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INNOVATIVE NANOCARRIER SYSTEMS FOR ENHANCED REPIGMENTATION IN VITILIGO: A REVIEW

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ABSTRACT

Vitiligo is a long-term cutaneous pigmentation disease characterized by gradual loss of melanocytes, which as a consequence causes a significant psychological and social burden. Conventional therapeutic approaches, including topical corticosteroids, calcineurin inhibitors, and phototherapy, often demonstrate limited efficacy, poor skin penetration, and considerable adverse effects, necessitating innovative treatment strategies. Currently, treatment options are not very effective, hence alternative methods are needed. Recent pharmaceutical innovations have introduced sophisticated nanodelivery platforms, including liposomes, solid lipid nanoparticles, nanoemulsions, nanostructured lipid carriers, and cubosomes, which demonstrate superior therapeutic potential compared to conventional formulations. These innovative systems offer remarkable advantages including enhanced dermal penetration, sustained drug release profiles, improved bioavailability, and targeted delivery to affected skin regions while minimizing systemic exposure and associated toxicity risks. This comprehensive review examines the transformative potential of advanced nanocarrier systems in revolutionizing vitiligo management through enhanced repigmentation outcomes. he integration of nanotechnology with traditional vitiligo treatments presents unprecedented opportunities for developing safer, more effective therapeutic interventions. Future research directions should focus on optimizing nanocarrier design, conducting comprehensive clinical trials, and establishing standardized protocols for successful clinical implementation of these promising therapeutic systems.

Keywords: Vitiligo, Herbal Cream, Psoralea corylifolia, Piperine, Skin Repigmentation, Topical Drug Delivery

1. INTRODUCTION

1.1 Vitiligo

A chronic acquired pigmentary disorder, vitiligo mostly affects the skin's and mucous membranes' melanocytes. This unique lesion is characterized by a chalky-white, non-scaly, entirely amelanotic macule with clear edges. The prevalence is thought to be between 0.5 and 2% worldwide, with some regions of India having rates as high as 8.8%[1].

Vitiligo causes loss of skin color. During the Aushoriya period, around 2200 BCE, vitiligo was first mentioned in literature around 1000 BCE under the name Kilăsa. Additionally, the Egyptian Ebers Papyrus also contains information about vitiligo, which dates back to 1550 BC[2]. It happens when hereditary and environmental variables interact dynamically, causing melanocytes to be destroyed by the immune system. Increased oxidative stress and melanocyte adhesion defects further strengthen the immunological response in vitiligo[3]. An international consensus in 2011 defined the term "vitiligo" to refer to all types of nonsegmental vitiligo and classified segmental vitiligo apart from all other types of vitiligo[4]. Multiple factors and mechanisms have been proposed for the etiopathogenesis of vitiligo, among which oxidative stress has been widely accepted as a key factor in initiating melanocyte loss. The altered redox status caused by oxidative stress, including the overproduction of reactive oxygen species (ROS) and the decreased activity of the antioxidant system in the skin, surrenders the resistance of melanocytes to exogenous or endogenous stimuli and eventually impairs the normal defense mechanism, leading to the absence of melanocytes[5].

Vitiligo is a common and recognizable condition among dermatologists, most physicians, and many informed members of the public. The condition is characterized by a loss of pigmentation that often first appears on the fingertips, joints, lips, eyes, toes, and around the genitals[6]. Vitiligo is caused by an immune system disorder in which CD8+ cytotoxic T cells attack epidermal melanocytes, causing apoptosis and subsequent depigmentation. Although there are currently no biomarkers to measure vitiligo activity, some clinical data are relevant to prognosis and the likelihood of repigmentation[7].

1.2 Classification:

According to the extent and location of the discoloration, vitiligo is divided into several classes and subclasses, as explained below:

Localized vitiligo

Refers to the discoloration that appears in a specific body area. At a higher level, this type of vitiligo can be divided into two subclasses:

Focal Vitiligo

A small, isolated injury in a specific body part represents focal vitiligo.

Segmental vitiligo

Refers to the appearance of white spots on one side of the body's skin alone. Usually, it involves a rapid expansion of the patches in a particular area, but it is then caught and can remain unchanged for a long period of time.

Non-segmental generalized vitiligo

Refers to discoloration in various body areas. This type is usually characterized by the ongoing spread of skin injuries over a large area. The same pattern frequently observed in patients' skin can also be used to distinguish it from localized vitiligo. The face and limbs are frequently where generalized vitiligo first appears, encompassing the following subtypes:

Acrofacial Vitiligo

Symptoms of acrofacial vitiligo include white spots on the hands, feet, and face. The fingertips and facial openings are often where it starts.

Vitiligo vulgaris

This condition is typically identified by its dissipated dispersion throughout the body.

Vitiligo universalis

The term "universal vitiligo" describes the widespread appearance of white spots on the body. Eventually, this causes the skin, mucous membranes, and hair to become completely discolored. Mucosal vitiligo is an additional type that affects the body's mucous layers. Although this type is typically categorized under the localized group, it can also be categorized under the generalized group because it is frequently linked to the progression of vitiligo vulgaris. Both the oral and genital areas are affected by mucosal vitiligo. Another type of vitiligo under investigation is contact or occupational vitiligo[8].

2.Pathophysiology:

According to the neural hypothesis, a neurochemical mediator typically kills melanocytes and reduces melanin synthesis. The melanocyte is destroyed by an intermediate or metabolic product of melanin synthesis in oxidant and antioxidant mechanisms. An innate anomaly that prevents melanocytes from growing and differentiating is known as an intrinsic defect. Another theory is cytotoxic or autoimmune, in which a change in humoral and cellular immunity results in the death or malfunction of melanocytes. The idea that nonsegmental vitiligo is more frequently linked to autoimmune diseases than segmental vitiligo is supported by this theory[9].

3.Topical delivery system

The history of topical medications is lengthy. Ancient Egyptians, Chinese, and Babylonians used ointments and salves made from animal, mineral, or plant extracts to treat a variety of illnesses thousands of years ago. Possibly the first transdermal patch, emplastra first appeared in China before the year 2000 BC. In addition to being the source of the discovery of some extremely effective monomers, topical medications are now widely used in many countries due to their high effectiveness[10].

Skin conditions are an especially complicated case. A desirable formulation should be able to increase the amount of active drugs that accumulate in the target tissue without increasing skin penetration to the point where the drugs enter the systemic circulation in potentially harmful amounts. Numerous factors influence how well drugs penetrate the skin. The stratum corneum (SC) is the largest obstacle to skin penetration. This skin structure is made

up of multilamellar layers of ceramides, fatty acids, cholesterol, and cholesterol esters24 (the "mortar") and corneocytes (the "bricks"), which are primarily made of hydrated keratin. These bilayers have very long chains, low hydration, high melting temperatures, and domains in both gel and liquid crystal phases. They are also highly hydrophobic[11].

Reaching the target site in vivo with an adequate dosage and no adverse effects is the ultimate goal of all topical medications. Four categories of topical medication can be distinguished based on the various target sites: 1) medications that are not absorbed (e.g., sunscreen, heavy metals); 2) medications that enter the skin and do not wish to spread (e.g., medications used to treat skin conditions); 3) medications that penetrate deeper tissues (e.g., anaesthetics, medications used to treat diseases of the muscles or joints); 4) medications that enter blood vessels through the skin and are carried to other tissues or organs (e.g., insulin).

4.Herbal Cream

Numerous herbal medications have been found to be effective in treating vitiligo, which has been linked to immunomodulatory effects or stimulation of melanogenesis, melanocyte migration, or proliferation. To create safe, efficient, and reasonably priced treatments for vitiligo, more research on herbal medications should be conducted.

Herbal extracts are the most used medicinal herbs in traditional oriental medicine. For thousands of years, it has been used to treat a variety of conditions and significantly improve skin health. Natural plant extracts have amazing properties that are being used all over the world right now[12]. Ayurvedic or traditional uses of plant resources to treat a variety of illnesses, including diabetes, cancer, arthritis, impotence, and skin conditions like vitiligo or hypopigmentation, are also becoming more popular.

5.Ideal properties of Herbal Cream

- Excellent penetration capabilities to ensure that the medication in the cream reaches the skin and produces the intended result.
- In order to prevent any negative effects on skin, like itching, rashes, or redness, it should be non-toxic.
- When applied topically, it should spread easily.
- It should be non-irritating and not cause skin inflammation.
- It should melt or liquefy at body temperature when applied to the skin[13].

6.Advantages of Herbal Cream

Several advantages of Herbal cream have been illustrated in Figure 1.

Fig. 1: Advantages of Herbal Cream

7. Marketed Herbal Creams for Vitiligo

Various Herbal creams manufactured for Vitiligo have been summarized in Table 1.

8. Nanotechnology

Advances and breakthroughs in formulations and delivery systems could be produced using nanotechnology. This rapidly evolving technology has been extensively used for both therapeutic and diagnostic applications. Nanotechnology-based cosmetic formulations are a relatively young, intensively researched, and promising field. It has been demonstrated that using nanotechnology in cosmetics can both improve formulation's usefulness and overcome the shortcomings of conventional cosmetics[14].

In the cutting-edge field of nanotechnology, structures, devices, and systems are designed, characterized, produced, and used by manipulating their size and shape at the nanometer scale, which spans the size range of 1 nanometer to 100 nanometers (nm), where 1 nanometer is equivalent to one billionth of a meter[15].

Nano-drug delivery used in Cosmetics:

Better solubility, transparency, chemical reactivity, and stability are only a few of the new advantages that can be ascribed to a smaller size. Liposomes, ethosomes, solid lipid nanoparticles, nanocapsules, dendrimers, nanocrystals, cubosomes, and nanoemulsions are among the multiple nanomaterials utilized in the cosmetics sector.

Liposomes:

Liposomes are spherical vesicles composed primarily of lipids, which make up the cell membrane. Liposomes can contain medications and have at least one bilayered lipid membrane. Liposomes typically have a diameter of 50–300 nm. Reverse-phase evaporation, solvent injection, detergent depletion, supercritical fluid, size reduction sonication, high-pressure homogenization, low-pressure extrusion, and thin film hydration are some methods for creating liposomes. Although liposomes can initiate and sustain the release of their payload, there hasn't been much of a correlation between the kinetics of release in vitro and in vivo[17].

Ethosomes:

In 1997, Touitou et al. created ethosomes, which are several types of lipid carriers made of water, phospholipids, and ethanol. The cutaneous administration of a variety of medications is said to be enhanced by them. It is thought that the intercellular area of the stratum corneum is how ethanol works as an effective penetration enhancer. The new vesicle carriers for improved distribution are these soft vesicles. Ethosome vesicles ranging in size from tens of nanometers to microns can be adjusted[18].

Solid Lipid Nanoparticles (SLNs):

In the early 1990s, solid lipid nanoparticles (SLN), an unconventional carrier system, were developed as an alternative to the traditional lipoidal carriers, such as liposomes and emulsions. Solid lipid nanoparticles range in size from 50 to 1000 nm. They are made up of a single shell layer with an oily or lipoidal core. The matrix drug, which is distributed or dissolved in the solid core matrix, contains solid lipids or combinations of lipids[19].

The first generation of lipid-based nanoparticles, known as solid lipid nanoparticles (SLNs), are mostly composed of solid lipids and have the

advantages of controlled release and a decreased risk of skin harm because there is less active ingredient that is released to the skin right away. The utilized lipids are solid at room temperature, which aids in the encapsulation and release of the active components. A number of variables, including the production process and the physicochemical characteristics of the active ingredients specifically, its lipophilicity have a significant impact on the effectiveness of SLNs[16].

Nanocapsules:

Polymeric NM capsules with an aqueous or fatty phase enclosing them are called nano capsules. Cosmetics employ nanocapsules to fix formulation component incompatibilities, reduce chemical smells, and safeguard ingredients. In addition to being used as an ingredient in semisolid formulations, polymeric nanocapsule suspensions can be applied directly to the skin as a finished product. The polymer and surfactant employed as basic materials can be used to adjust an ingredient's level of skin penetration[20].

Dendrimers:

A novel class of monodispersed macromolecules known as dendrimers or fractal polymers, which have emerged in the last ten years, are essential for producing functional nanoscale materials with special chemical, biological, and optical characteristics. Dendrimers have a highly branching,tree-like three-dimensional structure in contrast to traditional polymers. A central or core unit, arms of the same size, linking or branching points, and terminal functional groups are the four primary components of dendrimers, which are made up of a sequence of chemical shells encircling a tiny core molecule.

A cavity can be made by removing the core. Because the holes serve as binding sites for tiny guest molecules that can be released gradually, dendrimers hold promise as slow delivery agents[21].

Nanocrystals (NCs):

NCs are nanoscale particles, meaning they are smaller than 1000 nm. The single component of NCs are drug particles, which are stabilized by stabilizers and maintained in a dispersed state to prevent aggregation. In the formulation of NCs, polymeric, non-ionic, and ionic stabilizers are frequently utilized. The drug's cutaneous bioavailability, surface adhesion, saturation solubility, dissolution rate, and drug release rate can all be significantly increased by NC-based formulations. Because of its easy manufacturing, repeatability, low excipient concentration, and high therapeutic loading capacity, nanocrystals are superior to other nanocarriers[22].

Cubosomes:

Cubosomes are rounded, square particles that have apparent interior cubic lattices.Cubosomes are self-assembling nanoparticles made of surfactant and aqueous lipid systems. With their "honeycombed" structure of bicontinuous domains of lipid and water, where surfactant assembles into bilayers and twists into a minimum, three-dimensional, periodic surface, cubosomes are thermodynamically stable. They have distinct drug-loading methods and differ in internal cubic structure and content[23]. Since these special systems can produce a wide variety of hydrophobic, hydrophilic, and amphiphilic medications with enhanced loading potential and bioavailability, they are of interest for research. Monoolein–

water cubosomes, particularly those made up of binary systems, have the ability to self-assemble into cubic crystalline forms and are thermodynamically stable[24].

Nanoemulsion:

When two immiscible liquids (such water and oil) are combined and stabilized by an emulsifying agent, the result is an emulsion known as a nanoemulsion. Aqueous components, surfactants/co-surfactants (Smix), and an oil phase make up this homogenous, thermodynamically stable, and isotropic system. Nanoemulsions are frequently utilized in a variety of industries, including food, cosmetics, pharmaceuticals, and agriculture[25]. The effectiveness of nanoemulsions as topical medication delivery methods has lately been acknowledged because of their nanosize droplets' incredibly huge surface area. Usually made up of water, oil, and an emulsifier or mixture of emulsifiers, they might have a translucent or transparent look. The internal phase's kinetics of destabilization are slow because it typically ranges in size from 20 to 500 nm. Nanoemulsions are primarily produced using two techniques: high-energy and low-energy techniques. An ultrasonicator, microfluidizer, or high-pressure homogenizer are used in the high-energy approach. Nanoemulsions are often formed by the low-energy approach, which calls relatively basic equipment.

CONCLUSION

This review clearly shows that new nanocarrier drug delivery systems offer great promise for treating vitiligo more effectively than current methods. These tiny carriers, including liposomes, solid lipid particles, and nanoemulsions, work much better than regular treatments because they can deliver medicines deeper into the skin and keep them there longer. They also cause fewer side effects since less medicine enters the bloodstream. Traditional vitiligo treatments often fail because they cannot penetrate the skin properly or break down too quickly, but these nano-systems solve many of these problems. While the results look encouraging, there are still some hurdles to overcome before these treatments reach patients. Scientists need to figure out how to make these systems on a larger scale, get approval from health authorities, reduce costs, and make sure they are completely safe for long-term use.

Table 1: Marketed Herbal Creams

S.No.	Brand name	Actives	Manufacturing company
1	Vitilox® Pigmentation Cream	Lipoproteins, Kalahari Melon Oil, Vitamin E, Avocado Oil	Vitilox
2	Repigma Cream	L-Phenylalanine, PABA, Coenzyme Q10, Gluconolactone, Shea Butter, Vitamin E	Licoferma
3	DermaBest® Novitil® gel	Lipoproteins, Polypepetides, carboxymethylcellulose, Aloe barbadensis, Camphor, Menthol, Trace Elements	Dermabest
4	Clinica Vitiligo Cream	Herbal Extract (Specific active ingredients not disclosed)	Clinica
5	Verdura Mela Gain Cream	Psoralea corylifolia, Wrightia tinctoria, Indigofera tinctoria, Emblica Officinalis, Calamine, Bentonite, Zinc oxide	Verdura
6	Vensia Anti Vitiligo Cream	Tankan Amla, Lobhan Pushpa, Gandhak, Pudina Phool, Multani Mitti, Suranjan, Dev Daru, ShudhKuchala, Ginkgo, Mustard, Neem extract, Leucotomas, and Green tea.	Vensia
7	Meladerm®	Alpha Arbutin, Licorice Extract, Vitamin C, Morus Alba (White Mulberry) Root Extract, ScutellariaBaicalensis Root Extract	Civant
8	Melacare Cream	Hydroquinone, Tretinoin, Fluocinolone, Acetonide, Vitamin E	Ajantha pharma limited
9	SiddhayuRepigmenting Herbal Cream	Bakuchi (Psoralea corylifolia), Haldi (Curcuma longa), Mooli (Raphanus sativus)	Siddhayu
10	Vitinext Vitiligo Cream	Bavachi (Psoralea corylifolia), Katumbarchall (Ficus hispida), Krushanatil (Sesamum indicum), Manjishta (Rubia cordifolia), Chitrak (Plumbago zeylanica), Umber phal (Ficus carica), Vidang (Embeliaribes), Dantimul (Boliospermumnontanum), Amaltas gar (Cassia fistula), Muli beej (Raphanus sativus), Daruhaldi (Berberis aristata), Amaltas garcinia pedunculata fruit	E Mega Mart India

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CONFLICT OF INTEREST

Nil

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