

Topical treatment in vitiligo and the potential uses of new drug delivery systems

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ABSTRACT

Vitiligo is a psychologically devastating condition. Topical therapy is employed as first-line treatment in localized vitiligo. Currently, several topical agents are available in many forms viz. methoxsalen (solution and cream), trioxsalen (solution), corticosteroids (gel, cream, ointment and solution) and calcineurin inhibitors (ointment and cream). Although topical therapy has an important position in vitiligo treatment, side-effects or poor efficacy affect their utility and patient compliance. Novel drug delivery strategies can play a pivotal role in improving the topical delivery of various drugs by enhancing their epidermal localization with a concomitant reduction in their side-effects and improving their effectiveness. The current review emphasizes the potential of various phospholipid based carriers viz. liposomes, transferosomes, ethosomes, lipid emulsions, solid lipid nanoparticles and organogels in optimizing and enhancing the topical delivery of anti-vitiligo agents, whilst reducing the side effects of drugs commonly used in its topical treatment.

Key words: Novel drug delivery, phospholipid-based carriers, topical therapies, vitiligo

INTRODUCTION

Vitiligo is an acquired idiopathic, dermatological disorder characterized by well-circumscribed milky white macules devoid of identifiable melanocytes. These asymptomatic white macules can be psychologically extremely damaging, even leading to attempted suicide in some cases.^[1] It affects approximately 1% of the world's population and approximately 3-4% of the Indian population.^[2,3] The most common sites of involvement are the face (24.5%), neck (18.8%), and scalp (11.2%).^[4]

The exact etiology of vitiligo is unknown. It is believed that vitiligo is a polygenic trait and that a convergence theory combining elements of different etiological theories across a spectrum of expression is the most accurate etiology.^[5]

TREATMENT

In general, topical monotherapy is indicated for mild-to-moderate vitiligo. Current treatment options for vitiligo include medical, surgical and adjunctive treatments.^[6,7]

Medical treatment targets the immune system and helps to arrest the spread of depigmentation. In cases of stable vitiligo, repigmentation can be achieved by dermatosurgical techniques and adjunctives includes use of cosmetics. Both surgical and medical treatment have their own limitations. Adjunctive can only cover the patch and be used along with surgical or medical treatments.

MEDICAL THERAPIES

The best studied and most commonly used medical treatment options are corticosteroids, psoralens and depigmenting agents.

Corticosteroids: Topical steroids are often first-line therapy, especially in children or for localized disease. Moderately potent to potent topical corticosteroids are used.^[8,9] However, vitiligo requires prolonged use of these agents, often much longer than the usual "safe" recommended periods of use for inflammatory dermatoses. This results in significant, therapy-limiting side-effects like atrophy, hypertrichosis, peri-lesional hypopigmentation etc. It is obvious that

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currently available dosage formulations do not provide site-specific drug delivery.

Phototherapy: Phototherapy is one of the oldest forms of treatment of vitiligo and remains the bedrock of vitiligo therapy even today. Out of three [5-MOP (bergapten), 4, 5, 8-trimethylpsoralen (TMP) and 8-MOP (methoxsalen)] different types of psoralens, 8-MOP is the most commonly used. Topical psoralen photochemotherapy (PUVA) is often used for people with limited disease (affecting less than 20% of the body). It is also used for children 12 years and older, who have localized patches for vitiligo.^[10] Severe sunburn, blistering and abnormally dark repigmentation are major potential side-effects of topical PUVA therapy. This is due to the uncontrolled photo-reaction of psoralen with ultra-violet A irradiation in the epidermis because drug is freely available from currently available dosage formulations, for reaction on surface after topical application.^[11] In recent years, *narrow-band UVB* (NB-UVB, 311 nm) has become the preferred phototherapy for vitiligo.^[12,13]

Calcium modulators: Recently, calcium modulators, the vitamin D3 analogues (calcipotriol and tacalcitol), have also been tried in the treatment of vitiligo.^[14] Defective calcium transport has been shown in melanocytes and keratinocytes harvested from patients with vitiligo. Further, vitamin D3 has been shown to activate melanin synthesis.^[15] There are contradictory reports of their efficacy in vitiligo, both as monotherapy and in combination with both PUVA and NB-UVB phototherapy. The most common adverse effect of calcipotriol is lesional irritation and potential hypercalcemia if applied in quantity > 100mg in a week. So, controlled delivery can potentially deliver better results by modifying currently available dosage formulations, minimizing both systemic absorption and local irritation.

Calcineurin inhibitors: Calcineurin inhibitors (tacrolimus, pimecrolimus) are some of the newest topical drugs in dermatology.^[16,17] However, tacrolimus and pimecrolimus are effective only in vitiligo lesions on the head and neck region.^[18] The main difficulty with topical calcineurin inhibitors, and one that is probably responsible for lack of efficacy in non-facial vitiligo, is their high molecular weight. This precludes efficient delivery of the drug at the level of the basal cells, since the stratum corneum allows very poor absorption of any molecules over “500Da” in weight.^[19] This has recently been proved by an elegant study where greatly enhanced repigmentation

with pimecrolimus was achieved by using it after performing microdermabrasion on the lesional skin.^[20] Hence, carrier mediated drug delivery can substantially increase their effectiveness bypassing the stratum corneum barrier and delivering these drugs in adequate concentration to the melanocytes and keratinocytes.

ADJUNCTIVE THERAPIES

Depigmentation: Depigmentation is a more drastic form of treatment, when vitiligo is extensive i.e. vitiligo universalis. Depigmentation involves fading the rest of the skin on the body to match the already white areas by using permanent melanocytotoxic agents such as Monobenzyl ether of hydroquinone cream (Benoquin®). The major side-effect includes irritant dermatitis but rarely limits therapy.^[21] A more recent method of depigmentation utilizes topical 4-methoxyphenol (4-MP) and the Q-switched ruby laser (QSR).^[22]

Sunscreens: People who have vitiligo are more susceptible to sunburn and long term photodamage. To prevent sun-induced darkening of the surrounding normal skin, broad spectrum high protection factor sunscreens (SPF15-30) which provide protection from both UVB and UVA light should be used.

Cosmetics: Camouflage is often used to “cover” affected areas. This may be practical for patients that have minimal disease or segmental disease.^[23-25] Many brands of dyes Dermacolor® (Kryolan) and Dermablend® (L’Oreal) are available in India.

NEW DRUG DELIVERY SYSTEMS

In contrast to the traditional oral route, topical drug delivery for vitiligo has many advantages. It bypasses all major organ systems like GIT, liver, kidney etc. there by avoiding many issues of adverse effects, bioavailability etc. Nevertheless, topical application of drugs is not a simple matter. The major hurdle in producing the desired therapeutic action is the inability of the existing dosage forms like gels, lotions, creams and ointments to serve or deliver what is required, where it is required. Currently, material selection and designing of these dosage forms fails to account for the physiological and structural aspects of skin (e.g. the tough cornified stratum corneum as barrier to drug transport), while the drug related issues of high molecular weight, skin penetration, release parameters

and stability are not properly addressed.^[26,27] The complex lipid and cellular structure within the cornified layer of intra-follicular epidermis, composed of ceramides, cholesterol and free fatty acids contributes to the impermeability of skin.^[28] These reasons have been responsible for using systemic route for many a potential drug candidate for primary skin manifestations, whereas the topical route could have been the more appropriate choice. For example, the systemic delivery of potentially hazardous drugs like psoralen and corticosteroids through oral route has been in practice for vitiligo and many other skin diseases, as their topical products are either not very effective, or produce too many local adverse effects.^[29,30]

The failure of topical conventional dosage forms is mainly accounted for by poor penetration and inability to place the drug molecules at the desired site of action for a prolonged period without allowing systemic absorption. Also the conventional dosage forms are unable to provide the protection to the normal tissues leading to “innocent bystander” side effects like dermal atrophy with corticosteroids. The drug also needs to be shielded from the local metabolic milieu of the skin, so that it is protected from breakdown into inert or toxic metabolites. Inactive metabolites would curtail drug action, requiring repeated application and toxic metabolites can produce unacceptable adverse effects. Further, in a traditional approach, the major drawback is the non-consideration of the real requirement of the drug molecule at the particular site for desired action. In this regard, a tailored system is needed to transport and target the molecule in the most effective manner. In a nut shell, all the problems associated with the conventional formulations, suggest that modifications and innovations are required in the way topical therapy is administered.

Drug-carrier systems

Recently, a variety of materials and methods are being used to create some very exquisitely built carrier

systems.^[31,32] Some of these systems are mentioned in Table 1.

These carriers, with their own specificities, have attracted the formulations based on requirement and application of their field of work. The last decade has seen a phenomenal growth in the use of phospholipid-structured carriers in topical delivery. Simultaneously, it has been seen that the other carriers mentioned in Table 1 are also useful for oral and parenteral drug delivery.

Topical drug delivery systems

Phospholipid-structured carriers would be the vehicle of choice for topical delivery for vitiligo because optimized topical delivery employing these phospholipid-structured carrier systems was seen due to improved profile (pharmacokinetic and pharmacodynamic) of the chosen drug molecules for various skin diseases.^[33-35] This was due to various reasons discussed below:

- *Skin-friendly*: The carrier systems composed of phospholipids (e.g., lecithin) are shown to improve the skin condition by virtue of their nonirritating, non-sensitizing, and nontoxic, moisture retentive nature. Lecithin is a naturally occurring substance that is considered a very good skin conditioner furnishing excellent repair of the skin's barrier as well.
- *Transport across skin*: Enhanced drug penetration across the tough and dense lamellar lipidic matrix of stratum corneum may be achieved as a result of favorable hydro-lipophilic microenvironment of the drug molecules, which greatly influences the partitioning of the drug and facilitates skin transport. Simultaneous modification in the barrier function of stratum corneum due to incorporation of phospholipids (into skin layers) also favors the transport of drug across skin. The problems associated with poor skin penetration of tacrolimus, pimecrolimus due to their large molecule more than

Table 1: List of various drug-carriers used for drug delivery

Phospholipid-Structured Carriers	Cellular Carriers	Polymeric Carriers	Proteineous Carriers
Liposomes	Resealed Erythrocytes	Soluble synthetic polymeric	Lectin and Polysaccharides
Transferosomes,	Antibodies	Biodegradable	Proteins
Ethosomes	Platelets	Signal sensitive	Glycosylated
Lipid emulsion	Leukocytes	Bioerodible	Immunotoxin
Microparticles	Serum albumin	Bioadhesive	Soluble Polymers
Organogels			Monoclonal antibodies
Solid lipid nanoparticles			

500 Da (as per '500 Dalton rule'), can be improved using the carrier approach.

- **Super-solvent effect:** Phospholipid-based carrier systems, by virtue of the amphiphilicity and supramolecular association, provide a super-solvent effect, which keeps the active medicament in molecularly dispersed state so that the transfer across the skin is facilitated. These have ability to deliver both hydrophilic as well as lipophilic drugs. Carriers can provide super-solvent effect by keeping methoxsalen in dispersed state which has a crystalline nature otherwise.
- **Prolonged action:** Increased drug-localization in the skin strata is expected by the formation of micro-reservoirs, which may help in producing prolonged local action and reduced systemic effects. This would be of tremendous value in topical corticosteroids, minimizing dermal atrophy and telangiectasia whilst allowing less frequent application. In a chronic condition like vitiligo, it has been seen that patient compliance reduces markedly over time. Topical agents that have to be applied only once a day or perhaps even less frequently would increase patient compliance significantly.
- **Pronounced action:** Enhanced drug action, besides a prolonged presence, is another benefit that may be attributed to the presence of the therapeutic molecules at or near the target site. The drug in the proposed carrier may produce better drug-target interactions. In case of vitiligo, after using carrier mediated delivery of methoxsalen, reaction with UV-light will only occur at or near melanocytes (not on skin surface). Which would help in reducing phototoxic side effects.
- **Improved patient compliance:** Better patient acceptability with the carrier-based product is also an outcome due to the skin-moisturizing effect, which helps in keeping skin in the active state. And the favorable rheological properties of these systems, in contrast to greasy ointments, add to the patient acceptance. Simultaneously reduction in side effects may improve patient compliance.
- **Dose reduction and improved safety:** The safety of the drug is also expected to be increased as the enhanced drug action may allow reduction in the number of molecules to elicit the desired pharmacotherapeutic effect. And also the hydrating effect in the lipid-rich environment reduces the irritant effect of the molecules which is otherwise cyto-destructive. Carrier-based delivery can reduce the dose of calcipotriol in vitiligo treatment, which

would help in minimizing its local and systemic side effects and improve its utility.

- **Targeting to desired site:** Drug molecules can be targeted to the desired site by modifying the physicochemical nature of vesicular systems. The best known example is Doxil™ in cancer chemotherapy, which is pegylated (polyethylene glycol coated) liposome-encapsulated form of doxorubicin. This ligand-binding promotes efficient drug uptake into cells and enhances efficacy.^[36] In vitiligo therapy, although at present no ligand-based carrier systems are available, it is theoretically possible that this could be the most effective and safe method of delivery actives if melanocytes can specifically be made to take up the topically applied agents.
- **Enhance stability:** Vesicular systems enhance the stability of poorly stable drug like dithranol, tretinoin, etc. The proposed mechanism behind this is the entrapment of drug within the lamellae of the vesicle, making it unavailable to open atmosphere or to light.

Phospholipid-structured carriers

Vesicular approaches

Liposomes: Liposomes are microscopic, fluid-filled pouches whose walls are made of layers of phospholipids. Liposomes were first produced in England in 1961 by Alec D. Bangham but the potential value of liposomes for topical therapy was first introduced by Mezei and Gulasekharan. Cholesterol may be included to improve bilayers characteristics of liposomes; increasing microviscosity of the bilayers, reducing permeability of the membrane to water soluble molecules, stabilizing the membrane and increasing rigidity of the vesicles. Psorosome™, a liposomal-gel version of dithranol produced in our laboratory is one such example. Further, results of several studies [Table 2] indicate that liposomes were useful for drug delivery in vitiligo and other dermatological disorders.^[37-40]

Transferosomes: Cevc, et al, introduced the first generation of elastic vesicles, referred to as transferosomes. These self-optimized aggregates, with the ultraflexible membrane, are able to deliver the drug reproducibly either into or through the skin with high efficacy.^[41-43] The better skin penetration ability of these elastic vesicles in comparison to liposome is supported by various studies [Table 2].

Ethosomes: Ethosomes are lipid-based elastic vesicular systems embodying ethanol in relatively

Table 2: Some recent studies of topical drug delivery carriers

Carriers	Drugs	Results	References
Liposomes	Methoxsalen	Improved drug accumulation in epidermis and dermis	Sinico, et al, 2005
Liposomes	Dithranol	Decrease skin irritation, improve patient compliance	Saraswat, et al, 2007
Liposomes	Phycocyanin	Improving its anti-inflammatory activity of drug	Manconia, et al, 2009
Liposomes	Minoxidil	Improve drug delivery to pilosebaceous unit	Jain, et al, 2009
Transferosome	Colchicine	12.5-fold higher skin deposition as compared to drug solution	Singh, et al, 2009
Transferosomes	Hydrocortisone and dexamethasone	Increased biological potency, prolonged effect, and reduced therapeutic dosage	Cevc, et al, 2004
Transferosomes	Triamcinolone acetonide	Improve patient compliance	Fesq, et al, 2003
Ethosomes	5-aminolevulinic acid	11 to 15 fold higher drug deposition in contrast to controlled formulation	Yi-Ping, et al, 2008
Ethosomes	Finasteride	Higher drug accumulation in the skin	Yuefeng, et al, 2008
Ethosomes	Benzocaine	Improving its clinical effectiveness in topical anesthesia.	Maestrelli, et al, 2009
Lipid emulsion	Tetracaine hydrochloride	3.5-fold increase in drug accumulation in epidermis and 3.8 fold enhancement in upper dermis	Changez, et al, 2006
Lipid emulsion	Flurbiprofen	Improve drug delivery	Jia-You, et al, 2004
Lipid emulsion	Triptolide	Enhanced drug permeation	Huabing, et al, 2004
Lecithin organogels	Cyclosporine	Higher drug accumulation into the skin	Liu, et al, 2007
Lecithin organogels	Aceclofenac	Improved drug delivery	Shaikh, et al, 2006
Solid lipid nanoparticles	Miconazole nitrate	Enhanced skin targeting effect with more drug accumulation.	Bhalekar, et al, 2009
Solid lipid nanoparticles	Podophyllotoxin	Provide epidermal targeting	Chen, et al, 2006
Solid lipid nanoparticles	Psoralen	Minimize side effects	Fang, et al, 2008

high concentrations which enhance the topical drug delivery. The presence of ethanol prolongs the physical stability of the ethosomes with respect to liposomes. The enhanced delivery of actives incorporated in the ethosomes [Table 2] can be ascribed to the interactions between ethosomes and skin lipids. That may open the new pathways due to the malleability and fusion of ethosomes with skin lipids, which results in the penetration of drug into deeper skin layers.^[44-46]

Non-vesicular approaches

Lipid emulsion: Lipid emulsions are thermodynamically stable, isotropic, low viscosity colloidal dispersions consisting of micro-domains of oil and/or water, stabilized by an interfacial film of alternating surfactant and cosurfactant molecules. The incorporation of lipids improves the physical stability of emulsion by forming a mono- or multi-layer around the dispersed liquid droplets which reduces the interfacial tension or increases the droplet-droplet repulsion. As topical vehicle, lipid emulsions [Table 2] have potential to enhance the permeation and form local cargo or micro-reservoirs in the deeper skin layers to provide localized action.^[47-49]

Lecithin organogels (LOs): LOs are micro-structured biocompatible gels, which are chiefly comprised of phospholipids (lecithins) and appropriate organic

liquids. LOs are simple in the sense that they are formed spontaneously by virtue of their thermodynamic stability. A number of therapeutic agents have been incorporated in the LOs for their facilitated transport across the skin and improve their therapeutics.^[50,51] In the wake of the commercial availability of one class of LOs, known as PLOs (Pluronic lecithin organogels) as template vehicle for topical delivery of many therapeutic agents, the importance of research in this area has increased manifold [Table 2].

Solid lipid nanoparticles (SLNs): They are submicron sized carriers for controlled and targeted drug delivery. Nanoparticles are diverse both in shape and composition. SLNs combine the advantages of different colloidal carriers, for instance - emulsions and liposomes. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules.^[52-54]

CONCLUSION

A number of drugs [Table 3] are available in the market, which have achieved improved efficacy and safety after incorporating the active agents in carrier systems. Therefore, putting new life into erstwhile discarded drug molecules by transforming them

Table 3: Vesicular (liposomes)-based indigenous products in market

Name of Product	Company	Use/ Indication
Fungisome™ (Amphotericin B)	Lifecare Innovation Pvt. Ltd.	Anti-infective
LipoDox™ (Doxorubicin)	Sun Pharma Industries Ltd.	Anti-cancer
Psorisome™(Dithranol)	Lifecare Innovation Pvt. Ltd.	Anti-psoriatic
Fungisome Gel™ (Amphotericin B)	Lifecare Innovation Pvt. Ltd.	Anti-infective

into novel formulations can serve as viable and cost effective alternative to the expensive and time consuming search of newer chemical entities. In recent times, new excipients, refined processing techniques, and a better knowledge of the physicochemical properties of vehicles and drugs have led to the development of new delivery systems that have the potential to re-invent the topical treatments of vitiligo. The authors of this review hope that further research with enhanced collaboration between pharmaceutical and dermatology researchers will bring this hitherto untapped potential to fruition.

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4) **Legends:**

Legends for the figures/images should be included at the end of the article file.

Multiple Choice Questions

1. How much population is affected in India by vitiligo?
 - a) 1%
 - b) 9%
 - c) 2%
 - d) 3-4%
2. All of the following are used for topical treatment of vitiligo except:
 - a) Pimecrolimus
 - b) Trioxsalen
 - c) Sirolimus
 - d) Methoxsalen
3. The wave length used in narrowband UVB is:
 - a) 305 nm
 - b) 311 nm
 - c) 320 nm
 - d) 316 nm
4. Herbal extract used for the treatment of vitiligo is:
 - a) Calcipotriol
 - b) Khellin
 - c) Tacrolimus
 - d) Ginger
5. The main disadvantages of conventional treatments are:
 - a) Slow response
 - b) Repeated application
 - c) Systemic absorption
 - d) All of the above
6. Advantages of phospholipid-structured carriers for dermal delivery includes:
 - a) Skin -friendly
 - b) Non-toxic
 - c) Biodegradable
 - d) All of the above
7. The advantages of new drug delivery systems include:
 - a) Improved patient -compliance
 - b) Site-specific delivery
 - c) Sustained effect
 - d) All of the above
8. Phospholipid structured carriers are divided in to:
 - a) Two types
 - b) Three types
 - c) None of the above
 - d) Five types
9. The first generation of elastic vesicles is:
 - a) Liposomes
 - b) Transferosomes
 - c) Ethosomes
 - d) All of the above
10. In recent studies, drug delivery of methoxsalen improved by:
 - a) Liposomes
 - b) Solid lipid nanoparticles (SLNS)
 - c) None of the above
 - d) All of the above

Answers
1. d, 2. c, 3. b, 4. b, 5. d, 6. d, 7. d, 8. a, 9. c, 10. d