in revised form 25 July 2020; Accepted 28 July 2020
Available online 4 August 2020

Abbreviations

3-HC	3-hydroxycoumarin
AA2G	Ascorbic acid 2-glucoside
AP	Ascorbyl palmitate
AuNPs	Gold nanoparticles
AZA	Azelaic Acid
C60	Carbon 60
CMC	Critical micelle concentration
dArb	Deoxyarbutin
DOPA	Dihydroxyphenylalanine
DVT	Deep venous thrombosis
FSPT	Fitzpatrick skin phototype
GA	Glycolic acid
HQ	Hydroquinone
HTCC	N-(2-hydroxyl) propyl-3-trimethyl ammonium chitosan chloride
JSH18	6-methyl-3-phenethyl-3,4-dihydro-1H-quinazoline-2-thione
KA	Kojic acid
kDa	kilo Dalton
LNPs	Lipid nanoparticles
LUVs	Large unilamellar vesicles
MAP	Magnesium ascorbyl phosphate
MEs	Microemulsions
MHY498	(Z)-5-(2,4 dihydroxybenzylidene) thiazolidine-2,4-dione
MLVs	multilamellar vesicles
MSE	Melinjo (Gnetum gnemon L) seed extract
MSH	Melanocyte-stimulating hormone
MVVs	Multivesicular vesicles
NAG	N-Acetyl-d-glucosamine
NCAP	N-acetyl-4-S-cysteaminylphenol
NEs	Nanoemulsions
NHEM	Normal human epidermal melanocytes
NLCs	Nanostructured lipid carriers
NPs	Nanoparticles
PEs	Penetration enhancers
PEVs	Penetration enhancer vesicles
PIH	Post-inflammatory hyperpigmentation
PL	Polypodium leucotomos
PLGA	Poly (lactide-co-glycolide)
PMs	Polymeric micelles
PR	Phenylethyl Resorcinol
RA	Retinoic acid
RES	Resveratrol
ROS	Reactive oxygen species
SC	Stratum Corneum
SLNs	Solid lipid nanoparticles
SUVs	Small unilamellar vesicles
TA	Tranexamic acid
TC	Triple combination
TCA	Trichloroacetic acid
TYRP-1	tyrosinase related protein-1
TYRP-2	tyrosinase related protein-2
U.S. FDA	United states food and drug administration
UDVs	Ultra-deformable vesicular systems
UVA	Ultra-violet A
UVB	Ultra-violet B
VEGF	Vascular endothelial growth factor

exhibiting light to dark-brown color. Although the etiology of melasma is not definitely well-understood, some risk factors such as sun exposure, cosmetics, hormonal therapies, contraceptive pills, pregnancy, photo-sensitizing agents, genetic susceptibility and anti-seizure remedies represent the utmost provoking factors to such disorder [9–11]. It was reported that 90% of all melasma cases are commonly originated in women during their reproductive period [12]. In addition, differences in melasma susceptibility are distinguished between individuals and races according to Fitzpatrick skin phototypes [13]. The Fitzpatrick skin phototype (FSPT) classification system was utilized to estimate sunburn

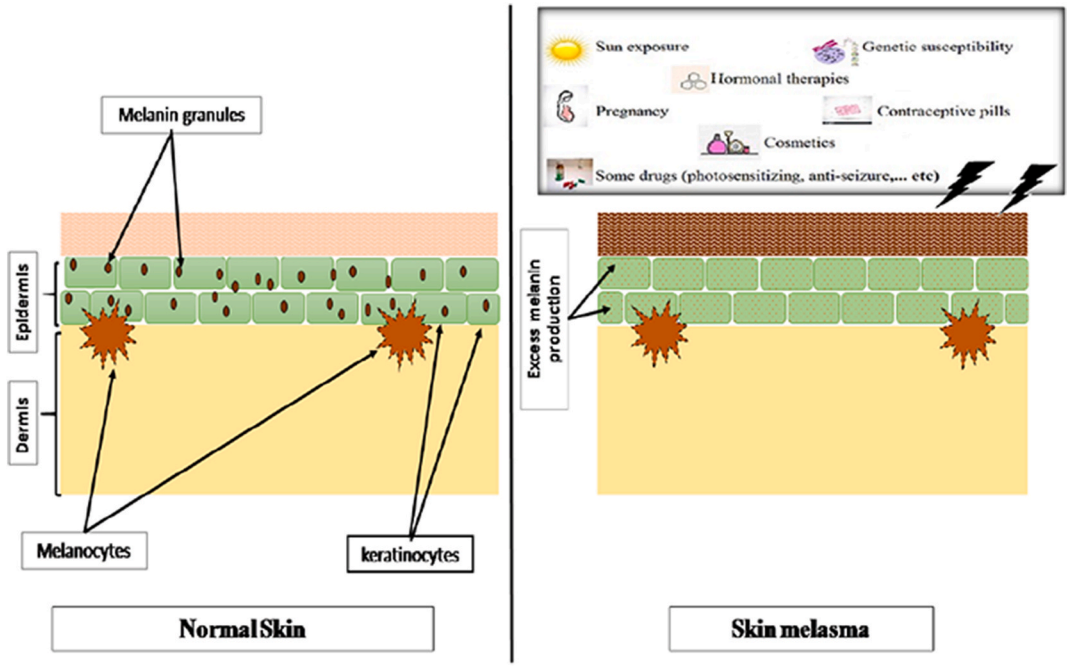

Fig. 1. Schematic diagram representing the difference between normal skin and melasma.

and suntan risk by assessing patient-reported sun sensitivity [14]. Fitzpatrick first arranged sun reactive skin phototypes from I to IV to involve individuals of white skin, and afterwards updated it to involve types V and VI for individuals of brown and black skin. A lower Fitzpatrick skin phototype indicates skin that easily burns and poorly tans, whereas, higher skin phototypes correspond to skin that rarely burns and extensively tans [15]. Pigmentary disorders including melasma are most common in Hispanic, African and Asian descendants with higher Fitzpatrick skin types [16], while lower phototypes as II and III usually occur owing to the existence of a family history [17].

Three basic patterns are considered on melasma clinical examination: centrofacial, malar, and the mandibular pattern [18]. The centrofacial is the most common including the forehead, nose, cheeks, upper lip and chin. The malar involves the malar and nasal areas, and the mandibular pattern involves the ramus of the mandible. However less common other areas such as the neck and arms may be entailed, resulting in an extrafacial type of melasma which may be accompanied by any of the other aforementioned patterns [19]. By applying Wood's lamp examination, melasma can be categorized into four histological types on basis of pigment deposition depth into epidermal, dermal, mixed type and indeterminate [18]. Wood's lamp is a beneficial tool to evaluate the depth of melanin with the aid of light-induced fluorescence [20]. The first and the most common type is the epidermal type, where intense pigmentation is revealed under Wood's light as melanin is dispersed throughout the epidermal layer. In this type of melasma, the topical treatment may be the leading modality [21]. The second type is the dermal melasma, in which pigmentation is not augmented under Wood's lamp. Pigmentation is attributed to large number of dermal melanophages [22]. In the mixed type, Wood's light can intensify pigmentation in certain areas while others remain unaltered. The pigmentation is ascribed to augmented epidermal melanin along with dermal melanophages [23]. Wood's lamp examination is unbeneficial in very dark persons, and this type is called indeterminate. This classification can only work in lighter skin phototypes and not in brown or black types [24].

Moreover, melasma can also be categorized according to the lesions' natural history into transient and permanent types [24]. The transient type vanishes within one year of the hormonal stimuli cessation such as pregnancy or oral contraceptive pills, while the persistent type exists for more than a year after removing the hormonal stimulus and is mainly caused by the action of UV radiation, hence accentuating the importance of the avoidance of sunlight exposure in controlling melasma [23].

Melanin index is an important parameter to be assessed in melasma patients, since it correlates with the degree of pigmentation and is dependent on the melanin content, hence it is considered as means of evaluating the effectiveness of treatment. In order to estimate the melanin index some methods have been utilized, such as Diffuse reflectance spectrophotometry (DRS) [25], which is an objective and non-invasive method used to determine constitutive skin color from the upper volar arm as an objective way of measuring skin pigmentation. This method detects the light which is scattered multiple times within the sample of interest, and has been widely used for the evaluation of melanin and hemoglobin concentrations in skin tissue and for the evaluation of pigmented lesions [26]. Other methods include Raman spectroscopy and Optical transmission spectroscopy [27], which offer an explanation for the excessive pigmentation in melasma regarding the molecular structure and concentration of melanin in the stratum corneum of melasma patients.

Many strategies have been adopted for treatment of melasma among which are mechanical based approaches such as chemical peels, physical therapies in the form of intense pulse light sources or different types of lasers, as well as dermabrasion and microneedling. In addition, photoprotective measures such as avoiding exposure to direct sun light and the regular application of sunscreens of broad-spectrum are constantly recommended. It is noteworthy that camouflage cosmetics are used only to conceal the pigmentation spots but not for the purpose of treatment. Moreover, oral remedies as well as topical single or combination therapies and advanced topical nanodelivery systems may aid in reducing hyperpigmentation. Advanced topical nanotechnology-based delivery systems can be employed for magnifying the potential effects of the topical hypopigmenting agents in prophylaxis and treatment. An overview of the various active topical and oral moieties counteracting melanogenesis as well as the most commonly exploited nanocarrier-based techniques for topical treatment of melasma (Fig. 2) will be briefly discussed in the current manuscript.

2. Pharmacotherapy employed in the treatment of melasma

2.1. Oral therapy

Oral therapy proved itself as a consequential treatment modality for melasma. Tranexamic acid (TA), glutathione and polypodium leucotomos (PL) are the most commonly used oral moieties for treatment of melasma. TA is an anti-plasmin agent, which reduces the production of melanocyte-stimulating hormone (MSH), thereby, causing a decrease in the formation of skin pigment, while also inhibiting tyrosinase enzyme activity [28,29]. A study demonstrated that TA may additionally reduce entothelin-1 and the vascular endothelial growth factor (VEGF), which are responsible for the increase of vascularity in melasma lesions [30]. Current studies proposed that 90% of patients receiving oral TA showed an improvement after two to six months as compared to the 95% who were topically treated with 2% TA formulations and improved after three months [31,32]. A study demonstrated the efficacy of oral TA for melasma treatment in the skin of Asian patients, even when administered in low doses over short time intervals [33]. Furthermore, **Cho et al.,** [34] investigated the efficacy of different types of laser treatments for hyperpigmentation with and without oral administration of TA, in which oral TA proved its ability to enhance the clinical efficacy of lasers in treatment of melasma. Notable side effects of oral TA uptake include headache, abdominal pain, menstrual irregularities, tinnitus and to some extent, deep venous thrombosis (DVT) [28]. Owing to the potential risk of developing DVT, assessment of thrombosis risk factors is crucial prior to treatment initiation. Other drug molecules, such as glutathione and PL were also orally applied as adjunctive remedies with promising outcomes [35–37]. PL; a natural phytochemical, was shown to reduce UV-induced photo skin damage and inhibit reactive oxygen species (ROS), which subsequently suppresses the T cell-mediated action that causes an increase in skin pigmentation and inflammation [36]. In a double-blind, randomized clinical study, oral PL proved its efficacy as an adjunctive treatment for hyperpigmentation in combination with a sun screening agent and topical 4% hydroquinone (HQ) [38]. On the other hand, glutathione; another phytochemical compound acting as an anti-oxidant has proven its efficacy in inhibiting skin hyperpigmentation

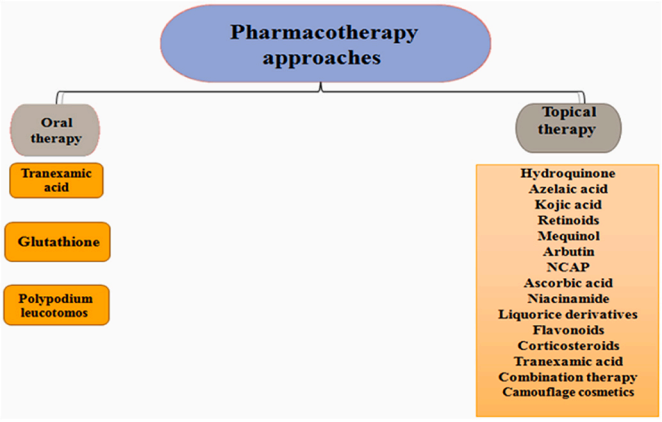

Fig. 2. Representation of pharmacotherapy approaches described in this review for melasma treatment.

by decreasing tyrosinase enzyme activity [39,40]. In a randomized clinical trial involving sixty patients, oral glutathione resulted in diminished skin melanin compared to those receiving placebo over a period of four weeks [37].

2.2. Topical therapy

At present, many topical hypopigmenting agents have been introduced and extensively applied for the enhancement of hyperpigmentation management and/or treatment. In the current section, the most common topical agents, their different mechanisms of action for suppressing hyperpigmentation as well as the trials or studies conducted to evaluate their clinical efficacy upon application will be overviewed. Fig. (3) represents the different mechanisms of action of topical hypopigmenting agents.

2.2.1. Hydroquinone (HQ)

Hydroquinone (HQ); the golden standard treatment of melasma, is structurally identical to melanin precursors. HQ has the ability to inhibit DOPA conversion to melanin by blocking the action of tyrosinase [41] as well as the development, melanization and disintegration of melanosomes. It has been utilized for treatment of skin hyperpigmentation for more than fifty years. Although many concerns exist regarding the long-term hydroquinone safety, its clinical efficacy in the treatment of skin hyperpigmentary disorders, both alone or combined with other molecules is well recognized [42]. The most commonly used HQ concentrations employed in melasma amelioration are 2–4% either as a monotherapy or in combination treatment. It is not recommended to use HQ formulations of 5% strength due to the possibility of skin irritation, except in the refractory cases [43,44]. Pigmentation lightening by hydroquinone becomes obvious after five to seven weeks of treatment. Treatment with hydroquinone should persist for not less than three months and up to one year. Patients who are on hydroquinone therapeutic regimen should perform a regular medical follow-up every three months for severe skin hyperpigmentation conditions and every six months for lighter skin cases [45]. A study reported that 2% HQ was superior to 0.025% tretinoin as an adjunct modality for the peeling agent trichloroacetic acid (TCA) in patients suffering from melasma, and it actually decreased the frequency of post-peel reactive hyperpigmentation [46]. Also, several studies reported that the application of 4% HQ resulted in a statistically significant enhancement of dyspigmentation [47]. Furthermore, **Ennes, et al**. [48], compared HQ 4% to a control over a three months period in forty-eight patients with melasma, and 38% of HQ patients experienced complete improvement, 57% showed partial improvement, while only 8% of the control patients achieved complete improvement and, 17% failed to recover. Common adverse events of HQ include burning and erythema. Other rare adverse effects are confetti-like depigmentation and ochronosis [49].

2.2.2. Azelaic acid (AZA)

AZA is a biologically derived, nonphenolic, dicarboxylic acid which competitively suppresses the action of tyrosinase enzyme [50]. AZA was originally introduced as a topical agent for treatment of acne, however, owing to its action on tyrosinase, it has also been utilized for the treatment of skin hyperpigmentary disorders. It acts by the inhibition of the mitochondrial enzymes and DNA synthesis, promoting its direct cytotoxic action towards the melanocytes [51]. Topical AZA possesses no hypopigmentary action towards normal pigmented skin, which may be ascribed to its high selectivity on abnormal melanocytes [52]. AZA also acts by reducing the production of free radicals, which have been reported to strongly contribute to hyperpigmentation disorders [53]. Another controlled study proved the superiority of azelaic acid to 2% HQ in melasma treatment [54]. A double-blind randomized clinical study demonstrated that 20% AZA was equally efficacious to 4% HQ in treating skin hyperpigmentation, excluding the latter side effects [55]. Furthermore, the combination of AZA with 15–20% glycolic acid or 0.05% tretinoin resulted in earlier, more significant skin lightening effects. Side effects of AZA involve burning, mild erythema and pruritus [56].

2.2.3. Kojic acid (KA)

KA is a natural, hydrophilic fungal derivative originated from

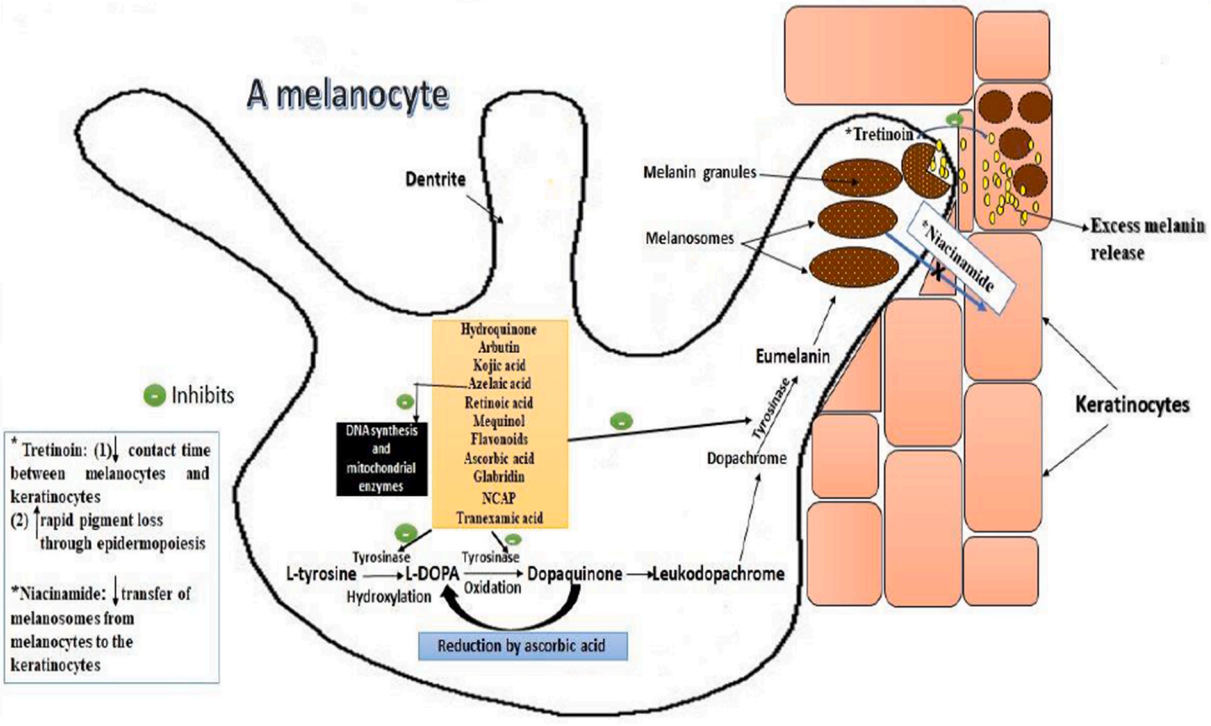

Fig. 3. Schematic representation of different mechanisms of action of topical hypopigmenting agents.

specific species of *Aspergillus, Acetobacter* and *Penicillium* [52]. It is well known as a potent antioxidant and it also acts by inhibiting the free tyrosinase production [57]. KA is usually utilized at concentrations of 1–4% [58]. A double-blind study utilizing 2% KA combined with 2% HQ showed efficacy to provide better clinical outcomes compared to 10% GA and 2% HQ [59]. Another double-blind study attempted to compare 5% GA in combination with either 4% KA or 4% HQ for a period of three months, in which both combinations proved to be similarly effective with pigmentation reduction in 52% of melasma patients [60]. KA proved its efficacy when patient experiences difficulty in enduring other first-line remedies, however, it may induce erythema and contact dermatitis [61].

2.2.4. Retinoids

Retinoids, such as tretinoin and retinoic acid, were initially applied in combination with HQ as penetration enhancers (PEs), however, they were discovered to possess some merits in melanogenesis [62,63]. Retinoids influence several steps in the pathway of melanization. Tretinoin induces epidermopoiesis, which in turn promotes rapid pigment loss and causes increase in epidermal turnover [64]. Retinoic acid (RA) inhibits UVB-induced hyperpigmentation by suppressing the activity of tyrosinase [65]. Tretinoin cream 0.1% was shown to significantly reduce hyperpigmentation in a randomized, controlled study including thirty-eight females [65]. Furthermore, a study confirmed the efficacy of 0.1% tretinoin topical formulation for melasma treatment in black patients with high efficacy and tolerability with no side effects [66]. Additionally, in a clinical study comprising twenty healthy female patients suffering from melasma, 10% tretinoin peeling mask was shown to suppress facial hyperpigmentation without exhibiting any side effects [67]. Compared to other phenolic compounds (e.g HQ), RA may take longer time to exert the required pharmacological action as clinically remarkable hypopigmenting effect becomes obvious after twenty four weeks [62].

Tretinoin monotherapy was shown to promote good therapeutic effects in clinical trials [66], yet, better outcome was observed when tretinoin was combined with another agents as corticosteroids and HQ [68]. Adverse effects of retinoids include inflammation, burning, dryness, stinging, scaling and erythema, in which inflammation may result in hyperpigmentation, especially in dark skin patients [62]. Subsequently, it is recommended to advise patients to apply sunscreens during treatment with retinoids. Adapalene, derived from naphthoic acid and exhibiting a retinoid activity was shown to be similarly effective to tretinoin in treatment of melasma, however, the former significantly exhibits more side effects compared to the latter [69].

2.2.5. Mequinol

Mequinol is a synthetic compound derived from HQ. Its mechanism of action is still debatable, however, being a tyrosinase enzyme substrate, it may competitively inhibit the production of melanin precursors [70]. It is currently applied at 2% concentration in combination with tretinoin (0.01%). A double-masked, randomized, parallel-group study comprising 216 patients reported that a solution of 2% mequinol together with 0.01% tretinoin was shown to be a well-tolerated and highly effective treatment modality for melasma lesions, being superior to 3% HQ in forearm lesions, and of comparable efficacy in face lesions [71]. A further case study including male patients suffering from melasma and treated with a topical solution of 2% mequinol and 0.01% tretinoin revealed that four out of five patients attained complete resolution after twelve weeks, and only one patient experienced moderate improvement. Adverse effects were insignificant and only included stinging in one patient. The whole patients kept up with results till the fourth month follow-up visit [72].

2.2.6. Arbutin

Arbutin is the natural *beta*-D-glucopyranoside hydroquinone derivative, which has been effectively utilized for the treatment of skin hyperpigmentation. The glycosidic bond present in arbutin is *in vivo* hydrolyzed resulting in the sustained release of HQ [73]. It acts by inhibiting the tyrosinase enzyme, which subsequently decreases melanin formation. Arbutin action is dose-dependent accompanied by less toxic effects compared to HQ [74]. **Choi et al.** [75], examined the inhibitory efficacy of arbutin on hyperpigmented human skin induced by UV radiation, in which arbutin was shown to reduce hyperpigmentation in a dose dependent manner. In another study, conducted on thirty females suffering from melasma, it was found to significantly inhibit melanin production by inhibiting tyrosinase activity [76]. Furthermore, in comparative *in-vitro* study of several molecules aiming to enhance the appearance of hyperpigmentation disorders, arbutin proved to be less toxic and more efficient in reducing hyperpigmentation compared to other hypopigmenting agents [52]. Recently, deoxyarbutin; a derivative of arbutin produced by hydroxyl groups' removal from the molecule was developed and applied in topical formulations as a potent skin-hypopigmenting agent with lesser side effects compared to HQ. It acts by producing reversible skin-whitening effect through direct suppression of tyrosinase enzyme [77]. Although adequate controlled clinical studies on arbutin and its derivatives are insufficient, primary *in-vitro* and *in-vivo* trials showed that they could be an effective and safe treatment modality for skin hyperpigmentary disorders [78,79].

2.2.7. N-acetyl-4-S-cysteaminylphenol (NCAP)

NCAP is a phenolic molecule acting as an alternative tyrosinase substrate, thereby suppressing the activity of the enzyme. Current studies reported its efficacy, better stability and less irritation compared to HQ [80]. In a study of twelve patients suffering from melasma utilizing NCAP (4%), 66% of patients demonstrated significant enhancement while 8% experienced a total clearance of melasma lesions. It is worthy to note that the frequent daily application of NCAP topical formulation resulted in significant effects after two to four weeks [81].

2.2.8. Ascorbic acid

Ascorbic acid or vitamin C is a potent antioxidant that can inhibit melanogenesis by causing the reduction of dopaquinone to DOPA as well as preventing the formation of free radicals and the absorption of UV radiation [73]. Upon comparing the effectiveness of 4% HQ to 5% ascorbic acid in sixteen patients suffering from hyperpigmentation in a randomized clinical study, results revealed that despite the fact that HQ demonstrated higher efficacy, ascorbic acid was also shown to positively affect melasma treatment. It is worth noting that ascorbic acid has lesser side effects than HQ, and it can be utilized alone or in combination with other agents [82]. Another study reported that formulating L-ascorbic acid (25%) with two chemical penetration enhancers such as dimethyl isosorbide and N-methyl-2-pyrrolidone was proven to exhibit a significant effect in melasma treatment [83,84]. However, its instability in aqueous solutions limited its use nowadays in topical formulations. Instead, stable esters as magnesium ascorbyl-2-phosphate (MAP) were synthesized offering a great protection from UVB radiation [85] besides suppressing melanogenesis *in-vitro* and *in-vivo* owing to its inhibitory effect on tyrosinase enzyme. Trials showed that MAP cream has the ability to deliver the drug into the epidermal skin layer and that 1.6% remained for two days after topical administration. The whitening effect was observed in 19 out of 34 subjects suffering from melasma and in 3 out of 25 with normal unpigmented skin [86].

2.2.9. Niacinamide

Niacinamide or nicotinamide; the naturally active amide derivative of vitamin B_3 (niacin), can inhibit melanogenesis by counteracting reversibly melanosomes transfer from the melanocytes to keratinocytes [87]. It exhibits null effect on the activity of tyrosinase. Recent clinical studies demonstrated the effectiveness of niacinamide in reducing hypermelanosis and causing skin lightening after one month of application [88,89].

2.2.10. Liquorice derivatives

Liquorice is derived from the root of *Glycyrrhiza glabra* perennial herb containing a number of natural phytochemical entities with potent therapeutic effects. Glabridin is an oily compound extracted from liquorice with proven inhibitory action towards tyrosinase besides its anti-inflammatory properties [90]. In an *in-vitro* study, **Yokota et al.,** [90] investigated the inhibitory effects of glabridin on melanogenesis of guinea pig skin and cultured B-16 murine melanoma cells. The authors reported the ability of glabridin to inhibit tyrosinase activity and reduce the pigment content in the skin, which in turn diminishes hyperpigmentation. A clinical study with liquiritin; another derivatized compound, showed its high efficacy in treating melasma in twenty females with epidermal type melasma over a period of one month, in which 80% showed excellent improvement, 10% experienced good improvement, and the last 10% showed fair improvement with mild pigmentation [91]. A study by **Zubair and Mujtaba** [92] comparing the efficacy of 2% and 4% liquiritin to 4% HQ revealed that more uniform skin lightness was observed with 4% liquiritin after eight weeks of treatment. In addition, liquiritin was shown to be tremendously efficacious when utilized in combination therapies. A study conducted by **Akram et al.,** [93] showed that the combination of 4% liquiritin with 5% ascorbic acid for melasma treatment was more effective after eight weeks of frequent application compared to 4% liquiritin alone.

2.2.11. Flavonoids

Flavonoids are naturally derived polyphenolic molecules possessing well-known antioxidant, antiviral, anti-inflammatory and anticarcinogenic properties [94]. Several flavonoid compounds of plant origin possess hypopigmentary effects as they proved to inhibit tyrosinase enzyme and tyrosinase-related protein synthesis and maturation. Flavonoids include aloesin (extracted from aloe tree), catechin combined with gallic acid (from leaves of green tea) and ellagic acid (from strawberry, eucalyptus, green tea, etc) [95]. **Choi et al.,** [75] proved the inhibitory effect of aleosin on human skin hyperpigmentation induced by ultra violet radiation in a dose-dependent manner. A study carried out on thirty females suffering from melasma and treated with ellagic acid, showed significant inhibition of melanin production through inhibiting tyrosinase activity [76]. Additionally, **Zhu and Gao** [96] demonstrated the ability of hesperidin; a flavonoid derived from citrus fruits' membranes, to inhibit the synthesis of melanin through the inhibition of tyrosinase activity in a dose-dependent manner in human melanocytes and when applied to laboratory animals' skin.

Other flavonoids with well-known effects on melanin pigmentation include alpha-lipoic acid, hesperetin, N-acetyl glucosamine, soybean and paper mulberry extracts and gentisic acid [97].

2.2.12. Corticosteroids

Corticosteroids are anti-inflammatory agents that provide antimetabolic action on melanocytes, causing a diminished epidermal turnover and consequently, resulting in significant melanin content reduction [98]. Corticosteroids are the major ingredient of most of the triple-combination hypopigmentation formulations. Triple preparations utilizing various corticosteroids such as dexamethasone, 1% hydrocortisone [99], mometasone [100,101], and fluorinated steroids [102] revealed efficacy for suppressing skin hyperpigmentation. A randomized controlled trial to investigate the efficacy and safety of a triple combination (TC) therapy comprising fluocinolone acetonide 0.01%, HQ 4% and tretinoin 0.05% compared to HQ 4% cream was conducted on 120 Asian patients suffering from moderate to severe melasma, with a significant reduction in melanin content in 64% of the patients in case of the TC therapy compared to HQ alone [102,103]. Moreover, a study performed on ten melasma patients receiving triple combination therapy of tretinoin, HQ and mometasone furoate in addition to glycolic acid peels revealed that 75% of the patients experienced excellent improvement while the rest showed fair to good response [100].

2.2.13. Tranexamic acid (TA)

In addition to its oral route of administration as mentioned before, TA was also claimed to exert its whitening efficacy when applied topically through the previously mentioned mechanism of action [104]. However, topical TA administration was shown to be superior to oral administration as it avoids serious side effects including oligomenorrhoea, palpitation and gastrointestinal upset [105]. In a double blind, prospective randomized study, the efficacy of topical 5% TA *versus* vehicle was investigated in twenty-three women suffering from epidermal melasma over a period of three months. It was observed that 78.2% of the patients showed an excellent improvement on either one or both sides of the face after three months, while the rest experienced moderate improvement compared to the vehicle [106]. In another study aiming at the evaluation of the efficacy and safety of the topical solution of TA compared to a combined solution of HQ and dexamethasone in fifty Iranian women, TA topical solution proved to be an effective treatment modality especially for the epidermal type melasma with a good response in 68% patients owing to its quite rapid outcomes with almost no significant or serious side effects compared to the combination of HQ and dexamethasone [107]. Moreover, a prospective, randomized, placebo-controlled study was conducted using 10% topical TA on forty melasma subjects, in which 8% showed excellent improvement, while 50% and 29% showed good and fair improvement, respectively [105].

2.2.14. Combination therapy

Several topical hypopigmenting molecules act on various stages of melanogenesis process, thereby offering a reason for drugs' combinations to promote higher therapeutic outcomes with lesser side effects; for example, topical corticosteroids may diminish the irritation reaction induced by retinoids or HQ, while retinoids may reduce cutaneous atrophy promoted by steroids [108]. Several topical agents' combinations have been contemplated and many were launched by the pharmaceutical companies. HQ is commonly the major ingredient of most of the combination treatments. It is usually utilized with other agents like corticosteroids, azelaic acid, glycolic acid, retinoic acid or kojic acid [23]. However, the most widely utilized and extensively studied combination therapy is the so-called "triple combination"; a preparation comprising corticosteroids, retinoic acid and HQ. Initially attempted by **Kligman and Willis** [109]. A primary applied combination comprising 0.1% dexamethasone, 0.1% tretinoin and 5% HQ was reported to be efficient in treating postinflammatory hyperpigmentation, ephelides and melasma. However, owing to its high tretinoin concentration, many concerns about the irritation potential of this combination were considered and several modifications were attempted, among which is utilizing 0.01% fluocinolone acetonide, 0.05% tretinoin and 4% HQ to yield better therapeutic outcomes in long-term clinical investigations [11]. This result was also confirmed in a randomized clinical study comprising 260 Asian melasma patients, in which the aforementioned combination therapy proved to be superior to 4% HQ monotherapy in treatment of melasma [102]. Additionally, a novel formulation containing 4% nicotinamide, 3% arbutin, 0.05% retinaldehyde and 1% bisabolol was shown to be a safe, effective, and tolerable treatment modality for patients with epidermal-type melasma [110]. It was strongly recommended that the first-line treatment of melasma should include effective topical agents, mostly in the form of triple combinations, unless the patient is hypersensitive to any of the ingredients [11].

On the account of melasma (chloasma) nature and the challenging prolonged duration of treatment, topical camouflage cosmetics were also utilized to ameliorate the psychosocial impacts of the disease as well as the quality of life [30]. They involve the application of cosmetic powders or creams in order to conceal discoloration or hyperpigmentation of face or body [111]. A study performed on a group of twenty-four patients with hyperpigmentary disorders revealed that camouflage cosmetics, including concealers and other pigmented cosmetics, were able to effectively disguise skin discoloration which in turn was significantly reflected on patients' psychosocial activity as well as

Table 1
Summarizes the different nanocarriers employed for the topical delivery of hypopigmenting agents together with the resultant outcomes.

Systems	Encapsulated drugs with reported hypopigmenting activity	Outcomes	References
Microemulsions (MEs)	Ascorbic acid	- Enhanced its permeation through skin - Provided better skin protecting activity	[123]
	Punica granatum extract	- Enhanced the delivery of the extract through different skin layers - Increased its efficacy on skin melanin content and erythema	[124]
	Kojic acid and arbutin	- Enhanced their stability against photo degradation compared to their aqueous solution	[125]
	Hesperetin	- Enhanced its skin deposition compared to both the isopropyl myristate suspension and aqueous solution of the same flavonoid - Offered superior skin whitening efficacy with reduced irritation	[126]
	Hydroquinone	- Increased its diffusivity across the stratum corneum - Improved its stability against photodegradation	[127,128]
	Lactic acid, arbutin and niacinamide	- Enhanced their stability and skin permeability - Improved their skin whitening efficacy	[129]
	Sompoi (*Acacia concinna Linn.*)	- Increased its solubility and stability compared to the extract's solution form	[130]
	Undecylenoyl phenylalanine	- Enhanced its stability and release profile	[131]
	Broussonetia Papyrifera leaf extract	- Improved its stability - Decreased skin irritation - Increased its antityrosinase activity compared to the extract solution	[132]
	Ascorbic acid 2-glucoside	- Enhanced its skin diffusivity and stability compared to the drug's solution form	[133]
	20(S)-protopanaxadiol	- Enhanced its solubility and skin permeability	[134]
Nanoemulsions (NEs)	Glabridin	- Increased its aqueous solubility - Prevented its oxidative degradation - Enhanced its skin permeation profile	[144,145]
	Kojic monooleate	- Enhanced its diffusivity across skin	[146]
	Deoxyarbutin	- Augmented its solubility and stability compared to traditional emulsions	[147]
	Kojic dipalmitate	- Enhanced its stability	[148]
	Heartwood of *Artocarpus Incisus* extract	- Increased its hypopigmenting action compared to the solution form of the extract	[149]
	Azelaic acid and hyaluronic acid	- Enhanced drug's deposition and tyrosinase inhibitory action	[150]
Solid lipid nanoparticles (SLNs)	6-methyl-3-phenethyl-3,4-dihydro-1H-quinazoline-2-thione	- Improved its solubility - Increased its diffusivity across the SC compared to its solution form	[155]
	N-Acetyl-d-glucosamine	- Ameliorated its skin penetration and tyrosinase inhibitory activity compared to the drug's solution	[156]
	-(Z)-5-(2,4-dihydroxybenzylidene)thiazolidine-2,4-dione	- Increased its skin permeability - Provided sustained drug release profile - Increased its anti-melanogenic efficacy compared to drug's solution	[157]
	Hydroquinone	- Increased drug stability against oxidation - Offered superior skin penetration with diminished systemic absorption	[158]
	Trans-resveratrol	- Enhanced its skin residence time and antimelanogenic activity compared to kojic acid	[159]
	Curcumin	- Enhanced its solubility - Improved its skin permeability and hypopigmenting activity	[160]
	Melinjo (*Gnetumgnemon L.*) seed extract	- Enhanced its stability, bioavailability in skin and hypopigmenting activity	[161]
	Green tea (*camellia sinensis L.*) leaves extract	- Increased its skin penetration profile compared to the extract solution	[162]
Nanostructured lipid carriers (NLCs)	Pomegranate peel extract	-Increased its skin penetration and antityrosinase inhibitory activity compared to its cream form	[163]
	Deoxyarbutin	-Provided high skin penetration	[147]
	Phenylethyl resorcinol	-Enhanced its solubility and photostability -Increased its antityrosinase activity in melanoma cells	[164]
	N-acetyl-glucosamine	-Enhanced its skin deposition and hypopigmenting activity	[165]
	Trans-resveratrol	-Promoted sustained release effect of the drug -Protected it from degradation provoked by temperature or light -Augmented its antimelanogenic activity.	[166]
	Hydroquinone	-Enhanced its stability -Diminished skin irritation	[167]
	Ascorbyl palmitate	-Enhanced its chemical stability compared to the same drug in NE formulation.	[168]
Liposomes	Hydroquinone	-Preserved its therapeutic efficacy for melasma treatment, however no superiority was noted compared to the conventional cream form	[174]
	Tranexamic acid	-Offered superior skin whitening efficacy compared to conventional hydroquinone	[175]
	Linoleic acid	-Enhanced its solubility and skin hypopigmenting efficacy compared to nonliposomal preparations	[176]
	Anthocyanin	-Augmented its photostability -Increased its antityrosinase activity compared to the drug solution form	[177]
	Aloe vera extract	-Increased its bioavailability with better skin hypopigmenting effect compared to the extract's solution form	[178]
	4 n-butyl resorcinol	-Enhanced its stability -Increased its skin penetrability -Ameliorated its tyrosinase inhibitory effect	[179]
	Asparagus Racemosus extract	-Significantly suppressed its tyrosinase enzyme activity compared to the extract solution	[180]
	Phenylethyl Resorcinol	-Enhanced its solubility -Improved skin permeation -Increased its physical stability and antityrosinase activity	[181,182]

(*continued on next page*)

Table 1 (*continued*)

Systems	Encapsulated drugs with reported hypopigmenting activity	Outcomes	References
		-Reduced skin irritation effects	
	Artocarpus Lakoocha extract	-Improved its skin permeation and whitening potential compared to the non-encapsulated extract	[183]
	Arbutin	-Enhanced its skin permeability and whitening efficacy	[184,185]
Aspasomes	Magnesium ascorbyl phosphate	-Enhanced its stability, skin permeation and retention compared to 15% trichloroacetic acid	[188]
Niosomes	N-acetyl glucosamine	-Enhanced the extent of its permeation into skin compared to the drug's hydroalcoholic solution	[193]
	Kojic acid and Hydroquinone	-Prevented their degradation -Showed a sustained release effect inside the skin	[194,195]
	Ellagic acid	-Augmented its solubility -Enhanced its skin permeability compared to its solution form	[196]
	Phenylethyl resorcinol	-Improved its stability and skin permeability	[197]
	Arbutin	-Enhanced its skin permeability and whitening efficacy	[198]
Transfersomes	Linoleic acid	-Enhanced its stability and skin deposition compared to its hydroalcoholic solution.	[200]
	Phenylethyl resorcinol	-Improved its solubility and stability -Reduced skin irritation -Increased its inhibitory activity towards tyrosinase enzyme and melanin content compared to the conventional liposomes	[182,201]
	Niacinamide	-Increased its skin permeation and whitening activity compared to conventional liposomes.	[202]
	Arbutin	-Enhanced its skin permeability and whitening efficacy	[203]
Ethosomes	Phenylethyl resorcinol	-Enhanced its transport of across skin layers -Established a drug depot inside the skin, promoting higher inhibitory potential towards skin tyrosinase and melanin content compared to conventional liposomal formulations -Augmented its solubility and stability	[201,206]
	Linoleic acid	-Promoted deeper skin penetration compared to transfersomes	[200]
Invasomes	Phenylethyl resorcinol	-Provided deeper penetration through the skin compared to the liposomes and transfersomes -Enhanced its inhibitory action towards tyrosinase enzyme up to 90% -Augmented its solubility and stability	[182,201]
Penetration enhancer vesicles (PEVs)	3-hydroxycoumarin	-Increased itstransport to deep skin layers -Inhibited the activity of tyrosinase enzyme in melanoma cells	[217]
Chitosan nanoparticles	Glabridin	-Improved its stability against various environmental factors, thus ameliorating its skin whitening activity	[227]
	Arbutin	-Enhanced its skin permeability and whitening efficacy	[228,229]
	Kojic acid	-Significantly lessened the level of melanin synthesis -Enhanced penetrability	[230]
Ethyl cellulose nanoparticles	Vitamin C	-Augmented its stability -Increased its skin diffusivity and antityrosinase activity	[231]
Polymeric micelles (PMs)	Glabridin	-Enhanced its skin permeability -Reduced irritation potential -Suppressed melanin synthesis	[234]
Fullerenes	Polyvinyl pyrrolidone (PVP)-wrapped fullerene derivative (called "Radical Sponge)	-Inhibited UVA-induced melanogenesis compared to another two skin whitening agents, L-ascorbic acid and arbutin	[246]
Gold nanoparticles (AuNPs)	Extract of *Panax ginseng* leaves	-Inhibited the activity of tyrosinase compared to arbutin solution	[249]

their level of confidence [112]. A variety of cosmetics' brands provide concealers and pigmented foundations that may unify skin tone and may also contain broad-spectrum UV blockers [113].

3. Application of nanocarriers for treatment of melasma

Many strategies have been proposed to attain successful delivery of topical hypopigmenting agents, among which is their encapsulation within nanocarrier-based delivery systems. This strategy offers several merits for example, the efficacy at low concentration, possibility of actives' targeting to different skin layers whether superficial or deep, increased solubility, rapid action, as well as sustained duration of action [114] and stability against degradation [115]. Accordingly, the utilization of nanocarrier drug delivery systems would be a very promising approach in this regard. An overview of the most frequently applied carriers for topical delivery of hypopigmenting agent will be briefly discussed in the coming sections (Table 1).

3.1. Lipid-based nanocarriers

3.1.1. Microemulsions (MEs) and nanoemulsions (NEs)

3.1.1.1. Microemulsions (MEs). MEs as shown in Fig. (4) are stabilized, transparent (or translucent) water and oil dispersions. They are spontaneously formed with a mean droplet diameter ranging from 10 to 140 nm [116–118], containing the surfactant/cosurfactant film as a boundary between the aqueous and oily phases. They are considered as liquid membrane carriers to transfer either hydrophilic drug molecules through the aqueous media or deliver the lipophilic ones across the lipidic phase [119].

MEs possess numerous advantages over conventional formulations as lotions, gels or creams for topical drug delivery. They are capable of increasing the solubilization of drugs as well as their thermodynamic activity, hence promoting the partitioning of drugs into the skin [120]. They are used to increase the depth and transfer rate of moisturizing agents into the skin. Additionally, it has been reported that microemulsions may disrupt the organized ordered structure of the stratum

corneum (SC) lipids, resulting in the loss of skin utmost barrier properties, thereby facilitating drugs delivery to deep skin layers [121]. Moreover, these systems have been reported to protect the incorporated moieties against oxidation, photo- and enzymatic degradation, thus maintaining drugs' stability and delineating them as promising systems for topical delivery [122].

MEs were successfully utilized for the topical delivery of several skin-hypopigmenting agents. Pakpayat et al., [123] reported that microemulsions incorporating ascorbic acid enhanced its permeation through the skin and provided better skin protecting activity. A study revealed that microemulsion encapsulation of *Punica granatum* extract known for its skin hypopigmenting effect showed an enhanced delivery of the extract through the different skin layers, in addition to a superior efficacy on skin melanin content and erythema [124]. An o/w microemulsion of KA and arbutin was formulated and the stability of the drugs against photodegradation by UVB irradiation was attempted in both microemulsion and aqueous solution of the two skin whiteners. It was observed that the stability of both drugs was higher in microemulsion compared to the aqueous solution [125]. Furthermore, **Tsai et al.,** [126] proved the effect of encapsulating hesperetin in microemulsion form on enhancing its *in-vitro* skin deposition compared to both the isopropyl myristate suspension and aqueous solution of the same flavonoid. In addition, hesperetin-loaded microemulsion demonstrated superior skin whitening efficacy with reduced irritation, indicating its effectiveness as a topical formulation for the treatment of hypermelanotic disorders. Another study reported that encapsulating HQ in microemulsion increased its diffusivity across the stratum corneum besides improving its stability against photodegradation [127,128]. Additionally, lactic acid, arbutin and niacinamide were encapsulated inside a microemulsion system to enhance their stability, skin permeability and to improve their skin whitening efficacy [129]. Moreover, **Poomanee et al.,** [130] reported that loading Sompoi (*Acacia concinna Linn.*) pod extract, possessing a high antityrosinase effect into microemulsions increased its solubility and stability compared to its solution form. A further study reported that loading undecylenoyl phenylalanine; a novel synthetic hypopigmenting agent into a microemulsion system enhanced its stability and release profile, hence promoting higher therapeutic outcomes for melasma treatment [131]. **Thungmungmee et al.,** [132] revealed that formulating *Broussonetia Papyrifera* leaf extract with a skin lightening activity into a ME improved its stability, decreased skin irritation and increased its antityrosinase activity compared to the extract solution. In addition, it was reported that the encapsulation of ascorbic acid 2-glucoside (AA2G) into MEs enhanced its skin diffusivity and stability compared to the drug's solution form [133]. Moreover, 20 (S)-protopanaxadiol; a ginsenoside with a marked skin-whitening effect, was incorporated into MEs, in which an enhancement in its solubility and skin permeability was observed [134].

3.1.1.2. Nanoemulsions (NEs). NEs as shown in Fig. (4) are defined as clear isotropically and thermodynamically unstable and kinetically stable dispersion systems of two immiscible phases; aqueous and oily, stabilized by a boundary of an interfacial film of surfactant molecules [135]. NEs are characterized by their uniform and extremely small size with an average droplet size range of 20–200 nm [136–141]. They are extremely fragile and in a metastable condition compared to MEs [142].

NEs are considered as promising topical drug delivery systems owing to their ability to increase the penetration of drugs across different skin layers and to target poorly soluble drugs. They proved their efficacy to enhance skin penetration of drugs and to increase their residence time in the target area, which in turn results in lesser adverse effects. Furthermore, they were shown to augment the affinity of drugs for vehicle-skin partitioning and subsequently increase their permeation into the skin [143].

NEs proved to be beneficial in the topical delivery of skin hypopigmenting agents. They were reported to increase the aqueous solubility of glabridin and prevent its oxidative degradation besides enhancing its skin permeation profile [144,145]. Also, Kojic monooleate (the esterified form of KA) was formulated in the form of o/w nanoemulsion showing enhanced diffusivity across skin [146]. Deoxyarbutin (dArb); a lipophilic skin whitening agent, is thermolabile and can be easily degraded in aqueous media. A study demonstrated that loading dArb into a NE system augmented its solubility and stability compared to traditional emulsions [147]. Furthermore, kojic dipalmitate was loaded into NEs, in which an enhancement in its stability was observed [148]. In addition, an *in-vivo* study was conducted on a NE system loading heartwood of *Artocarpus Incisus* extract, with a marked inhibitory activity on melanogenesis, in which the hypopigmenting activity of the formulated NE increased two folds compared to the solution form of the extract [149]. Moreover, azelaic acid-loaded NE with hyaluronic acid was developed as a double targeting approach, in which an enhancement in drug deposition and tyrosinase inhibitory action was noted [150].

3.1.2. Lipid nanoparticles (LNPs)

LNPs are colloidal drug delivery systems involving solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) [151]. SLNs consist of physiologically well-acceptable lipidic ingredients present in the solid state at ambient temperature with a particle size ranging from 50 to 1000 nm [152]. NLCs are a new generation of lipidic nanocarriers encompassing a mixture of solid and liquid lipids, in which the liquid lipid phase is incorporated within the solid lipid matrix [153].

SLNs and NLCs have been successfully exploited for dermal drug delivery as a consequence of their superior and acceptable cosmetic and dermatological features such as the increase of skin elasticity and hydration, increase of skin occlusion, enhancement of drug targeting and skin permeation, in addition to, prevention of drugs' degradation thus, maintaining their stability besides, their small submicronized size which allows a close contact with the SC lipids, hence augmenting skin penetration [154].

A number of studies reported the use of SLNs and NLCs for the topical skin delivery of hypopigmenting agents. A study reported that loading 6-methyl-3-phenethyl-3,4-dihydro-1H-quinazoline-2-thione (JSH18); a synthetic hypopigmenting agent, into SLNs improved its solubility and diffusivity across the SC compared to its solution form [155]. Also, N-Acetyl-d-glucosamine (NAG) loaded SLNs enhanced the skin penetration and tyrosinase inhibitory activity of the drug compared to its solution form [156]. Furthermore, another study reported the possibility of incorporating (Z)-5-(2,4-dihydroxybenzylidene)thiazolidine-2,4-dione (MHY498); a novel synthetic tyrosinase inhibitor, into SLNs, in which a higher skin permeability, sustained drug-release profile, and an increase in the antimelanogenic efficacy were noted compared to MHY solution form [157]. In addition, SLNs were shown to be promising for encapsulating HQ despite its hydrophilic character. they showed high drug stability against oxidation and superior skin penetration with diminished systemic absorption [158]. Also, loading trans-resveratrol (RES) into SLNs enhanced its skin residence time and antimelanogenic activity compared to KA [159]. Curcumin was loaded into SLNs, where an enhancement in its solubility, skin permeability and hypopigmenting activity was observed [160]. A study reported that incorporating Melinjo (*Gnetum gnemon L.*) seed extract (MSE) into SLNs enhanced its stability, skin bioavailability, as well as its hypopigmenting activity [161]. Moreover, green tea (*camellia sinensis L.*) leaves extract, containing polyphenolic compounds with antityrosinase activity, was effectively loaded into SLNs with increased skin penetration compared to the extract solution [162]. **Tokton et al.,** [163] reported that loading pomegranate peel extract with ellagic acid content into NLCs increased its skin penetration and antityrosinase inhibitory activity compared to its cream form. Another study was conducted in an attempt to compare the effect of NEs, NLCs and a conventional cream on the topical delivery of dArb, where NLCs were shown to provide the utmost skin penetration and subsequently the highest hypopigmenting activity [147].

Phenylethyl resorcinol-loaded NLCs were proven to enhance the solubility and photostability of the drug along, with increased antityrosinase activity in melanoma cells [164]. NLCs were also exploited for the topical delivery of N-acetyl-glucosamine (NAG), in which an enhancement in its skin deposition and hypopigmenting activity was observed [165]. **Fachinetti et al.,** [166] reported that loading trans-RSV into NLCs promoted sustained release effect of the drug, protected it from degradation provoked by temperature or light, besides augmenting its antimelanogenic activity. Moreover, it was reported that loading HQ into NLCs enhanced its stability, hence attaining better drug delivery and diminished skin irritation [167]. In addition, **Uner et al.,** [168] reported that loading ascorbyl palmitate of reported inhibitory effect on melanogenesis into SLNs and NLCs enhanced its chemical stability compared to the same drug in NE formulation.

3.1.3. Lipidic vesicular systems

3.1.3.1. Liposomes. Liposomes are simple microscopic vesicular systems constituting an outer lipid bilayer membrane encompassing an aqueous environment. There are several components found in liposomes, among which phospholipids and cholesterol are the major ingredients [169]. Liposomes are generally classified based on their lamellae number and size into small unilamellar vesicles (SUVs), around 100 nm, large unilamellar vesicles (LUVs), ranging from 200 to 800 nm and large multilamellar vesicles (MLVs) or multivesicular vesicles (MVVs), ranging from 500 to 5000 nm [170,171].

Liposomes are acceptable carriers for topical delivery of drugs owing to their ability to incorporate both lipophilic and hydrophilic drugs [172] and prevent their degradation. They also possess a great affinity to the keratin of skin horny layer and can permeate through the deep skin layers. For skin application, liposomes may aid in the solubilization of poorly soluble drugs, act as a penetration enhancer, or function as local depot thus reducing drugs' side effects [173].

A number of studies reported the effectiveness of liposomes for topical delivery of skin hypopigmenting agents. HQ was encapsulated into liposomes and compared to conventional HQ cream. It was observed that the liposomalization of HQ preserved its therapeutic efficacy for melasma treatment, however no superiority was noted compared to the conventional cream form [174]. In an attempt to compare conventional HQ and liposomal TA, another study was conducted, in which TA-loaded liposomes were shown to offer superior skin whitening efficacy compared to HQ [175]. Additionally, Shigeta et al., [176] reported that loading linoleic acid; one of the essential fatty acids having a significant inhibitory effect on tyrosinase, into liposomes enhanced its solubility and skin hypopigmenting efficacy compared to non-liposomal preparations. A further study reported that the liposomalization of anthocyanin; a flavonoid possessing antioxidant and tyrosinase inhibitory effects, augmented its photostability and antityrosinase activity compared to the drug solution form [177]. Also, *Aloe vera* extract, containing aloesin which inhibits the production of melanin in the skin demonstrated higher bioavailability with better skin hypopigmenting effect when encapsulated in liposomes compared to the solution form of the extract [178]. Furthermore, **Huh et al.,** [179] reported the possibility of encapsulating 4 n-butyl resorcinol; a resorcinol derivative possessing an inhibitory effect on the melanogenesis, into liposomes to enhance its stability and skin penetrability besides increasing its tyrosinase inhibitory effect. In addition, *Asparagus Racemosus* extract loaded liposomes proved to significantly suppress tyrosinase enzyme activity compared to the extract solution [180]. Phenylethyl Resorcinol (PR) is a phenolic compound derived from resorcinol and has shown to exhibit a potent skin-lightening activity. It was reported that the liposomalization of PR enhanced its solubility, skin permeation, physical stability, and antityrosinase activity with diminished skin irritation effects [181,182]. Moreover, when *Artocarpus Lakoocha* extract was encapsulated into liposomes, an improvement in its skin permeation and whitening potential was observed compared to the non-encapsulated extract [183]. Also, two studies reported that the incorporation of arbutin into liposomes caused an enhancement in its skin permeability and whitening efficacy [184,185].

3.1.3.2. Aspasomes. Aspasomes are vesicular systems exhibiting a biological function or a targeting activity in addition to their carrier merits. Unlike conventional liposomes, they are composed of a bilayer of ascorbyl palmitate (AP) instead of the phospholipid moieties, encompassing an aqueous environment [186]. AP (an ester of vitamin C) is an amphiphilic molecule possessing an antioxidant activity towards various skin disorders [187]. **Aboul-Einien et al.,** [188] showed that loading magnesium ascorbyl phosphate (MAP); an ascorbic acid derivative, into aspasomes enhanced its stability, skin permeation and retention compared to 15% TCA, a chemical peeling agent.

3.1.3.3. Niosomes. Niosomes are non-ionic surfactants based vesicles [189]. They are composed of a hydrophilic head zone along with hydrophobic tails of surfactant monomers shielded away from the center of the aqueous core. It was previously reported that adding cholesterol into niosomes' formation increased the rigidity of the membrane bilayer promoting limited drugs' leakage [190]. Generally, these vesicles are considered as second generation vesicles with lower production cost, enhanced chemical stability, better entrapment efficiency and enhanced penetrability compared to conventional liposomes [191]. Many studies proposed their efficacy for topical delivery of drugs as they can improve drugs' retention time in SC, and simultaneously lessen their systemic absorption [192]. The nonionic surfactants themselves as the main ingredients of niosomes promoting their flexibility may also act as penetration enhancers, hence contributing to high drugs' permeation from niosomes [143].

Shatalebi et al., [193] investigated the possibility of loading NAG into niosomes to improve its penetration across the skin. It was observed

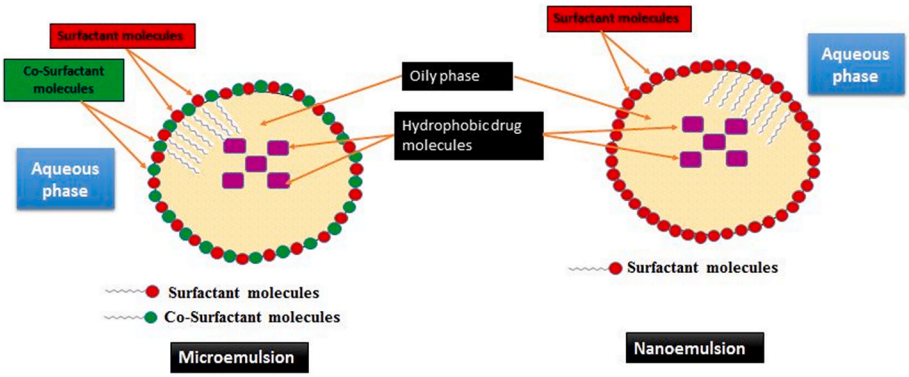

Fig. 4. Schematic diagram representing microemulsion and nanoemulsion droplets.

that niosomes significantly enhanced the extent of permeation of NAG into the skin compared to the drug's hydroalcoholic solution. Also, niosomes were used for topical delivery of KA and HQ by **Seiedi et al.,** [194] and **Divanbeygikermani et al.,** [195], in which niosomes managed to prevent the degradation of both drugs, and showed a sustained release effect inside the skin. Another study reported that loading ellagic acid into niosomes augmented its solubility and skin permeability as compared to its solution form [196]. **Buruschat and Amnuaikit,** [197] reported the ability of these nanovesicles to improve the stability and skin permeability of phenylethyl resorcinol for better skin whitening efficacy. Additionally, a study investigated the possibility of incorporating arbutin into niosomes, in which an enhancement in its skin permeability and whitening efficacy was noted [198].

3.1.3.4. Transfersomes. Transfersomes are ultra-deformable vesicular systems (UDVs) [190] consisting of lipids and biocompatible bilayer membrane softeners [199]. The lipid bilayer is constituted from phospholipids containing edge activators such as span 80, sodium cholate, or tween 80, enclosing an inner aqueous region.

Transfersomes proved to be efficient in topical delivery of many molecules. Being highly deformable vesicles they can squeeze themselves easily through the SC, following the transepidermal water flux and facilitating drug-skin deposition through their diffusion even through the smallest skin pores. This is a distinctive feature of transfersomes as compared to the nondeformable vesicles as liposomes and niosomes [143].

Celia et al., [200] formulated linoleic acid-loaded transfersomes, which significantly enhanced its stability and skin deposition compared to its hydroalcoholic solution. Transfersomes loaded phenylethyl resorcinol improved the solubility and stability of the drug, reduced its skin irritation, and showed higher tyrosinase inhibitory activity compared to the conventional liposomes [182]. Also, **Limsuwan et al.,** [201] reported the ability of these vesicles to augment the solubility and stability of phenylethyl resorcinol, thereby overcoming the limitations of its use as reflected by the conventional topical products. Furthermore, **Lee et al.,** [202] reported that loading niacinamide into transfersomes increased its skin permeation and whitening activity compared to conventional liposomes. Moreover, a study investigated the possibility of incorporating arbutin into transfersomes, in which an enhancement in its skin permeability and whitening efficacy was observed [203].

3.1.3.5. Ethosomes. Ethosomes are the ethanolic phospholipid ultradeformable vesicular systems [204] reported by Touitou et al. [205]. They are soft and malleable vesicles designed for enhancing the topical delivery of active substances. They are composed of a bilayer membrane of phospholipids, in addition to a high concentration of ethanol and water. They are mainly tailored to overcome the limitations of conventional liposomes, as liposomes permeation was shown to remain restricted to the upper skin layers, whereas ethosomes can fluidize and decrease the transition temperature of the SC lipids owing to their alcoholic content. This results in high drugs' diffusivity to deep skin layers, delineating them as more efficient systems for topical delivery [143].

Currently, a limited number of papers reported the use of ethosomes for topical delivery of skin hypopigmenting agents. *In-vitro* skin deposition and retention profiles demonstrated that ethosomes could enhance the transport of phenylethyl resorcinol across skin layers as well as establishing a drug depot inside the skin, hence promoting higher inhibitory potential towards tyrosinase and melanin content of the skin compared to conventional liposomal formulations [206]. Also, **Limsuwan et al.,** [201] reported the ability of these vesicles to augment the solubility and stability of phenylethyl resorcinol. Another study was conducted in an attempt to compare the characteristics of two UDVs namely; ethosomes and transfersomes and their effect on skin delivery of linoleic acid. It was observed that ethosomes could promote deeper skin penetration of linoleic acid compared to transfersomes owing to their ethanolic content which causes vesicle fluidity and disruption of SC lipids [200].

3.1.3.6. Invasomes. Invasomes are novel vesicular systems with enhanced dermal penetration compared to conventional liposomes. They are mainly composed of phospholipids (phosphatidylcholine), ethanol, and one or more of monoterpenes acting as penetration enhancers. Their penetration-enhancing activity is attributed to their ability to disrupt SC lipids and interact with intracellular proteins, which subsequently improve drugs' partitioning into the SC [207]. Ethanol enhances the ability of the vesicles to penetrate through the SC [208, 209] and assigns a net negative surface charge, thereby preventing vesicles coalescence due to electrostatic repulsion force [210]. Terpenes are naturally occurring volatile oils that are generally considered as safe molecules with low irritation potential at lower concentrations (1–5%), with reversible effect on SC lipids rendering them clinically acceptable penetration enhancers [211]. A synergistic effect between ethanol and terpenes on percutaneous absorption has been obviously noted [212].

Currently, limited research reported the use of invasomes for the topical delivery of skin hypopigmenting agents. A study aimed to compare the skin delivery of phenylethyl resorcinol using transfersomes, invasomes and conventional liposomes, and invasomes were proven to provide deeper phenylethyl resorcinol penetration through the skin owing to their high deformability by virtue of their ethanolic and terpenes content as compared to the other two vesicles. Also, it was observed that loading phenylethyl resorcinol into invasomes enhanced its inhibitory action towards tyrosinase enzyme up to 90% [182]. Similarly, **Limsuwan et al.,** [201] reported the ability of invasomes to augment the solubility and stability of phenylethyl resorcinol, thereby overcoming the limitations of its use in conventional topical formulations.

3.1.3.7. Penetration enhancer vesicles (PEVs). PEVs are vesicular systems containing penetration enhancers (PEs) along with their phospholipid bilayer, imparting flexibility to these vesicles [213]. PEs are molecules which can facilitate the penetrant (drug) absorption through skin layers by temporarily suppressing the impermeability of skin. Similar to edge activators present in transfersomes, PEs can interact with the proteins and lipids of skin-SC and modify their packing, resulting in an enhanced permeation across skin [214]. Also, they can interact with skin keratin and alter the solution properties of the SC, hence promoting high vesicle-drug partitioning through the SC [215]. The most common PEs exploited in the formulation of penetration enhancing vesicles include: ether alcohols as capryl-caproyl macrogol 8-glyceride (Labrasol®), diethylene glycol monoethyl ether (Transcutol®), fatty acids (e.g. oleic acid, etc.) and terpenes (e.g. L-menthol, cineole and limonene etc.) [216].

Schlich et al., [217] studied the use of PEVs for the topical delivery of skin hypopigmenting agents. They reported that loading 3-hydroxycoumarin (3-HC), with a strong inhibitory potential on tyrosinase into PEVs containing two PEs (namely; lauroylcholin chloride and monoolein) efficiently transported 3-HC to deep skin layers and inhibited the activity of tyrosinase enzyme in melanoma cells.

A schematic illustration of the different types of lipidic nanovesicular systems is represented in Fig. (5).

3.2. Polymer-based nanocarriers

Polymer-based nanocarriers are mostly composed of biodegradable and biocompatible polymers with a particle size ranging from 10 to 1000 nm [218]. Polymeric-based nanocarriers are classified into **a)** polymeric NPs which can be divided into natural polymeric NPs formulated from natural polymers such as chitosan, gelatin, alginate and albumin, and synthetic polymeric NPs which are classified into

biodegradable polymeric NPs made of biodegradable polymers such as poly (lactide-co-glycolide) (PLGA), and poly(ε-caprolactone) as well as non-biodegradable NPs made of polymers such as poly (methyl methacrylate), polyacrylates [219] and ethyl cellulose [220], **b)** polymeric vesicular systems such as polymerosomes and polymeric micelles (PMs) and **c)** drug-polymer conjugates such as cyclodextrans and dendrimers [221,222].

3.2.1. Polymeric nanoparticles

Depending on the preparation method, polymeric-NPs can form two types of structures: nanosphere and nanocapsule. Nanocapsules are reservoir type system and nanospheres are a matrix type [142]. Polymeric NPs are extensively exploited for topical delivery of drugs. They are able to alter the activity of drugs, delay and control their release and augment their adhesion or residence time in skin, thereby improving their penetration through deeper skin layers [223].

There are a number of mechanisms which control the release of drugs from polymeric NPs such as: (i) polymer swelling by hydration followed by the release of drugs through diffusion [223], (ii) enzymatic cleavage causing polymer degradation or rupture and drugs release from the inner core or (iii) drugs dissociation from the polymer and its desorption from the polymeric systems [224]. Among the numerous types of polymeric NPs; chitosan and ethyl cellulose NPs have been utilized for topical delivery of hypopigmenting agents.

3.2.1.1. Chitosan nanoparticles. Chitosan is the most prominent derivative of chitin, formed by detaching chitin's acetate moieties (deacetylation). It is almost derived from fungi cell walls or the shells of crustaceans such as those from crabs or prawns. It is a naturally occurring polysaccharide, highly basic, cationic, biocompatible, biodegradable, mucoadhesive polymer that is approved by the U.S. FDA for dermal drugs' delivery [225,226].

Currently, a few studies reported the use of chitosan NPs for topical delivery of skin hypopigmenting agents. **Park et al.,** [227] reported that loading glabridin into chitosan NPs improved its stability against various environmental factors, thus ameliorating its skin whitening activity. Also, two studies reported the incorporation of arbutin into chitosan NPs, in which an enhancement in its skin permeability and whitening efficacy was observed [228,229]. Moreover, a derivative of chitosan, named N-(2-hydroxyl) propyl-3-trimethyl ammonium chitosan chloride (HTCC), was surface decorated onto the liposomes, sequestering KA for an ameliorated skin whitening effect, in which results demonstrated that the level of melanin synthesis was significantly lessened along with enhanced penetrability in case of KA delivery *via* HTCC-coated liposomes compared to traditional liposomal formulation [230].

3.2.1.2. Ethyl cellulose nanoparticles. Ethyl cellulose is a synthetic, hydrophilic, non-biodegradable polymer which produces strong and tough films with high adhesion at lower concentrations [220]. **Duarah et al.,** [231] reported that the incorporation of vitamin C within ethyl cellulose polymeric nanoparticles augmented its stability, skin diffusivity and antityrosinase activity, hence promoting its skin lightening potential.

3.2.2. Polymeric vesicular systems

3.2.2.1. Polymeric micelles (PMs). PMs are self-assembled core-shell nanostructured systems consisting of amphiphilic block copolymers produced in aqueous solutions [232]. The arrangement of micelles in aqueous solutions takes place when the block copolymer concentration exceeds a specific concentration called the critical micelle concentration (CMC). At CMC, the hydrophobic fragments of the block copolymers begin to assemble to limit their contact with the molecules of water, resulting in the development of a vesicular or core-shell micellar composition. PMs are also among the effective delivery systems that ameliorate the transport of drugs through the skin. PMs were shown to augment drugs' aqueous solubility, prevent their degradation, increase skin hydration effect, as well as enhance their penetrability across different skin layers [233].

A recent study reported that loading glabridin into the amphiphilic cationic chitosan micelles enhanced its skin permeability with diminished irritation potential along with suppressing melanin synthesis [234].

3.2.2.2. Polymerosomes. Lipidic vesicular systems are well known as micro- or nano-sized spherical vesicles made up of phospholipids, which self-assemble to create the lipidic bilayer membranes [235]. Polymersomes are similar to lipidic vesicular nanocarriers, however the bilayer membrane is formed of an amphiphilic copolymer instead of phospholipids [236,237]. It has been reported that the typical polymerosomes' bilayer thickness (~10 nm) is larger than that of lipid vesicular ones (4–5 nm) and that the block copolymer's hydrophilic part represents from 20 up to 40 wt % [238]. No published work involved the application of polymerosomes for the treatment of melasma yet, however, they represent a promising futuristic means of delivery of hypopigmenting agents.

3.3. Inorganic nanocarriers

This type of nanocarriers is made of inorganic materials such as gold, silver, or iron oxide [239]. They generally comprise two regions; a core encompassing the inorganic ingredient such as silica, gold, iron oxide or quantum dots, and a shell containing the organic polymers (or metals), providing an appropriate substrate for biomacromolecules' conjugation or protecting the core region from the undesired physicochemical interactions occurring with the outer biological microenvironment [240]. They were proven effective for topical drug delivery, in which they could offer better mechanical and chemical stability, control drugs release through the skin, as well augment dermal adhesion or retention time, thus improving their permeation [241]. These show several merits not only in the cosmetics field, such as in anti-acne and anti-aging remedies, or other skin care products, yet also in treating several skin pathogenesis such as vitiligo and skin cancer [242]. They include fullerenes, carbon nanotubes, iron oxide, gold and silver nanoparticles and quantum dots. However, among these types, only fullerenes and gold NPs were reported to be utilized in the treatment of melasma till current date.

3.3.1. Fullerenes

Fullerenes (singular: Fullerene) are carbon-based spheroidal ball-shaped NPs. Currently, the so-called buckyballs or buckminster fullerenes C60, are the most adequate exploited molecules of that kind [142]. Their large internal volume allows small biomolecules to be incorporated, and their external surface can be chemically altered to help load drugs for effective skin delivery [243]. It was reported that once fullerenes come in contact with the skin, they can diffuse intercellularly, hence enhancing the penetrability of various molecules [244]. Accordingly, fullerenes are expected to be effective in loading and releasing active ingredients into different skin layers for augmented topical delivery. They are currently applied in cosmetics as potent antioxidants for skin aging, strong skin whitening and UV protective agents [245].

The C60-fullerene derivatives are utilized as advanced and powerful anti-oxidants that are able to protect skin effectively from UVA-promoted oxidative stress, which was reported to promote melanogenesis. It was observed that a hydrophilic polyvinylpyrrolidone (PVP)-wrapped fullerene derivative (called "Radical Sponge" due to its antioxidant potential) significantly inhibited UVA-induced melanogenesis in normal human epidermal melanocytes (NHEM) owing to its antityrosinase activity as compared to another two skin whitening agents, L-ascorbic acid and arbutin [246].

3.3.2. Gold nanoparticles (AuNPs)

AuNPs are small gold particles, which once dispersed in aqueous solutions, can also be known as colloidal gold [247]. The characteristics of AuNPs differ from their bulk form, as bulk gold is a yellow inert solid in nature whereas AuNPs are solutions with wine red color and an anti-oxidant activity [248]. Also, they possess various shapes such as sub-octahedral, spherical, tetrahedral, octahedral, decahedral, multiple twined, icosahedral multiple twined, irregular shape, nanorods, nanoprisms, nanotriangles and hexagonal platelets [247].

Recently, a research was published on the effectiveness of the extract of Panax ginseng leaves-AuNPs on the activity of tyrosinase in murine melanoma B16BL6 cell lines, tyrosinase gene expression as well as cellular melanin content. It was reported that these NPs were able to inhibit the activity of tyrosinase in a dose dependent manner compared to arbutin solution and suppress tyrosinase at the transcriptional level, suggesting its efficacy in skin whitening and decrease the melanin content in B16 cells induced with α-melanocyte-stimulating hormone [249].

Since melasma is categorized on the basis of histological types and pigment deposition depth into epidermal, dermal and mixed type, therefore the choice of the appropriate drug-loaded nanocarrier could be made on the basis of the specific skin-penetration mechanisms of the nanocarriers, particularly the depth of their penetration. For example, for the epidermal melasma type, it would be advised to use a nanocarrier which preferentially deposits in the epidermis, or creates a depot in the stratum corneum from which the drug could be released to the epidermis. In this case, it would be suggested to use nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, in addition to the non-deformable vesicular systems such as liposomes, niosomes and aspasomes, or alternatively polymeric nanocarriers. The aforementioned systems were reported to exhibit sufficient lipophilicity or rigidity which restricts their deep penetration, and allows their fusion with the skin lipids, hence preferentially depositing the drug in the stratum corneum and epidermal layers.

On the other hand, the inclusion of penetration enhancers such as surfactants, solubilizers such as ethanol led to a new generation of deep skin penetrating nanocarriers such as microemulsions, transfersomes, ethosomes, invasomes and penetration enhancer vesicles, which mostly allow the penetration of drugs into the dermis, and sometimes even to the systemic circulation achieving transdermal action. This trait would be well-suited for the treatment of dermal and mixed melasma types, in which a high skin-penetration power is required.

Therefore based on the authors' experience in treatment of dermatological diseases using nanocarriers, we need to emphasize the importance of formulation optimization in terms of composition and concentration of components, since they affect the physicochemical properties of the nanocarriers, and play a major role in dictating the depth of their penetration. An important characterization test to be considered is the *ex vivo* skin deposition that we reported in some of our previously published work [119,187,250–253], which is based on the quantification of the amount of drug in the individual skin layers after its extraction.

4. Conclusion

Melasma, mostly a dermatological facial disease, presents itself as one with utmost psychosocial relevance. Different chemical and instrumental approaches have been used for treatment of melasma. Nanotechnology represents a very promising strategy exploited for the encapsulation of different hypopigmenting agents in an attempt to augment their physico-chemical stability and enhance their penetrability to deeper skin layers for managing melasma of epidermal as well as dermal origin. Owing to their enhanced skin penetration, nanotechnology-based systems for the topical delivery of hypopigmenting agents will indeed be the first line of treatment where oral route can serve as adjunctive treatment modality in some cases.

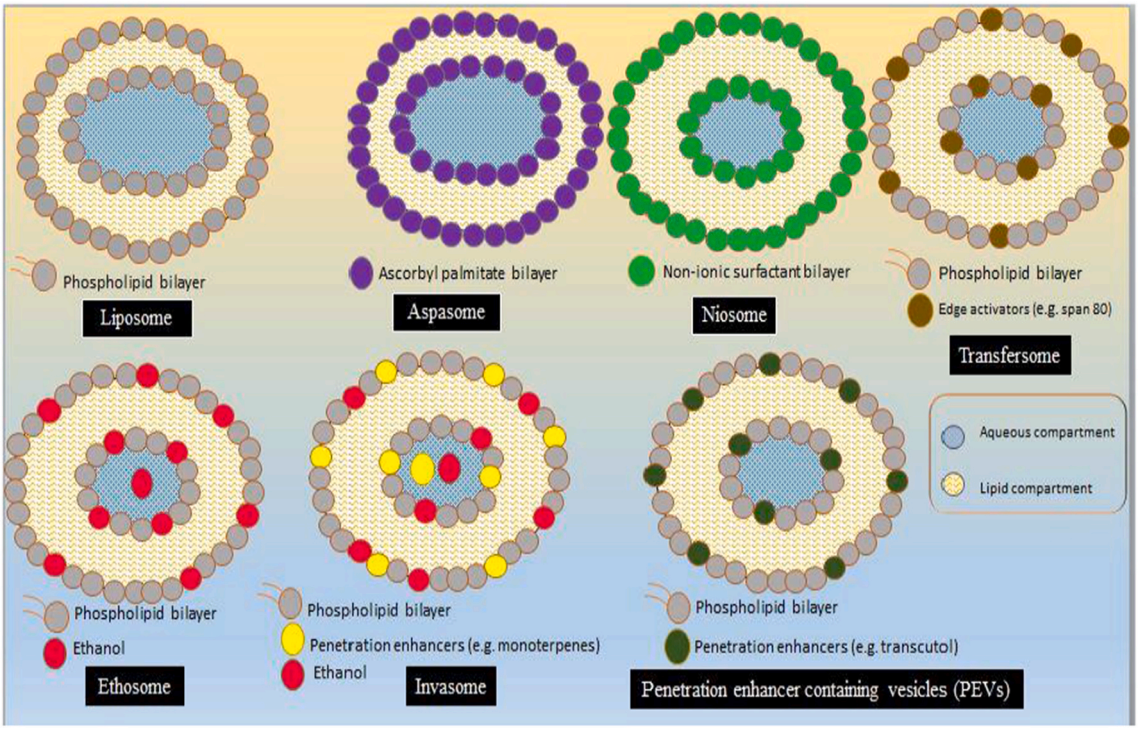

Fig. 5. Schematic diagram representing lipidic vesicular systems.

Ethics approval and consent to participate

Not applicable.

Human and animal rights

Not applicable.

Consent for publication

Not applicable.

Declaration of competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

References

[1] I.F.d.S. Videira, D.F.L. Moura, S. Magina, Mechanisms regulating melanogenesis, An. Bras. Dermatol. 88 (2013) 76–83.
[2] F. Milette, Review of the pigmentary system: physiology and pathophysiology by, in: James J. Nordlund, Raymond E. Boissy, Vincent J. Hearing, et al. (Eds.), Dermatol Pract Concept, vol. 4, 2014, pp. 89–91.
[3] R.E. Boissy, Melanosome transfer to and translocation in the keratinocyte, Exp. Dermatol. 12 (2003) 5–12.
[4] V. Virador, N. Matsunaga, J. Matsunaga, J. Valencia, R.J. Oldham, K. Kameyama, G.L. Peck, V.J. Ferrans, W.D. Vieira, Z.A. Abdel-Malek, Production of melanocyte-specific antibodies to human melanosomal proteins: expression patterns in normal human skin and in cutaneous pigmented lesions, Pigm. Cell Res. 14 (2001) 289–297.
[5] H. Ando, H. Kondoh, M. Ichihashi, V.J. Hearing, Approaches to identify inhibitors of melanin biosynthesis via the quality control of tyrosinase, J. Invest. Dermatol. 127 (2007) 751–761.
[6] R.A. Sturm, R.D. Teasdale, N.F. Box, Human pigmentation genes: identification, structure and consequences of polymorphic variation, Gene 277 (2001) 49–62.
[7] J.C. García-Borrón, F. Solano, Molecular anatomy of tyrosinase and its related proteins: beyond the histidine-bound metal catalytic center, Pigm. Cell Res. 15 (2002) 162–173.
[8] S. Briganti, E. Camera, M. Picardo, Chemical and instrumental approaches to treat hyperpigmentation, Pigm. Cell Res. 16 (2003) 101–110.
[9] L.D.B. Miot, H.A. Miot, M.G.d. Silva, M.E.A. Marques, Physiopathology of melasma, An. Bras. Dermatol. 84 (2009) 623–635.
[10] T.W. Tse, E. Hui, Tranexamic acid: an important adjuvant in the treatment of melasma, J. Cosmet. Dermatol. 12 (2013) 57–66.
[11] M. Rendon, M. Berneburg, I. Arellano, M. Picardo, Treatment of melasma, J. Am. Acad. Dermatol. 54 (2006) S272–S281.
[12] F. Prignano, J.P. Ortonne, G. Buggiani, T. Lotti, Therapeutical approaches in melasma, Dermatol. Clin. 25 (2007) 337–342.
[13] A.Y. Lee, An updated review of melasma pathogenesis, Dermatol. Sin. 32 (2014) 233–239.
[14] S.Y. He, C.E. McCulloch, W.J. Boscardin, M.-M. Chren, E. Linos, S.T. Arron, Self-reported pigmentary phenotypes and race are significant but incomplete predictors of Fitzpatrick skin phototype in an ethnically diverse population, J. Am. Acad. Dermatol. 71 (2014) 731–737.
[15] T.B. Fitzpatrick, The validity and practicality of sun-reactive skin types I through VI, Arch. Dermatol. 124 (1988) 869–871.
[16] R.M. Halder, P.K. Nootheti, Ethnic skin disorders overview, J. Am. Acad. Dermatol. 48 (2003) S143–S148.
[17] D. Hexsel, D.A. Lacerda, A.S. Cavalcante, C.A.M. Filho, C.L.P. Kalil, E.L. Ayres, L. Azulay Abulafia, M.B. Weber, M.S. Serra, N.F. Lopes, Epidemiology of melasma in B razilian patients: a multicenter study, Int. J. Dermatol. 53 (2014) 440–444.
[18] E. Nicolaidou, C. Antoniou, A.D. Katsambas, Origin, clinical presentation, and diagnosis of facial hypermelanoses, Dermatol. Clin. 25 (2007) 321–326.
[19] M. Vázquez, H. Maldonado, C. Benmamán, J.L. Sanchez, Melasma in men: a clinical and histologic study, Int. J. Dermatol. 27 (1988) 25–27.
[20] L.K. Gupta, M. Singhi, Wood's lamp, Indian J. Dermatol. Venereol. Leprol. 70 (2004) 131–135.
[21] H.Y. Kang, J.-P. Ortonne, What should be considered in treatment of melasma, Ann. Dermatol. 22 (2010) 373–378.
[22] Z.I. Shaikh, A.A. Mashood, Treatment of refractory melasma with combination of topical 5% magnesium ascorbyl phosphate and fluorescent pulsed light in Asian patients, Int. J. Dermatol. 53 (2014) 93–99.
[23] D. Bandyopadhyay, Topical treatment of melasma, Indian J. Dermatol. 54 (2009) 303–309.
[24] S.-K. Hann, S. Im, W.S. Chung, Pigmentary disorders in the south east, Dermatol. Clin. 25 (2007) 431–438.
[25] F.J. González, M. Martínez-Escanamé, R. Muñoz, B. Torres-Álvarez, B. Moncada, Diffuse reflectance spectrophotometry for skin phototype determination, Skin Res. Technol. 16 (2010) 397–400.
[26] I. Nishidate, K. Sasaoka, T. Yuasa, K. Niizeki, T. Maeda, Y. Aizu, Visualizing of skin chromophore concentrations by use of RGB images, Opt. Lett. 33 (2008) 2263–2265.
[27] B. Moncada, L.K. Sahagún-Sánchez, B. Torres-Álvarez, J.P. Castanedo-Cázares, J. D. Martínez-Ramírez, F.J. González, Molecular structure and concentration of melanin in the stratum corneum of patients with melasma, Photodermatol. Photoimmunol. Photomed. 25 (2009) 159–160.
[28] H.C. Lee, T.G. Thng, C.L. Goh, Oral tranexamic acid (TA) in the treatment of melasma: a retrospective analysis, J. Am. Acad. Dermatol. 75 (2016) 385–392.
[29] M.S. Kim, S.H. Bang, J.H. Kim, H.J. Shin, J.H. Choi, S.E. Chang, Tranexamic acid diminishes laser-induced melanogenesis, Ann. Dermatol. 27 (2015) 250–256.
[30] O.A. Ogbechie-Godec, N. Elbuluk, Melasma: an up-to-date comprehensive review, Dermatol. Ther. 7 (2017) 305–318.
[31] Y. Li, Q. Sun, Z. He, L. Fu, C. He, Y. Yan, Treatment of melasma with oral administration of compound tranexamic acid: a preliminary clinical trial, J. Eur. Acad. Dermatol. Venereol. 28 (2014) 393–394.
[32] S. Wu, H. Shi, H. Wu, S. Yan, J. Guo, Y. Sun, L. Pan, Treatment of melasma with oral administration of tranexamic acid, Aesthetic Plast. Surg. 36 (2012) 964–970.
[33] H.R. Bala, S. Lee, C. Wong, A.G. Pandya, M. Rodrigues, Oral tranexamic acid for the treatment of melasma: a review, Dermatol. Surg. 44 (2018) 814–825.
[34] H.H. Cho, M. Choi, S. Cho, J.H. Lee, Role of oral tranexamic acid in melasma patients treated with IPL and low fluence QS Nd: YAG laser, J. Dermatol. Treat. 24 (2013) 292–296.
[35] A.M. Ahmed, L. Lopez, F. Perese, R. Vasquez, L.S. Hynan, B. Chong, A.G. Pandya, A randomized, double-blinded, placebo-controlled trial of oral Polypodium leucotomos extract as an adjunct to sunscreen in the treatment of melasma, JAMA Dermatol 149 (2013) 981–983.
[36] S.Z. Choudhry, N. Bhatia, R. Ceilley, F. Hougeir, R. Lieberman, I. Hamzavi, H. W. Lim, Role of oral Polypodium leucotomos extract in dermatologic diseases: a review of the literature, J. Drugs Dermatol. JDD 13 (2014) 148–153.
[37] N. Arjinpathana, P. Asawanonda, Glutathione as an oral whitening agent: a randomized, double-blind, placebo-controlled study, J. Dermatol. Treat. 23 (2012) 97–102.
[38] C.L. Goh, S.Y. Chuah, S. Tien, G. Thng, M.A. Vitale, A. Delgado-Rubin, Double-blind, placebo-controlled trial to evaluate the effectiveness of polypodium leucotomos extract in the treatment of melasma in asian skin: a pilot study, J Clin Aesthet Dermatol 11 (2018) 14–19.
[39] A.F. Alexis, P. Blackcloud, Natural ingredients for darker skin types: growing options for hyperpigmentation, J. Drugs Dermatol. JDD 12 (2013) s123–s127.
[40] S. Sonthalia, A.K. Jha, A. Lallas, G. Jain, D. Jakhar, Glutathione for skin lightening: a regnant myth or evidence-based verity? Dermatol. Pract. Concept. 8 (2018) 15–21.
[41] P.W. Hsieh, S.A. Al-Suwayeh, C.L. Fang, C.F. Lin, C.C. Chen, J.Y. Fang, The co-drug of conjugated hydroquinone and azelaic acid to enhance topical skin targeting and decrease penetration through the skin, Eur. J. Pharm. Biopharm. 81 (2012) 369–378.
[42] Z.D. Draelos, Skin lightening preparations and the hydroquinone controversy, Dermatol. Ther. 20 (2007) 308–313.
[43] A.L. Haddad, L.F. Matos, F. Brunstein, L.M. Ferreira, A. Silva, D. Costa Jr., A clinical, prospective, randomized, double-blind trial comparing skin whitening complex with hydroquinone vs. placebo in the treatment of melasma, Int. J. Dermatol. 42 (2003) 153–156.
[44] A.D. Katsambas, A.J. Stratigos, Depigmenting and bleaching agents: coping with hyperpigmentation, Clin. Dermatol. 19 (2001) 483–488.
[45] T.W. Tse, Hydroquinone for skin lightening: safety profile, duration of use and when should we stop? J. Dermatol. Treat. 21 (2010) 272–275.
[46] S. Nanda, C. Grover, B.S. Reddy, Efficacy of hydroquinone (2%) versus tretinoin (0.025%) as adjunct topical agents for chemical peeling in patients of melasma, Dermatol. Surg. 30 (2004) 385–389.
[47] R. Monteiro, B. Kishore, R. Bhat, D. Sukumar, J. Martis, H. Ganesh, A comparative study of the efficacy of 4% hydroquinone vs 0.75% kojic acid cream in the treatment of facial melasma, Indian J. Dermatol. 58 (2013) 157–174.
[48] S. Ennes, R. Paschoalick, M. Alchorne, A double-blind, comparative, placebo-controlled study of the efficacy and tolerability of 4% hydroquinone as a depigmenting agent in melasma, J. Dermatol. Treat. 11 (2000) 173–179.
[49] V. Zawar, S. Mhaskar, Exogenous ochronosis following hydroquinone for melasma, J. Cosmet. Dermatol. 3 (2004) 234–236.
[50] J.S. Yu, A.K. Kim, Effect of combination of taurine and azelaic acid on antimelanogenesis in murine melanoma cells, J. Biomed. Sci. 17 (2010) 1–5.
[51] Q.H. Nguyen, T.P. Bui, Azelaic acid: pharmacokinetic and pharmacodynamic properties and its therapeutic role in hyperpigmentary disorders and acne, Int. J. Dermatol. 34 (1995) 75–84.
[52] R. Halder, G. Richards, Topical agents used in the management of hyperpigmentation, Skin Therapy Lett 9 (2004) 1–3.
[53] N.J. Lowe, D. Rizk, P. Grimes, M. Billips, S. Pincus, Azelaic acid 20% cream in the treatment of facial hyperpigmentation in darker-skinned patients, Clin. Therapeut. 20 (1998) 945–959.
[54] M. Garcia-Lopez, Double-blind comparison of azelaic acid and hydroquinone in the treatment of melasma, Acta Derm. Venereol. 143 (1989) 58–61.

[55] L.M. Baliña, K. Graupe, The treatment of melasma 20% azelaic acid versus 4% hydroquinone cream, Int. J. Dermatol. 30 (1991) 893–895.
[56] C. Lynde, J. Kraft, C. Lynde, Topical treatments for melasma and postinflammatory hyperpigmentation, Skin Therapy Lett 11 (2006) 1–12.
[57] V. Kahn, Effect of kojic acid on the oxidation of DL-DOPA, norepinephrine, and dopamine by mushroom tyrosinase, Pigm. Cell Res. 8 (1995) 234–240.
[58] R. Sarkar, P. Arora, K.V. Garg, Cosmeceuticals for hyperpigmentation: what is available? J. Cutan. Aesthetic Surg. 6 (2013) 4–11.
[59] J.T.E. Lim, Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid, Dermatol. Surg. 25 (1999) 282–284.
[60] A. Garcia, J.E. Fulton Jr., The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions, Dermatol. Surg. 22 (1996) 443–447.
[61] M. Nakagawa, K. Kawai, K. Kawai, Contact allergy to kojic acid in skin care products, Contact Dermatitis 32 (1995) 9–13.
[62] A.K. Gupta, M.D. Gover, K. Nouri, S. Taylor, The treatment of melasma: a review of clinical trials, J. Am. Acad. Dermatol. 55 (2006) 1048–1065.
[63] J.P. Ortonne, Retinoid therapy of pigmentary disorders, Dermatol. Ther. 19 (2006) 280–288.
[64] D. Rigopoulos, S. Gregoriou, A. Katsambas, Hyperpigmentation and melasma, J. Cosmet. Dermatol. 6 (2007) 195–202.
[65] C. Griffiths, L. Finkel, C. Ditre, T. Hamilton, C. Ellis, J. Voorhees, Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial, Br. J. Dermatol. 129 (1993) 415–421.
[66] C.K. Kimbrough-Green, C.E. Griffiths, L.J. Finkel, T.A. Hamilton, S.M. Bulengo-Ransby, C.N. Ellis, J.J. Voorhees, Topical retinoic acid (tretinoin) for melasma in black patients: a vehicle-controlled clinical trial, Arch. Dermatol. 130 (1994) 727–733.
[67] I. Ghersetich, M. Troiano, B. Brazzini, M. Arunachalam, T. Lotti Melasma, Treatment with 10% tretinoin peeling mask, J. Cosmet. Dermatol. 9 (2010) 117–121.
[68] A.T.A. Al Hassan, N.C. Abdul-Zahra, Combination therapy with hydroquinone, tretinoin and steroid for treatment of melasma in Iraqi patients, KPHRS (2011) 218–227.
[69] S. Dogra, A.J. Kanwar, D. Parsad, Adapalene in the treatment of melasma: a preliminary report, J. Dermatol. 29 (2002) 539–540.
[70] S.Y. Lee, N. Baek, T.-g. Nam, Natural, semisynthetic and synthetic tyrosinase inhibitors, J. Enzym. Inhib. Med. Chem. 31 (2016) 1–13.
[71] M. Jarratt, Mequinol 2%/tretinoin 0.01% solution: an effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines, Cutis 74 (2004) 319–322.
[72] J. Keeling, L. Cardona, A. Benitez, R. Epstein, M. Rendon, Mequinol 2%/tretinoin 0.01% topical solution for the treatment of melasma in men: a case series and review of the literature, Cutis 81 (2008) 179–183.
[73] M. Picardo, M. Carrera, New and experimental treatments of cloasma and other hypermelanoses, Dermatol. Clin. 25 (2007) 353–362.
[74] P. Migas, M. Krauze-Baranowska, The significance of arbutin and its derivatives in therapy and cosmetics, Phytochem Lett 13 (2015) 35–40.
[75] S. Choi, Y.I. Park, S.K. Lee, J.E. Kim, M.H. Chung, Aloesin inhibits hyperpigmentation induced by UV radiation, Clin. Exp. Dermatol. 27 (2002) 513–515.
[76] I. Ertam, B. Mutlu, I. Unal, S. Alper, B. KivÇak, O. Ozer, Efficiency of ellagic acid and arbutin in melasma: a randomized, prospective, open-label study, J. Dermatol. 35 (2008) 570–574.
[77] S. Chawla, M. DeLong, M. Visscher, R. Wickett, P. Manga, R. Boissy, Mechanism of tyrosinase inhibition by deoxyArbutin and its second-generation derivatives, Br. J. Dermatol. 159 (2008) 1267–1274.
[78] R. Mov, Comparative efficacy and safety of deoxyarbutin, a new tyrosinase-inhibiting agent, J. Cosmet. Sci. 57 (2006) 291–308.
[79] R.E. Boissy, M. Visscher, M.A. DeLong DeoxyArbutin, A novel reversible tyrosinase inhibitor with effective in vivo skin lightening potency, Exp. Dermatol. 14 (2005) 601–608.
[80] J. Ebanks, R. Wickett, R. Boissy, Mechanisms regulating skin pigmentation: the rise and fall of complexion coloration, Int. J. Mol. Sci. 10 (2009) 4066–4087.
[81] K. Jimbow, N-acetyl-4-S-cysteaminylphenol as a new type of depigmenting agent for the melanoderma of patients with melasma, Arch. Dermatol. 127 (1991) 1528–1534.
[82] L.E. Espinal-Perez, B. Moncada, J.P. Castanedo-Cazares, A double-blind randomized trial of 5% ascorbic acid vs. 4% hydroquinone in melasma, Int. J. Dermatol. 43 (2004) 604–607.
[83] S.W. Hwang, D.J. Oh, D. Lee, J.W. Kim, S.W. Park, Clinical efficacy of 25% L-ascorbic acid (C'ensil) in the treatment of melasma, J. Cutan. Med. Surg. 13 (2009) 74–81.
[84] S.W. Hwang, D.J. Oh, D. Lee, J.W. Kim, S.W. Park, Clinical efficacy of 25% L-ascorbic acid (C'ensil) in the treatment of melasma, J. Cutan. Med. Surg. 13 (2009) 74–81.
[85] S. Kobayashi, M. Takehana, S. Itoh, E. Ogata, Protective effect of magnesium-L-ascorbyl-2 phosphate against skin damage induced by UVB irradiation, Photochem. Photobiol. 64 (1996) 224–228.
[86] K. Kameyama, C. Sakai, S. Kondoh, K. Yonemoto, S. Nishiyama, M. Tagawa, T. Murata, T. Ohnuma, J. Quigley, A. Dorsky, Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis in vitro and in vivo, J. Am. Acad. Dermatol. 34 (1996) 29–33.
[87] A. Greatens, T. Hakozaki, A. Koshoffer, H. Epstein, S. Schwemberger, G. Babcock, D. Bissett, H. Takiwaki, S. Arase, R.R. Wickett, Effective inhibition of melanosome transfer to keratinocytes by lectins and niacinamide is reversible, Exp. Dermatol. 14 (2005) 498–508.
[88] T. Hakozaki, L. Minwalla, J. Zhuang, M. Chhoa, A. Matsubara, K. Miyamoto, A. Greatens, G. Hillebrand, D. Bissett, R. Boissy, The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer, Br. J. Dermatol. 147 (2002) 20–31.
[89] J. Navarrete-Solís, J. Castanedo-Cázares, B. Torres-Álvarez, C. Oros-Ovalle, C. Fuentes-Ahumada, F. González, J. Martínez-Ramírez, B. Moncada, A double-blind, randomized clinical trial of niacinamide 4% versus hydroquinone 4% in the treatment of melasma, Dermatol Res Pract 2011 (2011) 1–5.
[90] T. Yokota, H. Nishio, Y. Kubota, M. Mizoguchi, The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation, Pigm. Cell Res. 11 (1998) 355–361.
[91] M. Amer, M. Metwalli, Topical liquiritin improves melasma, Int. J. Dermatol. 39 (2000) 299–301.
[92] S. Zubair, G. Mujtaba, Comparison of efficacy of topical 2% liquiritin, topical 4% liquiritin and topical 4% hydroquinone in the management of melasma, JPAD 19 (2016) 158–163.
[93] S. Akram, F. Sattar, R. Tahir, G. Mujtaba, Efficacy of topical 4% liquiritin compared with topical 4% liquiritin mixed in 5% ascorbic acid in the treatment of melasma, JPAD 23 (2016) 149–152.
[94] F. Solano, S. Briganti, M. Picardo, G. Ghanem, Hypopigmenting agents: an updated review on biological, chemical and clinical aspects, Pigment cell res 19 (2006) 550–571.
[95] Y.J. Kim, H. Uyama, Tyrosinase inhibitors from natural and synthetic sources: structure, inhibition mechanism and perspective for the future, Cell. Mol. Life Sci. 62 (2005) 1707–1723.
[96] W. Zhu, J. Gao, The use of botanical extracts as topical skin-lightening agents for the improvement of skin pigmentation disorders, J. Invest. Dermatol. Symp. Proc. 13 (2008) 20–24.
[97] S. Parvez, M. Kang, H.S. Chung, H. Bae, Naturally occurring tyrosinase inhibitors: mechanism and applications in skin health, cosmetics and agriculture industries, Phytother Res. 21 (2007) 805–816.
[98] A. Menter, Rationale for the use of topical corticosteroids in melasma, J. Drugs Dermatol. JDD 3 (2004) 169–174.
[99] F.C. Victor, J. Gelber, B. Rao Melasma, a review, JCMS. 8 (2004) 97–102.
[100] K.V. Godse, Triple combination of hydroquinone, tretinoin and mometasone furoate with glycolic acid peels in melasma, Indian J. Dermatol. 54 (2009) 92–93.
[101] P. Kulhalli, T. Chevli, R. Karnik, M. Sheth, N. Mulgaonkar, Comparative potency of formulations of mometasone furoate in terms of inhibition of˙PIRHR'in the forearm skin of normal human subjects measured with laser Doppler velocimetry, Indian J. Dermatol. Venereol. Leprol. 71 (2005) 170–174.
[102] R. Chan, K. Park, M. Lee, E. Lee, S. Chang, Y. Leow, A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma, Br. J. Dermatol. 159 (2008) 697–703.
[103] H. Torok, S. Taylor, L. Baumann, T. Jones, J. Wieder, N. Lowe, M. Jarret, P. Rich, D. Pariser, E. Tschen, A large 12-month extension study of an 8-week trial to evaluate the safety and efficacy of triple combination (TC) cream in melasma patients previously treated with TC cream or one of its dyads, J. Drugs Dermatol. JDD 4 (2005) 592–597.
[104] J. Na, S. Choi, S. Yang, H. Choi, H. Kang, K.C. Park, Effect of tranexamic acid on melasma: a clinical trial with histological evaluation, Am. J. Clin. Dermatol. 27 (2013) 1035–1039.
[105] S. Saka, G.R.R. Rao, R. BKomaram, S. Kotha, R. Tatavarthi, L. Chitturi, Efficacy of 10% topical tranexamic acid in melasma - a randomized placebo-controlled split face study, IJPSR 10 (2019) 2583–2586.
[106] P. Kanechorn Na Ayuthaya, N. Niumphradit, A. Manosroi, A. Nakakes, Topical 5% tranexamic acid for the treatment of melasma in Asians: a double-blind randomized controlled clinical trial, Cosmet Laser Ther 14 (2012) 150–154.
[107] B. Ebrahimi, F.F. Naeini, Topical tranexamic acid as a promising treatment for melasma, J. Res. Med. Sci. 19 (2014) 753–757.
[108] V.N. Sehgal, P. Verma, G. Srivastava, A.K. Aggarwal, S. Verma, Melasma: treatment strategy, J. Cosmet. Laser Ther. 13 (2011) 265–279.
[109] A.M. Kligman, I. Willis, A new formula for depigmenting human skin, Arch. Dermatol. 111 (1975) 40–48.
[110] E. Crocco, J. Veasey, M. Boin, R. Lellis, R. Alves, A novel cream formulation containing nicotinamide 4%, arbutin 3%, bisabolol 1%, and retinaldehyde 0.05% for treatment of epidermal melasma, Cutis 96 (2015) 337–342.
[111] M. Downie, Camouflage therapy, Australas. J. Dermatol. 25 (1984) 89–91.
[112] S. Holme, P. Beattie, C. Fleming, Cosmetic camouflage advice improves quality of life, Br. J. Dermatol. 147 (2002) 946–949.
[113] C. Antoniou, C. Stefanaki, Cosmetic camouflage, J. Cosmet. Dermatol. 5 (2006) 297–301.
[114] M. El-Kayal, M. Nasr, S. Elkheshen, N. Mortada, Colloidal (-)-epigallocatechin-3-gallate vesicular systems for prevention and treatment of skin cancer: a comprehensive experimental study with preclinical investigation, Eur. J. Pharmaceut. Sci. 137 (2019) 1–58.
[115] M. Shaaban, M. Nasr, A.A. Tawfik, M. Fadel, O. Sammour, Novel bergamot oil nanospanlastics combined with PUVB therapy as a clinically translatable approach for vitiligo treatment, Drug Deliv Transl Res. (2019) 1–11.
[116] S.A. Ramez, M.M. Soliman, M. Fadel, F. Nour El-Deen, M. Nasr, E.R. Youness, D. M. Aboel-Fadl, Novel methotrexate soft nanocarrier/fractional erbium YAG laser combination for clinical treatment of plaque psoriasis, Artif Cell Nanomed B 46 (2018) 996–1002.

[117] R. Al-Karaki, A. Awadallah, H.M. Tawfeek, M. Nasr, Preparation, characterization and cytotoxic activity of novel oleuropein microemulsion against HCT-116 colon cancer cells, Der Pharma Chem. 53 (2020) 1118–1121.
[118] O. Abu-Azzam, M. Nasr, In vitro anti-inflammatory potential of phloretin microemulsion as a new formulation for prospective treatment of vaginitis, Pharmaceut. Dev. Technol. (2020 May 13) 1–6, https://doi.org/10.1080/10837450.2020.1764032, epub ahead of print.
[119] M. Nasr, S. Abdel-Hamid, Optimizing the dermal accumulation of a tazarotene microemulsion using skin deposition modeling, Drug Dev. Ind. Pharm. 42 (2016) 636–643.
[120] S. Khanna, O. Katre, S. Drabhu, Lecithinized microemulsion for topical delivery of tretionoin, Int. J. Drug Dev. Res. 2 (2010) 711–719.
[121] A.A. Badawi, S.A. Nour, W.S. Sakran, S.M.S. El-Mancy, Preparation and evaluation of microemulsion systems containing salicylic acid, AAPS PharmSciTech 10 (2009) 1081–1084.
[122] A.S. Khodakiya, J. Chavada, N. Jivani, B.N. Patel, M.S. Khodakiya, A.P. Ramoliya, Microemulsions as enhanced drug delivery carrier: an overview, Am. J. PharmTech Res. 2 (2012) 206–226.
[123] N. Pakpayat, F. Nielloud, R. Fortuné, C. Tourne-Peteilh, A. Villarreal, I. Grillo, B. Bataille, Formulation of ascorbic acid microemulsions with alkyl polyglycosides, Eur. J. Pharm. Biopharm. 72 (2009) 444–452.
[124] R. Parveen, N. Akhtar, T. Mahmood, Topical microemulsion containing Punica granatum extract: its control over skin erythema and melanin in healthy Asian subjects, Postepy Dermatol Alergol 31 (2014) 351–355.
[125] M. Gallarate, M. Carlotti, M. Trotta, A. Grande, C. Talarico, Photostability of naturally occurring whitening agents in cosmetic microemulsions, J. Cosmet. Sci. 55 (2004) 139–148.
[126] Y.H. Tsai, K.F. Lee, Y.B. Huang, C.T. Huang, P.C. Wu, In vitro permeation and in vivo whitening effect of topical hesperetin microemulsion delivery system, Int. J. Pharm. 388 (2010) 257–262.
[127] L. Nazernezhad, A. Salimi, Preparation and evaluation of topical microemulsions containing hydroquinone, Res Pharm Sci 7 (2012) S248.
[128] A. Salimi, Enhanced stability and dermal delivery of hydroquinone using microemulsion-based system, Asian J. Pharm. 11 (2018) S773–S781.
[129] S. Surini, T. Mellani, Formulation and physical evaluation of microemulsion and w/o/w multiple emulsions dosage forms with alpha arbutin, lactic acid, and niacinamide as skin-whitening cosmetics, Int. J. Appl. Pharm. 9 (2017) 67–70.
[130] W. Poomanee, W. Chaiyana, R.R. Wickett, P. Leelapornpisid, Stability and solubility improvement of Sompoi (Acacia concinna Linn.) pod extract by topical microemulsion, Asian J. Pharm. Sci. 12 (2017) 386–393.
[131] A. Olejnik, A. Glowka, I. Nowak, Release studies of undecylenoyl phenylalanine from topical formulations, Saudi Pharmaceut. J. 26 (2018) 709–718.
[132] S. Thungmungmee, K. Ingkaninan, P. Tuntijarukorn, T. Pitaksuteepong, Skin lightening microemulsion formulation of Broussonetia papyrifera leaf extract and human skin irritation test, JIN 2 (2013) 71–76.
[133] C.C. Lin, Y.C. Lin, M.Y. Gao, Y.P. Fang, In vitro evaluation of permeation ability and in vivo whitening of ascorbic acid 2-glucoside in microemulsion, Int. J. Pharma Sci. Res. 3 (2016) 114–119.
[134] K.T. Kim, M.H. Kim, J.H. Park, J.Y. Lee, H.J. Cho, I.S. Yoon, D.D. Kim, Microemulsion-based hydrogels for enhancing epidermal/dermal deposition of topically administered 20 (S)-protopanaxadiol: in vitro and in vivo evaluation studies, J Ginseng Res 42 (2018) 512–523.
[135] R.K. Mishra, G. Soni, R. Mishra Nanoemulsion, A novel drug delivery tool, Int. J. Pharm. Rev. Res. 3 (2014) 32–43.
[136] D. Shaker, R. Ishak, A. Ghoneim, M. Elhuoni Nanoemulsion, A review on mechanisms for the transdermal delivery of hydrophobic and hydrophilic drugs, Sci. Pharm. 87 (2019) 17–51.
[137] M. Nasr, Development of an optimized hyaluronic acid-based lipidic nanoemulsion co-encapsulating two polyphenols for nose to brain delivery, Drug Deliv. 23 (2016) 1444–1452.
[138] A. Gupta, H.B. Eral, T.A. Hatton, P.S. Doyle, Nanoemulsions: formation, properties and applications, Soft Matter 12 (2016) 2826–2841.
[139] A. Ismail, M. Nasr, O. Sammour, Nanoemulsion as a feasible and biocompatible carrier for ocular delivery of travoprost: improved pharmacokinetic/pharmacodynamic properties, Int. J. Pharm. 583 (2020 Jun 15) 119402, https://doi.org/10.1016/j.ijpharm.2020.119402. Epub 2020 May 5.
[140] Z.H. Mahdi, N.K. Maraie, Overview on nanoemulsion as a recently developed approach in drug nanoformulation, Res. J. Pharm. Technol. 12 (2019) 5554–5560.
[141] R. Aboofazeli, Nanometric-scaled emulsions (nanoemulsions), Iran, J. Pharm. (Lahore) 9 (2010) 325–326.
[142] B. Sharma, A. Sharma, Future prospect of nanotechnology in development of anti-ageing formulations, Int. J. Pharm. Pharmaceut. Sci. 4 (2012) 57–66.
[143] S. Hatem, M. Nasr, S.A. Elkheshen, A.S. Geneidi, Recent advances in antioxidant cosmeceutical topical delivery, Curr. Drug Deliv. 15 (2018) 953–964.
[144] C.W. Hsieh, P.H. Li, I.C. Lu, T.H. Wang, Preparing glabridin-in-water nanoemulsions by high pressure homogenization with response surface methodology, J. Oleo Sci. 61 (2012) 483–489.
[145] C. Liu, J. Hu, H. Sui, Q. Zhao, X. Zhang, W. Wang, Enhanced skin permeation of glabridin using eutectic mixture-based nanoemulsion, Drug Deliv Transl Res 7 (2017) 325–332.
[146] S.N.A. Syed Azhar, S.E. Ashari, N. Salim, Development of a kojic monooleate-enriched oil-in-water nanoemulsion as a potential carrier for hyperpigmentation treatment, Int. J. Nanomed. 13 (2018) 6465–6479.
[147] R.P. Tofani, Y.C. Sumirtapura, S.T. Darijanto, Formulation, characterisation, and in vitro skin diffusion of nanostructured lipid carriers for deoxyarbutin compared to a nanoemulsion and conventional cream, Sci. Pharm. 84 (2016) 634–645.
[148] S. Al-Edresi, S. Baie, Formulation and stability of whitening VCO-in-water nano-cream, Int. J. Pharm. 373 (2009) 174–178.
[149] S. Buranajaree, P. Donsing, R. Jeenapongsa, J. Viyoch, Depigmenting action of a nanoemulsion containing heartwood extract of Artocarpus incisus on UVB-induced hyperpigmentation in C57BL/6 mice, J. Cosmet. Sci. 62 (2011) 1–14.
[150] S. Berlitz, D.D. Villa, L. Inácio, S. Davies, K. Zatta, S. Guterres, I. Külkamp-Guerreiro, Azelaic acid-loaded nanoemulsion with hyaluronic acid–a new strategy to treat hyperpigmentary skin disorders, Drug Dev. Ind. Pharm. 45 (2019) 642–650.
[151] E.A. Bseiso, M. Nasr, O. Sammour, N.A. Abd El Gawad, Recent advances in topical formulation carriers of antifungal agents, Indian J. Dermatol. Venereol. Leprol. 81 (2015) 457–463.
[152] M. Hanumanaik, S.K. Patel, K.R. Sree, Solid lipid nanoparticles; A review, Int. J. Pharma Sci. Res. 4 (2013) 928–940.
[153] S.S. Amer, M. Nasr, W. Mamdouh, O. Sammour, Insights on the use of nanocarriers for acne alleviation, Curr. Drug Deliv. 16 (2019) 18–25.
[154] A.A. Hajare, S.S. Mali, A.A. Ahir, J.D. Thorat, S.S. Salunkhe, S.J. Nadaf, N. M. Bhatia, K. Chitranagari, Lipid nanoparticles: a modern formulation approach in topical drug delivery systems, J Adv Drug Deliv 1 (2014) 30–37.
[155] J.W. So, S. Kim, J.S. Park, B.H. Kim, S.H. Jung, S.C. Shin, C.W. Cho, Preparation and evaluation of solid lipid nanoparticles with JSH18 for skin-whitening efficacy, Pharmaceut. Dev. Technol. 15 (2010) 415–420.
[156] J. Marto, C. Sangalli, P. Capra, P. Perugini, A. Ascenso, L. Goncalves, H. Ribeiro, Development and characterization of new and scalable topical formulations containing N-acetyl-d-glucosamine-loaded solid lipid nanoparticles, Drug Dev. Ind. Pharm. 43 (2017) 1792–1800.
[157] M. Al-Amin, J. Cao, M. Naeem, H. Banna, M.S. Kim, Y. Jung, H.Y. Chung, H. R. Moon, J.W. Yoo, Increased therapeutic efficacy of a newly synthesized tyrosinase inhibitor by solid lipid nanoparticles in the topical treatment of hyperpigmentation, Drug Des. Dev. Ther. 10 (2016) 3947–3957.
[158] S. Ghanbarzadeh, R. Hariri, M. Kouhsoltani, J. Shokri, Y. Javadzadeh, H. Hamishehkar, Enhanced stability and dermal delivery of hydroquinone using solid lipid nanoparticles, Colloids Surf., B 136 (2015) 1004–1010.
[159] R.B. Rigon, N. Fachinetti, P. Severino, M.H. Santana, M. Chorilli, Skin delivery and in vitro biological evaluation of trans-resveratrol-loaded solid lipid nanoparticles for skin disorder therapies, Molecules 21 (2016) 116–129.
[160] S. Shrotriya, N. Ranpise, P. Satpute, B. Vidhate, Skin targeting of curcumin solid lipid nanoparticles-engrossed topical gel for the treatment of pigmentation and irritant contact dermatitis, Artif Cells Nanomed Biotechnol 46 (2018) 1471–1482.
[161] I.N. Ayuningtyas, A. Mun'Im, S. Sutriyo, The study of safety and skin whitening efficacy of melinjo (Gnetum gnemon L.) seed extract-loaded lipid particle gel, Pharmacogn. Res. 10 (2018) 432–436.
[162] S. Dzulhi, E. Anwar, T. Formulation Nurhayati, Characterization and in vitro skin penetration of green tea (camellia sinensis L.) leaves extract-loaded solid lipid nanoparticles, J. Appl. Pharmaceut. Sci. 8 (2018) 57–62.
[163] N. Tokton, A. Ounaroon, P. Panichayupakaranant, W. Tiyaboonchai, Development of ellagic acid rich pomegranate peel extract loaded nanostructured lipid carriers (NLCS), Int. J. Pharm. Pharmaceut. Sci. 6 (2014) 259–265.
[164] B.S. Kim, Y.G. Na, J.H. Choi, I. Kim, E. Lee, S.Y. Kim, J.Y. Lee, C.W. Cho, The improvement of skin whitening of phenylethyl resorcinol by nanostructured lipid carriers, Nanomat (Basel) 7 (2017) 241–257.
[165] L. Aliasgharlou, S. Ghanbarzadeh, H. Azimi, M.H. Zarrintan, H. Hamishehkar, Nanostructured lipid carrier for topical application of N-acetyl glucosamine, Adv. Pharmaceut. Bull. 6 (2016) 581–587.
[166] N. Fachinetti, R.B. Rigon, J.O. Eloy, M.R. Sato, K.C. Dos Santos, M. Chorilli, Comparative study of glyceryl behenate or polyoxyethylene 40 stearate-based lipid carriers for trans-resveratrol delivery: development, characterization and evaluation of the in vitro tyrosinase inhibition, AAPS PharmSciTech 19 (2018) 1401–1409.
[167] W. Pey-Shiuan, L. Chih-Hung, K. Yi-Ching, L. Chih-Chien, Formulation and characterization of hydroquinone nanostructured lipid carriers by homogenization emulsification method, J. Nanomater. 2017 (2017) 1–7.
[168] M. Uner, S.A. Wissing, G. Yener, R.H. Muller, Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for application of ascorbyl palmitate, Pharmazie 60 (2005) 577–582.
[169] S. Biju, S. Talegaonkar, P. Mishra, R. Khar, Vesicular systems: an overview, Indian J. Pharmaceut. Sci. 68 (2006) 141–153.
[170] V.P. Torchilin, Recent advances with liposomes as pharmaceutical carriers, Nat. Rev. Drug Discov. 4 (2005) 145–160.
[171] S.M. Jadhav, P. Morey, M. Karpe, V. Kadam, Novel vesicular system: an overview, J. Appl. Pharmaceut. Sci. 2 (2012) 193–202.
[172] M. Nounou, L.K. El-Khordagui, N.A. Khalafallah, S.A. Khalil, In vitro drug release of hydrophilic and hydrophobic drug entities from liposomal dispersions and gels, Acta Pharm. 56 (2006) 311–324.
[173] M. Nasr, S. Mansour, N.D. Mortada, A. Elshamy, Vesicular aceclofenac systems: a comparative study between liposomes and niosomes, J. Microencapsul. 25 (2008) 499–512.
[174] F. Taghavi, M. Banihashemi, N. Zabolinejad, M. Salehi, M.R. Jaafari, H. Marhamati, F. Golnouri, M. Dorri, Comparison of therapeutic effects of conventional and liposomal form of 4% topical hydroquinone in patients with melasma, J. Cosmet. Dermatol. 18 (2018) 870–873.

[175] M. Banihashemi, N. Zabolinejad, M.R. Jaafari, M. Salehi, A. Jabari, Comparison of therapeutic effects of liposomal Tranexamic Acid and conventional Hydroquinone on melasma, J. Cosmet. Dermatol. 14 (2015) 174–177.
[176] Y. Shigeta, H. Imanaka, H. Ando, A. Ryu, N. Oku, N. Baba, T. Makino, Skin whitening effect of linoleic acid is enhanced by liposomal formulations, Biol. Pharm. Bull. 27 (2004) 591–594.
[177] J.M. Hwang, H.C. Kuo, C.T. Lin, E.S. Kao, Inhibitory effect of liposome-encapsulated anthocyanin on melanogenesis in human melanocytes, Pharm. Biol. 51 (2013) 941–947.
[178] M. Ghafarzadeh, A. Eatemadi, Clinical efficacy of liposome-encapsulated Aloe vera on melasma treatment during pregnancy, J. Cosmet. Laser Ther. 19 (2017) 181–187.
[179] S.Y. Huh, J.W. Shin, J.I. Na, C.H. Huh, S.W. Youn, K.C. Park, Efficacy and safety of liposome-encapsulated 4-n-butylresorcinol 0.1% cream for the treatment of melasma: a randomized controlled split-face trial, J. Dermatol. 37 (2010) 311–315.
[180] N. Therdphapiyanak, M. Jaturanpinyo, N. Waranuch, L. Kongkaneramit, N. Sarisuta, Development and assessment of tyrosinase inhibitory activity of liposomes of Asparagus racemosus extracts, Asian J. Pharm. Sci. 8 (2013) 134–142.
[181] H. Fan, Y. Li, Y. Huang, G. Liu, Q. Xia, Preparation and evaluation of phenylethyl resorcinol liposome, Integrated Ferroelectrics Int. J. 151 (2014) 89–98.
[182] T. Amnuaikit, T. Limsuwan, P. Khongkow, P. Boonme, Vesicular carriers containing phenylethyl resorcinol for topical delivery system; liposomes, transfersomes and invasomes, Asian J. Pharm. Sci. 13 (2018) 472–484.
[183] V. Teeranachaideekul, S. Nithitanakool, T. Junhunkit, L. Ponpanich, N. Nopporn, U. Detamornrat, M. Chulasiri, Liposomes: a novel carrier system for Artocarpus lakoocha extracts to improve skin whitening, JAASP 2 (2013) 243–253.
[184] A.H. Wen, M.K. Choi, D.D. Kim, Formulation of liposome for topical delivery of arbutin, Arch Pharm. Res. (Seoul) 29 (2006) 1187–1192.
[185] J.J. Liu, S. Nazzal, T.S. Chang, T. Tsai, Preparation and characterization of cosmeceutical liposomes loaded with avobenzone and arbutin, J. Cosmet. Sci. 64 (2013) 9–17.
[186] S.S. Amer, M. Nasr, R.T.A. Abdel-Aziz, N.H. Moftah, A. El Shaer, E. Polycarpou, W. Mamdouh, O. Sammour, Cosm-nutraceutical nanovesicles for acne treatment: physicochemical characterization and exploratory clinical experimentation, Int J. Pharm. 577 (2020) 119092.
[187] S. Hatem, M. Nasr, N.H. Moftah, M.H. Ragai, A.S. Geneidi, S.A. Elkheshen, Melatonin vitamin C-based nanovesicles for treatment of androgenic alopecia: design, characterization and clinical appraisal, Eur. J. Pharmaceut. Sci. 122 (2018) 246–253.
[188] M. Aboul-Einien, S. Kandil, E. Abdou, H. Diab, M. Zaki, Ascorbic acid derivative-loaded modified aspasomes: formulation, in-vitro, ex-vivo and clinical evaluation for melasma treatment, J. Liposome Res. (2019) 1–40.
[189] A. Singh, S. Kumar, G. Kumar, G. Garima, Approaches used for penetration enhancement in transdermal drug delivery, Int J Pharm Sci 2 (2010) 708–716.
[190] C. Chiranjeevi, M. Muthukumaran, B. Krishnamoorthy, A review on potency of vesicular systems in targeting drug delivery, Res. J. Pharmaceut. Biol. Chem. Sci. 4 (2013) 156–170.
[191] N. Atrux-Tallau, A. Denis, K. Padois, V. Bertholle, T.T.N. Huynh, M. Haftek, F. Falson, F. Pirot, Skin absorption modulation: innovative non-hazardous technologies for topical formulations, Open Dermatol. J. 4 (2010) 3–9.
[192] S.B. More, T.D. Nandgude, S.S. Poddar, Vesicles as a tool for enhanced topical drug delivery, Asian J. Pharm. Sci. 10 (2016) S196–S209.
[193] M. Shatalebi, S. Mostafavi, A. Moghaddas, Niosome as a drug carrier for topical delivery of N-acetyl glucosamine, Res Pharm Sci 5 (2010) 107–117.
[194] M. Seiedi, A. Pardakhty, A. Amanatfard, Kojic acid and hydroquinone niosomes for topical application, Pharmaceut. Sci. 20 (2014) 47.
[195] M. Divanbeygikermani, A. Pardakhty, A. Amanatfard, Kojic acid and hydroquinone non-ionic surfactant vesicles for topical application, Int Pharm Acta 1 (2018) 110.
[196] V.B. Junyaprasert, P. Singhsa, J. Suksiriworapong, D. Chantasart, Physicochemical properties and skin permeation of Span 60/Tween 60 niosomes of ellagic acid, Int. J. Pharm. 423 (2012) 303–311.
[197] J. Buruschat, T. Amnuaikit, Preparation of phenylethyl resorcinol niosomes for cosmetic formulation; effects of brij (TM) 72 and cholesterol, Lat. Am. J. Pharm. 35 (2016) 1640–1644.
[198] R. Desnita, S. Luliana, S. Anggraini, In vitro penetration of alpha arbutin niosome span 60 system in gel preparation, Pharmaciana 7 (2017) 249–256.
[199] M. Fadel, N. Samy, M. Nasr, A.A. Alyoussef, Topical colloidal indocyanine green-mediated photodynamic therapy for treatment of basal cell carcinoma, Pharmaceut. Dev. Technol. 22 (2017) 545–550.
[200] C. Celia, F. Cilurzo, E. Trapasso, D. Cosco, M. Fresta, D. Paolino, Ethosomes® and transfersomes® containing linoleic acid: physicochemical and technological features of topical drug delivery carriers for the potential treatment of melasma disorders, Biomed. Microdevices 14 (2012) 119–130.
[201] T. Limsuwan, P. Boonme, T. Amnuaikit, Enhanced stability of phenylethyl resorcinol in elastic vesicular formulations, Trop. J. Pharmaceut. Res. 17 (2018) 1895–1902.
[202] M.H. Lee, K.K. Lee, M.H. Park, S.S. Hyun, S.Y. Kahn, K.S. Joo, H.C. Kang, W. T. Kwon, In vivo anti-melanogenesis activity and in vitro skin permeability of niacinamide-loaded flexible liposomes (Bounsphere™), J. Drug Deliv. Sci. Technol. 31 (2016) 147–152.
[203] S. Bian, M.K. Choi, H. Lin, J. Zheng, S.J. Chung, C.K. Shim, D.D. Kim, Deformable liposomes for topical skin delivery of arbutin, J Pharm Investig 36 (2006) 299–304.
[204] B. Godin, E. Touitou Ethosomes, New prospects in transdermal delivery, Crit. Rev. Ther. Drug Carrier Syst. 20 (2003) 63–102.
[205] P. Verma, K. Pathak, Therapeutic and cosmeceutical potential of ethosomes: an overview, "J. Adv. Pharm. Technol. Research"" (JAPTR)" 1 (2010) 274–282.
[206] T. Limsuwan, P. Boonme, P. Khongkow, T. Amnuaikit, Ethosomes of phenylethyl resorcinol as vesicular delivery system for skin lightening applications, BioMed Res. Int. 2017 (2017) 1–12.
[207] M.A. El-Nabarawi, R.N. Shamma, F. Farouk, S.M. Nasralla, Dapsone-loaded invasomes as a potential treatment of acne: preparation, characterization, and in vivo skin deposition assay, AAPS PharmSciTech 19 (2018) 2174–2184.
[208] D. Ainbinder, E. Touitou, Testosterone ethosomes for enhanced transdermal delivery, Drug Deliv. 12 (2005) 297–303.
[209] D. Paolino, G. Lucania, D. Mardente, F. Alhaique, M. Fresta, Ethosomes for skin delivery of ammonium glycyrrhizinate: in vitro percutaneous permeation through human skin and in vivo anti-inflammatory activity on human volunteers, J. Contr. Release 106 (2005) 99–110.
[210] N. Dragicevic-Curic, D. Scheglmann, V. Albrecht, A. Fahr, Temoporfin-loaded invasomes: development, characterization and in vitro skin penetration studies, J. Contr. Release 127 (2008) 59–69.
[211] B. Sapra, S. Jain, A. Tiwary, Percutaneous permeation enhancement by terpenes: mechanistic view, AAPS J. 10 (2008) 120–132.
[212] S.M. Shah, M. Ashtikar, A.S. Jain, D.T. Makhija, Y. Nikam, R.P. Gude, F. Steiniger, A.A. Jagtap, M.S. Nagarsenker, A. Fahr, LeciPlex, invasomes, and liposomes: a skin penetration study, Int. J. Pharm. 490 (2015) 391–403.
[213] M. Manconi, C. Caddeo, C. Sinico, D. Valenti, M.C. Mostallino, S. Lampis, M. Monduzzi, A. Fadda, Penetration enhancer-containing vesicles: composition dependence of structural features and skin penetration ability, Eur. J. Pharm. Biopharm. 82 (2012) 352–359.
[214] S. Aldalaen, M. Nasr, R.I. El-Gogary, Angiogenesis and collagen promoting nutraceutical-loaded nanovesicles for wound healing, J. Drug Deliv. Sci. Technol. 56 (2020) 101548.
[215] K. Jaydatt, S. Sreenivas, Review on chemical permeation enhancer used in Transdermal drug delivery system, IJSID 2 (2012) 204–217.
[216] E.A. Bsieso, M. Nasr, N.H. Moftah, O.A. Sammour, N.A. Abd El Gawad, Could nanovesicles containing a penetration enhancer clinically improve the therapeutic outcome in skin fungal diseases? Nanomed 10 (2015) 2017–2031.
[217] M. Schlich, M. Fornasier, M. Nieddu, C. Sinico, S. Murgia, A. Rescigno, 3-hydroxycoumarin loaded vesicles for recombinant human tyrosinase inhibition in topical applications, Colloids Surf., B 171 (2018) 675–681.
[218] O.M. Koo, I. Rubinstein, H. Onyuksel, Role of nanotechnology in targeted drug delivery and imaging: a concise review, Nanomedicine 1 (2005) 193–212.
[219] A.T. Rangari, P. Ravikumar, Polymeric nanoparticles based topical drug delivery: an overview, Asian J Biomed Pharm Sci 5 (2015) 5–12.
[220] Z. Urbán-Morlán, S.E. Mendoza-Elvira, R.S. Hernández-Cerón, S. Alcalá-Alcalá, H. Ramírez-Mendoza, A. Ciprián-Carrasco, E. Piñón-Segundo, D. Quintanar-Guerrero, Preparation of ethyl cellulose nanoparticles by solvent-displacement using the conventional method and a recirculation system, J. Mex. Chem. Soc. 59 (2015) 173–180.
[221] R. Tong, J. Cheng, Anticancer polymeric nanomedicines, J. Macromol. Sci. Polym. Rev. 47 (2007) 345–381.
[222] D. Lombardo, M.A. Kiselev, M.T. Caccamo, Smart nanoparticles for drug delivery application: development of versatile nanocarrier platforms in biotechnology and nanomedicine, J. Nanomater. 2019 (2019) 1–26.
[223] S.S. Guterres, M.P. Alves, A.R. Pohlmann, Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous applications, Drug Target Insights 2 (2007), 147–15.
[224] R. Singh, J.W. Lillard Jr., Nanoparticle-based targeted drug delivery, Exp. Mol. Pathol. 86 (2009) 215–223.
[225] H. Abd-Allah, R.T.A. Abdel-Aziz, M. Nasr, Chitosan nanoparticles making their way to clinical practice: a feasibility study on their topical use for acne treatment, Int. J. Biol. Macromol. 156 (2020) 262–270.
[226] M. Mohammed, J. Syeda, K. Wasan, E. Wasan, An overview of chitosan nanoparticles and its application in non-parenteral drug delivery, Pharmaceutics 9 (2017) 53–78.
[227] Y.S. Park, H.J. Park, J. Lee, Stabilization of glabridin by chitosan nano-complex, J Korean Soc Appl Biol Chem 55 (2012) 457–462.
[228] P. Leelapornpisid, P. Leesawat, S. Natakarnkitkul, P. Rattanapanadda, Application of chitosan for preparation of arbutin nanoparticles as skin whitening, JMMM 20 (2010) 101–105.
[229] N.S. Ayumi, S. Sahudin, Z. Hussain, M. Hussain, N.H.A. Samah, Polymeric nanoparticles for topical delivery of alpha and beta arbutin: preparation and characterization, Drug Deliv Transl Res 9 (2019) 482–496.
[230] Y.-W. Wang, C.-H. Jou, C.-C. Hung, M.-C. Yang, Cellular fusion and whitening effect of a chitosan derivative coated liposome, Colloids Surf. B Biointerfaces 90 (2012) 169–176.
[231] S. Duarah, R.D. Durai, V.B. Narayanan, Nanoparticle-in-gel system for delivery of vitamin C for topical application, Drug Deliv Transl Res 7 (2017) 750–760.
[232] G. Riess, Micellization of block copolymers, Prog. Polym. Sci. 28 (2003) 1107–1170.
[233] W. Xu, P. Ling, T. Zhang, Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs, J Drug Deliv 2013 (2013) 1–15.
[234] H. Seino, Y. Arai, N. Nagao, N. Ozawa, K. Hamada, Efficient percutaneous delivery of the antimelanogenic agent glabridin using cationic amphiphilic chitosan micelles, PloS One 11 (2016) 1–15.

[235] J.S. Lee, J. Feijen, Polymersomes for drug delivery: design, formation and characterization, J. Contr. Release 161 (2012) 473–483.
[236] H.K. Cho, I.W. Cheong, J.M. Lee, J.H. Kim, Polymeric nanoparticles, micelles and polymersomes from amphiphilic block copolymer, Korean J Chem 27 (2010) 731–740.
[237] X.-y. Zhang, P.-y. Zhang, Polymersomes in nanomedicine-A review, Curr. Nanosci. 13 (2017) 124–129.
[238] E. Mabrouk, D. Cuvelier, L.-L. Pontani, B. Xu, D. Lévy, P. Keller, F. Brochard-Wyart, P. Nassoy, M.-H. Li, Formation and material properties of giant liquid crystal polymersomes, Soft Matter 5 (2009) 1870–1878.
[239] A. Pugazhendhi, T.N.J.I. Edison, I. Karuppusamy, B. Kathirvel, Inorganic nanoparticles: a potential cancer therapy for human welfare, Int. J. Pharm. 539 (2018) 104–111.
[240] M. Swierczewska, S. Lee, X. Chen, Inorganic nanoparticles for multimodal molecular imaging, Mol. imaging 10 (2011), 7290-2011.
[241] J.J. Giner-Casares, M. Henriksen-Lacey, M. Coronado-Puchau, L.M. Liz-Marzan, Inorganic nanoparticles for biomedicine: where materials scientists meet medical research, Mater. Today 19 (2016) 19–28.
[242] S. Gupta, R. Bansal, S. Gupta, N. Jindal, A. Jindal, Nanocarriers and nanoparticles for skin care and dermatological treatments, Indian Dermatol J 4 (2013) 267–272.
[243] Z.P. Xu, Q.H. Zeng, G.Q. Lu, A.B. Yu, Inorganic nanoparticles as carriers for efficient cellular delivery, Chem. Eng. Sci. 61 (2006) 1027–1040.
[244] J.G. Rouse, J. Yang, J.P. Ryman-Rasmussen, A.R. Barron, N.A. Monteiro-Riviere, Effects of mechanical flexion on the penetration of fullerene amino acid-derivatized peptide nanoparticles through skin, Nano Lett. 7 (2007) 155–160.
[245] M. Lens, Use of fullerenes in cosmetics, Recent Pat. Biotechnol. 3 (2009) 118–123.
[246] L. Xiao, K. Matsubayashi, N. Miwa, Inhibitory effect of the water-soluble polymer-wrapped derivative of fullerene on UVA-induced melanogenesis via downregulation of tyrosinase expression in human melanocytes and skin tissues, Arch. Dermatol. Res. 299 (2007) 245–257.
[247] A. Khan, R. Rashid, G. Murtaza, A. Zahra, Gold nanoparticles: synthesis and applications in drug delivery, Trop. J. Pharmaceut. Res. 13 (2014) 1169–1177.
[248] S. Deb, H.K. Patra, P. Lahiri, A.K. Dasgupta, K. Chakrabarti, U. Chaudhuri, Multistability in platelets and their response to gold nanoparticles, Nanomed. Nanotechnol. Biol. Med. 7 (2011) 376–384.
[249] Z.E. Jiménez-Pérez, P. Singh, Y.-J. Kim, R. Mathiyalagan, D.-H. Kim, M.H. Lee, D. C. Yang, Applications of Panax ginseng leaves-mediated gold nanoparticles in cosmetics relation to antioxidant, moisture retention, and whitening effect on B16BL6 cells, J. Ginseng Res. 42 (2018) 327–333.
[250] S. Hatem, M. Nasr, N.H. Moftah, M.H. Ragai, A.S. Geneidi, S.A. Elkheshen, Clinical cosmeceutical repurposing of melatonin in androgenic alopecia using nanostructured lipid carriers prepared with antioxidant oils, Expet Opin. Drug Deliv. 15 (2018) 927–935.
[251] E. Elmowafy, R.I. El-Gogary, M.H. Ragai, M. Nasr, Novel antipsoriatic fluidized spanlastic nanovesicles: in vitro physicochemical characterization, ex vivo cutaneous retention and exploratory clinical therapeutic efficacy, Int. J. Pharm. 568 (2019) 118556.
[252] M. Nasr, S. Abdel-Hamid, N.H. Moftah, M. Fadel, A.A. Alyoussef, Jojoba oil soft colloidal nanocarrier of a synthetic retinoid: preparation, characterization and clinical efficacy in psoriatic patients, Curr. Drug Deliv. 14 (2017) 426–432.
[253] M. Nasr, H. Karandikar, R.T.A. Abdel-Aziz, N. Moftah, A. Paradkar, Novel nicotinamide skin-adhesive hot melt extrudates for treatment of acne, Expet Opin. Drug Deliv. 15 (2018) 1165–1173.