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Topical Dosage Form & Delivery System for Pigmentation Control: A Review

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Abstract

Hyperpigmentation is one of the most commonly seen skin disorders which is not a concerning health issues but it may affect the psychological aspect of a person. Hyperpigmentation is caused by the presence of excess melanin, which is the brown pigment of the skin. Products that aimed to reduce the pigmentations act by inhibiting the tyrosinase enzyme, which is the rate-limiting enzyme in the synthesis of melanin. There are many products that are currently available in the market that aims to reduce pigmentation of the skin. These products are conventionally formulated into different dosage forms such as cream, lotion and emulgel, which gains popularity due to its convenience on application. However, due to the drawbacks that these dosage forms possess such as poor stability and absorption, new formulations are presented which incorporate novel drug delivery system into the conventional dosage forms. These novel drug delivery systems are, inter alia, liposome, niosomes and microsphere. They carry benefits of controlled drug delivery, enhanced skin penetration and reduce drug toxicity as compared to the conventional dosage form, which resulted in the increase in marketed product diving into this pathway. This present article will discuss the various dosage forms, drug delivery system, its advantages, disadvantages and marketed product for pigmentation control.

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INTRODUCTION

Pigmentation is not a concerning health issue but is rather unpleasant aesthetically. Going back to the root that leads to pigmentation, it all arises from tyrosinase, being the rate-limiting enzyme to produce melanin, the brown pigmentation that causes pigmentation of the skin. Products that aimed to reduce pigmentation usually target at inhibiting the tyrosinase enzyme, which is the rate-limiting enzyme for the melanogenesis process.

The advancement of pharmaceutical technology has driven formulation scientist to explore into dosage forms other than parenteral or oral route, which is of more convenient and less invasive. Topical dosage form refers to the dosage form that aims to deliver the drug locally through anywhere in the body, such as ophthalmic, rectal or skin. Skin is the largest organ of the body and is also considered to be the main target for most topical dosage forms. Topical preparations can be used to target locally on the skin surface or even systemically. In this context, the excipients employed will play an important role in determining whether the preparation will act locally or systemically.

Dosage form indicates the physical form of the drug

as solid, liquid or gas. It essentially refers to the end product in which the product is marketed for use, which includes the active ingredient, excipients as well as material that is neither an ingredient nor excipients such as capsule shell. On the other hand, drug delivery system refers to the way in which the active ingredients are administered in order to reach the site of action and achieve its therapeutic effect.

There are currently many topical dosage forms for cosmeceutical products that are available in the market, including cream, gel, lotion and emulsion. It is a widely accepted form of dosage form due to its non-invasiveness as well as convenience. Preparations applied topically can also bypass hepatic first pass metabolism as well as the acidity of the gastric acid that orally administered drug would encounter. Not to mention, due to its conveniency, this will improve the user's compliance and acceptance on the product. The systemic toxicity caused by the active ingredient can also be held to the minimum with the use of topical dosage form (Malik *et al.*, 2016).

However, the challenges in these conventional topical dosage forms are its stability, which largely depends upon its active ingredients as well as excipients, its ability to cross the lipophilic and tight skin barrier, thus relating to its lipophilicity, and not to mention, is whether it is accepted cosmetically, which for example, should be of less greasy (Bhowmik, 2016). These conventional formulations also possess certain drawbacks such as the low bioavailability (1 to 15%) although there is a high level of the pharmacological agent at the site of application.

Hence, in order to address the drawbacks brought upon by the conventional dosage forms, topical dosage forms are prepared using various delivery systems such as liposome, niosomes and microsphere. Depending on the formulations, these novel drug delivery systems are able to be incorporated into the conventional dosage forms, which carries advantages such as improved stability and improved skin penetration.

Topical Dosage Forms Available (Cream, Gel Ointment etc.)

Cream

Creams are dosage form that is intended to be applied on the skin. It has a consistency thicker than solution and is also known as a semi-solid emulsion being either water-in-oil or oil-in-water emulsion. Creams are used in cosmetics for cleansing, beautifying and are also used for therapeutic purposes. Active components incorporated into cream formulations are intended to provide a local effect, delivering the component to a particular area beneath the skin layers, or the mucous membrane. Oil-in-water creams consist of small oil droplets dispersing in an external aqueous phase, while water-in-oil creams consist of small water droplets dispersing in the external oily phase. In general, most of the creams used for cosmetic purposes are in the form of oil-in-water as it is less greasy, more comfortable and is accepted cosmetically. Most of the depigmentation products available in the market currently are in the form of cream. Hydroquinone, tretinoin, corticosteroids, azelaic acid, kojic acid, glycolic acid, zinc sulfate and some herbal extracts such as arbutin are the active ingredients employed in the formulation of topical bleaching cream. Based on the study conducted by Susan Farshi which compared 20% azelaic acid cream and 4% of hydroquinone cream in treating melasma, it was shown that 20% azelaic acid cream when applied two times a day is effective in treating mild melasma (Farshi, 2011). It is also reported that the triple combination therapy of 4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone acetonide as an oil-in-water cream is more effective than monotherapy and is also tolerable by the patients who received the therapy (Malakooti, 2020).

Based on the study conducted by Nicholas J. Lowe *et al.* on the treatment of hyperpigmentation on the face with azelaic acid cream, it was shown that 20% azelaic acid cream is effective in reducing the hyperpigmentation and most of the study participants perceived the medicated cream used as non-greasy or slightly greasy (Lowe, 1998). In addition, none of the study participants rated the creams used as very or extremely drying. This is further supported by the study conducted by Jaya Gade and co-investigators on the formulation of herbal cream on 16 volunteers. In the study, it was reported that the formulation showed a good spreadibility, homogeneity, non greasy and function as an emollient (Gade *et al.*, 2015). Besides, cream or topical dosage forms also have the advantage of less systemic absorption, resulting in lesser possibility of systemic toxicity. The table below (Table 1) summarizes the advantages and disadvantages of topical cream dosage form as well as the various marketed depigmentation cream (Table 2)

Gel

Pigmentation products in the market are also formulated in the form of gel. For example, PCA skin pigment gel and NEOSTRATA Enlighten Pigment Lightening Gel is in the form of gel dosage form (Table 2). Gel is classified as a semisolid, with the external sol-

vent phase being either hydrophobic or hydrophilic and is immobilized within the space present in a three-dimensional network structure. Gels consist mostly of fluid solvent, with a lesser percentage consisting of a solid matrix. The greatest difference between gel and cream is that gel consists of a higher water content, allowing a greater dissolution of drugs, and facilitate the movement of drug through the vesicle. The higher amount of aqueous component of gel enhances the dissolution of drug and eases the migration of drug through a liquid vehicle when compared with ointment or cream base.

The advantage of employing gel as a topical dosage form is due to it being colourless, thus high cosmetic acceptability, good homogeneity and spreadability, as well as smooth in texture which is reported in the study conducted by (Alzomor *et al.*, 2014). The good quality of gel can also be seen in the study conducted by C-H. Hong on the preference for topical therapy by psoriasis patients. Most of the patients recruited in the study preferred gel over ointment and cream due it being non-greasy and free of odour (Hong, 2017). However, the drawback of gel can be seen in the study conducted by Donatas Grina, in which colour changes occur in all formulations of gel when it is stored in room temperature in a plastic container. The author concluded that the colour change may be attributed to the incompatibility of gel with the plastic container. In the same study, it can also be seen that gel preparation has instability issue as it has a greater tendency to undergo recrystallisation at room temperature as compare to cream and ointment dosage forms (Grina, 2011). The various advantages and disadvantages of gel are summarized in Table 1.

Ointment

Ointment is a semisolid dosage form that is intended to be applied externally on the skin or mucous membrane. The active ingredients and excipients are dissolved, suspended or emulsified in the ointment base. However, its greasiness resulted in a lesser aesthetic acceptability as well as poor spreadability which were shown in the study conducted by (Grina, 2011). In the study conducted by C-H. Hong on 213 patients with psoriasis, it was shown that ointment resulted in poor consumer satisfaction, with a poor score in the section 'not greasy', 'dried quickly', 'no staining' and 'quickly absorbed' (Hong, 2017). Although tacrolimus ointment were used mainly for atopic eczema, however a study conducted by N Al-Mutairi showed that tacrolimus ointment has promising effect on the treatment of Lichen planus pigmentation (Al-Mutairi and El-Khalawany, 2010). In addition to those mentioned earlier, other benefits and drawbacks of ointment dosage form are listed in Table 3.

Emulgel

Although gels can provide faster drug release compared with ointments and creams, the delivery of hydrophobic drugs has been a major problem due to the high amount of aqueous or hydroalcoholic liquid in the gel formulation. A combination of emulsions and gels termed as emulgel has shown enhanced stability at high temperature. The incorporation of a gelling agent into the aqeous phase of emulsion converts the conventional emulsion into emulgel. In a study conducted by LuanaPerioli and coinvestigator, it can be seen that depending on the formulation, emulgel can result in a good consistency and stability. *In vivo* test conducted in this study has also showed that emulgel possess good tolerability, comfortable and is not irritating. In addition, emulgel also exhibits benefits when applied topically, such as grease-free, good spreadability, good stability and it is accepted cosmetically. Azelaic acid that has been known for its ability to treat acne and hyperpigmentation has been formulated in the form of emulgel to solve its poor permeability and solubility issue. Emulgel has also shown to improve the release of lycopene extracted from the fruit of *S. Lycopersicum* based on the study conducted by M. Sohail and coinvestigator (Sohail, 2018). However, the drawback of emulgel is that it is better suited for hydrophobic drug, the possibility of bubble formation during formulation and poor absorption of large drug particles when applied topically (Table 4) (Baibhav, 2011). Example of several available depigmentation emulgel products are listed in Table 5.

Lotion

According to USP35 Chapter <1151>, lotions are defined as an "emulsified liquid dosage form generally intended for external application to the skin". In terms of characteristic, lotion and creams shares many similarities. However, the major difference is that lotion being a liquid dosage form is more fluid in nature as compared to cream which is a semisolid. As a result, lotion exhibits a greater spreadability than cream. The benefit of lotion is that it is not greasy and evaporates rapidly, leaving a cooling sensation when rubbed onto the skin. On the other hand, due to its fluidity, it is easily washed or rubbed off, resulting in a short contact time. Preservatives that are added may also cause irritation to the skin (Table 4). Examples of several depigmentation lotions currently available in the market are listed in Table 5.

Table 1: Advantages and Disadvantages of cream and gel dosage form

Cream	
Advantages	Disadvantages
Non greasy	Less stable than ointment
Good spreadibility	Requires low storage temperature
Good homogeneity	The use of preservative is essential
Emollient action	
Can be washed easily	
Less systemic toxicity	
Gel	
Non greasy	Incompatible with plastic container
Good spreadibility	Higher tendency of recrystallisation as compared to ointment and cream
Good homogeneity	
Colourless	
Non-greasy	
Ease of application	

Table 2: Marketed depigmentation cream and gel

Cream	
Product Name	Brand
Eucerin Anti-Pigment Night Cream	Eucerin
Tidal Brightening Enzyme Water Cream	Sunday Riley
Anthelios Pigmentation Tinted Cream	La Roche-Posay
Dark Spot Therapeutic Cream	Advanced Clinicals
Skin Radiance Cream	Re'equil
Lemongrass anti-pigmentation massage cream	Vaadi Herbals
Tri-Luma cream	Tri-Luma
Sente Dermal Repair Cream	Sente
Optimals Even Out Replenishing Night Cream	Oriflame
Gel	
Pigment gel	PCA Skin
Pigment Lightening Gel	Neostrata
Enlighten Pigment Lightening Gel	Neostrata
Skin Whitening Gel	ExpertGlow
Skin Whitening Gel	NutriGlow
Skin Whitening Face Gel	Rexsol
Vitamin C Face Gel	Nicci

Table 3: Advantages and Disadvantages of ointment dosage form

Advantages	Disadvantages
Provides occlusive dressing	Poor spreadibility
Enhanced contact time	Greasy
Emollient	Less aesthetic acceptability
Better stability as cream	Dry slowly
	Produces Stain
	Absorbs slowly

Table 4: Advantages and Disadvantages of emulgel and lotion dosage form

Emulgel	
Advantages	Disadvantages
Good tolerability	More suited for hydrophobic drug
Non-irritant	Possibility of bubble formation
Grease-free	Poor absorption of large drug particles
Good spreadibility	
Good stability	
Accepted cosmetically	
Lotion	
Non-greasy	Short contact time
Evaporated rapidly	Preservatives present may cause irritation
Cooling sensation when rubbed onto the skin	
High cosmetic acceptability	

Table 5: Marketed depigmentation emulgel and lotion

Emulgel	
Product Name	Brand
Skin Lightening Emulgel	Melasure
Lotion	
Perfect Whitening Body Lotion	Dr. Morita
Skin Repair Whitening & Firming Cream	Rosken
Milk Body Lotion	Bioaqua
Glutalight Intensive Whitening Lotion	Dr. Wu
Premium Whitening Lotion	HadaLabo

Delivery system

Liposome

Liposomes are human-made spherical shaped microscopic vesicle. It consists of phospholipids which are arranged into one or more concentric bilayers. It is arranged in such a way that the hydrophilic portion faces outwards towards the environment as well as inwards in the vesicle, surrounding the hydrophobic portion which is sandwiched between the outer and inner hydrophilic portion. With these characteristics, hydrophilic, lipophilic as well as amphiphilic substances are able to be carried by liposomes, resulting in a large number of potential applications.

The use of liposomes is able to improve the delivery of drug topically via two mechanisms, improving the penetration through the skin and by the entry of the intact vesicle through the stratum corneum. This was shown when the cumulative ketotifen that permeated the skin was significantly increased when encapsulated in deformable liposomes as compared to control group (Elsayed, 2006). Stability of drugs can also be improved by encapsulating with liposome. For example, free curcumin which degrades rapidly (16% remaining) when it is incubated for 3 hours was fully protected when it is encapsulated with liposome after incubating at 37^{o}C for 3 hours (Chen, 2009). When salicylic acid is entrapped in liposome, it was shown that the cumulative amount of salicylic acid permeating is lesser in liposomal salicylic acid, thus indicating that the application of liposome is able to prolong the release of active ingredient. Since salicylic acid produces irritating effect to the skin, the controlled release of active ingredient is able to reduce its irritant effect (Bhalerao and Harshal, 2003). Not to mention, since liposome is made up of phospholipid, it is biodegradable and biocompatible in nature. Nevertheless, liposome does possess some drawback as well. One of it includes it is not suited for encapsulating highly sensitive substances due to the exposure to high mechanical stress during production as well as possible harmful chemicals (Mozafari, 2005). Adding on to that, liposome prepared by sonication method is susceptible to oxidation and hydrolysis of the fatty acid chains of phospholipid (Uhumwangho and Okor, 2005). Osmotic sensitivity of liposome can also

be seen when dioleoylphosphatidylcholine(DOPC) vesicle showed a change in hydrodynamic radius when subjected to hyperosmotic sodium chloride solutions (Table 6) (Pencer *et al.*, 2001).

Pigmentation cream containing liposome-encapsulated 4-n-butylresorcinol and resveratrol has reported to reduce lesional melanin index and improve melasma without causing serious adverse effects (Kwon, 2020). A study conducted by Shrotriya et al. which involved the incorporation of curcumin solid lipid nanoparticles into the Carbopol gel has shown better *in vitro* tyrosinase inhibitory activity compared with the reference kojic acid and curcumin plain gel, suggesting the potential of the formulated gel for skin depigmentation (Davis and Callender, 2010). Moreover, the liposomal formulation of linoleic acid (LA) in hydrogel has also demonstrated a significant skin whitening effect compared to the free LA in ethanol and non-liposomal LA in hydrogel (Shigeta, 2004). Marketed depigmentation product containing liposomes are shown in Table 7.

Niosome

Niosomes are nanoparticles similar to liposomes, however it is made up of non-ionic surfactant instead of phospholipid and may or may not have cholesterol or their lipids being incorporated. The arrangement of the surfactant is similar to that of liposome, forming a bilayer in aqeous medium. The structure of the vesicle is maintained by forces acting from within the vesicle, such as van der waals forces and repulsive forces between the surfactant molecules. Based on the characteristic describe, the non-ionic surfactant employed must therefore possess hydrophilic and hydrophobic portion in order to form a niosome. The dialkyl ether chain surfactant has been found to more closely resemble phospholipid, and is of less toxic and less permeable to entrap solutes than surfactant containing single alkyl ether chain. Surfactant that contains ester linkage however are susceptible to degradation by esterases and therefore is important to prevent the carrier from accumulating in the cell, hence causing it to be less toxic than ether-linked surfactant. The use of niosome is able to overcome the disadvantages of liposome mentioned above, such as the high cost and susceptibility to oxidation and hydrolysis.

N-acetyl glucosamine (NAG) which is an amino sugar that is present naturally in human tissue is well known for its effect in improving hydration due to it being the precursor of hyaluronic acid. It was also found that NAG produces a dose dependant decrease in the amount of melanin when it is applied topically onto cell cultures, thereby showing a promising effect on depigmentation (Bissett, 2007). M.A. Shatalebi *et al* had encapsulated NAG into niosome and study its penetration across the skin of rat using Franz diffusion cells. It was found that the encapsulation of NAG in a niosome resulted in an improved localization of NAG in the skin as compared to hydroalcoholic solution. The skin permeation of NAG was also much greater from hydroalcoholic solution than from niosome, which resulted in a greater systemic absorption, and thus niosome can help reduce the side effect of drug as a result of systemic absorption (Shatalebi *et al.*, 2010). Some advantages and disadvantages of niosomes are mentioned below (Table 8), and the marketed whitening product containing niosome are mentioned in Table 9.

Microparticle delivery system

Microparticulate drug delivery system possesses advantages such as the ability to produce a modified and targeted drug release and delivery, to improve the stability of the preparation and also to produce a more expected pharmacokinetic. The polymer in which the ingredients are loaded into protects them from the surrounding (such as temperature, pH) or even protects the body from the potentially irritating substance. Different types of microparticulate drug delivery system can be prepared, depending on whether the drug is in the free form, confined within a cavity or is homogenously dispersed, resulting in microparticle, microcapsule and microsphere respectively (Padalkar and Shahi, 2011).

Microparticles are particles having the size of 1-1000 μm. Microcapsules are small spheres encapsulating the drugs within a uniform wall and a microcapsule has a size of about 1μm to 7mm. Microcapsule can be used to enclose solid, liquid and gaseous material. However, it may affect the size and shape of the microcapsule. Microspheres are a matrix system consisting of homogeneously dispersed drugs, either being dissolved or homogeneously suspended. It is a reservoir, present in microscopic size, surrounded by polymer which controls the release of the content from the reservoir (Lengyel, 2019).

"Microsponges are polymeric delivery systems composed of porous microspheres." Microsponges are biologically inert polymer particles that absorb, trap, or bind drugs or other chemical compounds. The macroporous beads, which are 10 to 25μm in diameter, release its content over time or in response to particular stimuli, such as change in pH or temperature. For drugs that are water insoluble can be incorporated into these beads, which are very small and hence resulting in a large sur-

Table 6: Advantages and Disadvantages of liposome delivery system

Advantages	Disadvantages
Enhance skin penetration	Not suited for sensitive substances
Improve stability	Susceptible to oxidation and hydrolysis reaction
Control release of ingredients	High cost of raw material
Reduce toxicity	Osmotically sensitive
Biodegradable and biocompatible	

Table 7: Marketed depigmentation product containing liposome

Product Name	Brand
Capture Totale	Dior
Decorte Moisture Liposome Eye Cream	Decorte
C-Vit Liposomal Serum	Sesderma

Table 8: Advantages and Disadvantages of niosome delivery system

Advantages	Disadvantages
Control drug delivery	Physically instable
Osmotically active and stable	Aggregation or fusion may occur
Increase the stability of drug	Leakage of entrapped drug
No special condition required for handling and storing the surfactants	

Table 9: Marketed depigmentation product containing niosome

Product Name	Brand
Niosome plus	Lancome
MayuNiosome Base Cream	Laon cosmetic
EusuNiosomeMakam Pom Whitening Facial Cream	Eusu

face and an increased solubility. Microsponge also offers an advantage over liposomes in that it doesn't require the incorporation of preservatives. Microsphere encapsulation protects the stability of drugs. Liposomes also need ultrapure raw materials for quality control, which makes them more expensive, unlike microsponge technology.

Besides, the novel drug delivery system of microsponge with the formulation of hydroquinone 4% and retinol 0.15% was also employed in the treatment of melasma and post-inflammatory hyperpigmentation. The gradual and prolonged drug release from the microsponges has proven to be effective in improving hyperpigmentation with well patient tolerability (Bhowmik, 2016).

The advantages and disadvantages of microparticulate drug delivery system are summarized in the table below (Table 10), while the examples of marketed whitening product containing microparticles are listed in Table 11.

DISCUSSION

Other types of existing topical dosage forms that are currently not available for the treatment of pigmentation includes pastes. Pastes are semisolid dosage form often containing 50% or more of finely dispersed solid. They are less fluid in nature and do not flow under normal body temperature. It is also opaque, resulting in a poor cosmetic acceptability. Hence, less or no formulations for depigmentation are available in the form of pastes.

Dosage form in the form of patches or plaster can also be tapped in the future in which the active ingredients for resolving pigmentation can be applied onto the patch and plaster, which is then adhere to the pigmented area. This can prevent the formulation being rubbed or washed away unintentionally.

Another form of nanoparticle is known as dendrimers. Traditionally, more focus was placed on linear macromolecules which may or may not con-

Table 10: Advantages and Disadvantages of microparticulate delivery system

Advantages	Disadvantages
Control release of drug	Aggregation is possible
No preservatives required	Limited drug loading
Protect stability of drugs	Burst release

Table 11: Marketed depigmentation product containing microparticulate drug delivery system

Product Name	Brand
Lumablanc cream	Pevonia
Hydroquinone Time Release Cream 4%	Perrigo

tain some smaller or longer branches. However, sometime later, highly branched macromolecules was found to have properties different from the conventional polymers.

Dendrimers are formed by the engraftment of successive series of branches on a core, resulting in a three-dimentional spherical structure. Dendrimers are classified into generations based on the total number of series of branches. For example, dendrimers consisting of one series of branches are considered to be the first-generation, two series of branches are second-generation (Klajnert and Bryszewska, 2015).

The biocompatibility of dendrimers, the ability to control its degradation and the ability to control its molecular weight and size shows potential in formulating it into a depigmentation product.

CONCLUSIONS

Most of the depigmentation product currently available in the market is in the form of cream or gel because of its non-greasiness and have a high cosmetic acceptability. Although ointment is one of the well-known conventional dosage forms, however there are few or no depigmentation ointment in the market due to its greasy after-feeling and it may also leave stains. Due to the limitations of the conventional topical dosage form such as instability and bioavailability problem, novel drug delivery system has been developed in order to overcome these problems. Nanoparticle drug delivery system such as liposomes and niosomes are more widely adopted into novel depigmentation product as compared to microparticulate drug delivery system, probably due to it being smaller in size, and hence a larger surface area and loading capacity.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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