Progress in psoriasis therapy via novel drug delivery systems

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Abstract

Psoriasis is a lifelong condition which is caused by the negative signals produced by immune system, which leads to hyper proliferation and other inflammatory reactions on the skin. In this case, keratinocytes which are the outermost layer of skin possess shortened life cycle and results in the alteration of desquamation process where the cytokines will come out through lesions of affected patients and as a result, scaling marks appears on the skin. These conditions may negatively affect the patient's quality of life and lead to psychosocial stress. Psoriasis can be categorized as mild, moderate and severe conditions. Mild psoriasis leads to the formation of rashes, and when it becomes moderate, the skin turns into scaly. In severe conditions, red patches may be present on skin surface and becomes itchy. Topical therapy continues to be one of the pillars for psoriasis management. Drug molecules with target effect on the skin tissues and other inflammations should be selected for the treatment of psoriasis. Most of the existing drugs lead to systemic intoxication and dryness when applied in higher dose. Different scientific approaches for topical delivery are being explored by researches including emollient, modified gelling system, transdermal delivery, spray, nanogels, hydrogels, micro/nano emulsion, liposomes, nano capsules etc. These topical dosage forms are evaluated for various physico chemical properties such as drug content, viscosity, pH, extrudability, spreadability, toxicity, irritancy, permeability and drug release mechanism. This review paper focus attention to the impact of these formulation approaches on various anti-psoriasis drugs for their successful treatment.

Introduction

Psoriasis is one of the life threatening skin diseases. It is an immune-mediated disorder with hyperkeratosis and other inflammatory reactions. Psoriasis can be categorized as mild, moderate and severe conditions. Mild psoriasis leads to the formation of rashes, and when it becomes moderate, the skin turns into scaly.[1,2] In severe conditions, red patches may be present on skin surface and becomes itchy. Topical delivery of drug is always prescribed for psoriasis for local action and to avoid first pass metabolism. Conventional methods of drug delivery systems are inefficient to provide target effect and higher bioavailability with its short half life and instability of the drug. Novel Drug Delivery Systems (NDDS) are the systems other than conventional delivery systems which include liposomes, niosomes, microemulsions, transferosomes, ethosomes, emulsomes, invasomes, dendrimers, nanoparticles, hydrogel, etc.[3-5] Novel drug delivery systems help to target into the tissues through skin layers and can provide better therapy for topical treatment of psoriasis. Stratum corneum (SC) is the major challenge for the drug to get into the target tissues, via skin layers. Penetration enhancers added in the drug carriers help to increase the penetration capacity of drug through the outermost layer of the skin. The most favorable drug delivery should provide high penetration through SC and should not cause any irreversible changes to the skin barrier.[6-8]

There are many challenges in transdermal delivery of drugs. There will be variability in percutaneous absorption due to site, disease, age, etc. Skin irritation may happen and if the toxicities due to drug are more, the skin gets damaged. The *first pass* metabolic effect of skin is also one of the challenges for topical delivery.[9-11] Novel drug delivery systems have lot of advantages. They increase safety and efficacy levels. Drug targeting specificity and lowering systemic drug toxicity are the important merits of NDDS. Also they have the ability to improve absorption rates and will prevent biochemical degradation of pharmaceuticals.[12,13]

Skin: a route for novel drug delivery

Skin is considered to be the largest and outermost organ of the human body. Among three important layers of skin, epidermis functions as a protective barrier of the body.[12,14,15] There are a lot of blood vessels and layers present in the epidermis. Sub layers are also present in this outermost layer such as stratum lucidum, stratum corneum, stratum spinosum, stratum granulosum, and stratum germinativum. Dermis is present beneath the outermost layer, which is composed of connective tissues.[16,17] Hypodermis is situated under the dermis layer. For the treatment of psoriasis, percutaneous absorption of drugs is one of the widely accepted way of drug delivery. The challenge that offered by topical treatment is the presence of SC as a barrier.[18-21] Conventional forms of drug delivery through skin have come across with many side effects and other application difficulties. Disruption of SC and targeting to the deeper layers of skin are not possible with ointments, creams etc. So, novel dermal delivery systems help to overcome these limitations, thereby enhance the bioavailability and potential of drug and are widely used for the treatment for psoriasis recently.[22]

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Importance of topical medication

For the treatment of psoriasis, topical treatment is mostly prescribed method since transdermal delivery of drug is the first line of defense for psoriatic skin. Psoriasis occurs when there is excess growth of skin cells due to faulty signals produced by immune system. These rapidly growing skin cells can be easily controlled by the novel topical medications which are meant for manipulating the functions of skin barrier.[23,24] Direct administration of drugs to dermis and epidermis can be achieved by these drug delivery methods. Apart from psoriasis, many other systemic treatments are carried out by topical delivery of drugs (Table 1).[25-27]

Novel formulation approaches for the treatment of psoriasis

Solid in oil nanocarriers

Solid in oil (S/O) nanocarriers were used as the vehicles for the transdermal delivery of methotrexate (MTX). MTX is an anti-neoplastic agent which was used to treat severe and

moderate psoriasis. The side effects caused by the systemic use of Methotrexate include hepatic toxicity, loss of vision, headache, hair loss etc. All these side effects can be reduced by effective topical delivery of MTX which were capable of targeting diseased cells. The problem associated with the drug was its solubility in water and ionized nature at physiological pH which reduce the passive diffusion through skin. So penetration enhancers were widely used in conventional delivery systems to increase the permeation. Liposomal delivery of MTX was a novel approach to reduce drug resistance offered by SC. The lipophilic conjugates inside the liposome as well as lipophilic nature of MTX enhance passive diffusion through plasma membrane.

Fan Yang *et al.*[28] have conducted the studies on solid in oil nanosuspensions which was a kind of oil based nanocarriers. Here, suspension type nanocarrier was introduced as a reverse micellar system into which MTX coated non-ionic surfactants (ER290, ER190 or L-195) complex was incorporated. The oil based nanocarriers help in the penetration of MTX through SC. Compared to other conventional drug delivery systems such as liposomes, niosomes etc, the S/O nanocarriers possessed higher penetration capacity. Due to lipophilic nature and nano level size of the carrier it could enhance the fusion of MTX and stratum corneum which enhanced the permeation capacity. Also, this system possessed better dispersability as well as excellent stability. These nanocarriers were highly soluble in organic solvents and became transparent solution when mixed with isopropyl myristate (IPM). Absence of water in the formulation makes it as an anhydrous medium so that the risk of oxidation and biochemical degradation could be reduced effectively.

In that study, to increase the solubility of drug, a complex of amino acids and MTX have been prepared and enhanced stability was achieved by introducing the surfactant coating technique. S/O oil suspension nanocarrier could accommodate multidrug such as MTX, amino acids and urea. Urea had an important role in the releasing mechanism of MTX from the nanocarriers. Uniform size distribution was achieved by the addition of IPM (50-100 nm).[28]

Nano gel

Gillian S. Leslie Singka *et al.*[29] have developed nano gels for the topical delivery of MTX varies from 100 nm to 1 µm in size. The swelling nature of the colloidal particles in many solvents was one of the reasons for the wide application of this delivery. The monomers used in nanogels were having vital importance in volume phase transition depending on various stimuli such as temperature, solvent type and ionic strength. Styrene, divinyl benzene, methyl methacrylate etc could be used for the production of nanogels. The most widely used monomer is NIPAM (N-isopropylacrylamide) since it could collapse at low temperature (32-34°C). So in that study, the nanogel was prepared with co-polymer of NIPAM and non ionic monomer butacrylate (Figure 1).

The nanogel could undergo de-swelling and the expulsion of MTX was influenced by change in temperature during penetration through skin. The incorporation of saturated Na_2CO_3 could enhance MTX flux from nanogel and by the use of NIPAM monomers, the biosynthesis of PEG_2 could be reduced which was known to be an inflammation mediator.[29]

Hydrogels

Hydrogels could be produced by the cross linking of polymer chains and lead to the formation of polymer gel with high molecular weight. Hydrogen bonding is the main mechanism by which large amount of water is entrapped by hydrogel.

Hydrogels were used to increase the effectiveness of topical delivery of MTX by iontophoretic delivery. The effectiveness of delivery of MTX by iontophoretic mechanism depended on the type of hydrogel used and the amount of drug loaded into it. So, in the topical treatment of psoriasis, hydrogels have shown vital importance especially in the delivery of MTX.[28]

Sanjula Baboota *et al*.[30] have found out the use of nano carrier hydrogels for the topical delivery of Betamethasone dipropionate to treat psoriasis. Betamethasone dipropionate is a corticosteroid with anti-inflammatory activi-

Table 1. Novel transdermal delivery of topical drugs for psoriasis treatment.

Drugs	Type of drug delivery systems
Methotrexate	Solid in oil (S/O) nanocarriers, nanogel,hydrogels, microemulsions, deformable liposomes
Cyclosporin	Pro-dispersion liposphere
Clobetasol propionate	Microemulsion based gel, nanoemulsion
Calcipotriol	PEGylated liposomes
Betamethasone	Nano carrier hydrogels
Tazarotene	Hydrophilic ointment
Temoporfin	Liposomes
Tretinoin	Solid lipid nanoparticles, semisolid nanomedicine

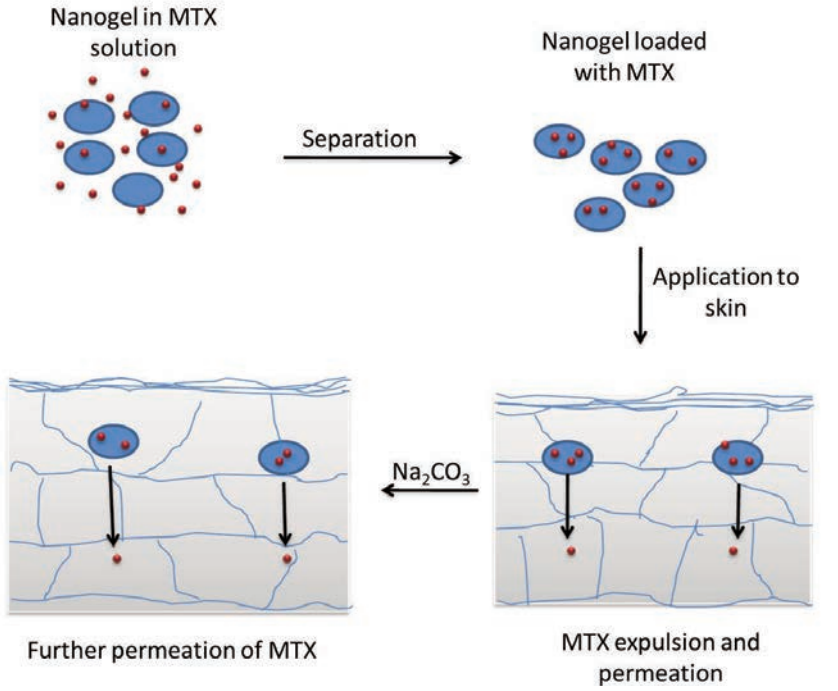

Figure 1. The proposed mechanism of methotrexate delivery.

ty. There are various conventional dosage forms of Betamethasone dipropionate such as ointment, creams, lotions and foams. But, the poor permeability of this drug reduces its effectiveness after application. Nano carrier hydrogels could help to increase the permeability without any chemical enhancers and without any side effects to skin. Incorporation of salicylic acid into this system enhanced the descaling of skin and stability of formulation. Also, it has many advantages including enhanced drug loading capacity, low skin irritation etc.[31]

Micro emulsions

Micro emulsions are stable formulations containing a mixture of oil, water and surfactant. Salts are present in the aqueous phase and hydrocarbons, olefins etc. are present in the oil phase. Three kinds of micro emulsions are present such as direct, reversed and bicontinuous. Direct type of micro emulsion is formed by dispersing oil in water and in the case of reversed type, water is dispersed in oil.

Micro emulsions were used for the passive delivery of MTX. The effectiveness of delivery of MTX was more in the case of direct type of micro emulsion and large amount of MTX could be detected on skin surface.[28]

Micro emulsion based gel

Colloidal carriers were one of the major delivery systems for Clobetasol propionate. But, among all the colloidal carriers such as nano structured lipid carriers, lipid nano spheres, polymeric nano capsules etc, micro emulsions offered many advantages. The preparation of micro emulsion was quiet easy compared to other formulations. Both hydrophilic and lipophilic drugs could be highly distributed in micro emulsions so that incorporation of Clobetasol propionate into the micro emulsion globules resulted in the increased permeation through SC. Efficient dermal delivery and long-term stability of the micro emulsions helped them to be used for transdermal delivery of drugs. The major disadvantage associated with microemulsion was its low viscosity. The retention capacity in the skin may get reduced due to this reason and so gelling agents could be incorporated in micro emulsions. These gelling agents helped to increase the viscosity and could improve the topical delivery application.[31]

Nano emulsion

Nano emulsions are novel formulations for the topical delivery of drugs. The main advantage of nano emulsion is the loading of less amount of drug so that it will reduce the risk of adverse effects of high dose drugs and it can deliver poorly water soluble drugs into the bottom of skin layer. The absorption rate of drug can be increased since the drug particles are in sub-micron size (up to 10-200 nm). Nano emulsions are reproducible and controlled release of drug in the target site is the another major advantages.

Clobetasol propionate iwa also delivered through nano emulsions which was an advanced delivery system for the topical administration of drug. Effectiveness of psoriasis treatment was purely based on the prolonged action of drug, without any adverse effects. Replacing conventional systems with NDDS was found to be more important to improve safety. Sarfaraz Alam *et al.* have developed oil in water nano emulsions in which oil phase was composed of Clobetasol propionate.[32]

Pro-dispersion liposphere

Pro-dispersion formulations are novel drug delivery systems composed of solid fat, amphiphilic solvents and dispersing agents. Cyclosporin is an important drug widely used to treat psoriasis and has the ability to suppress immune reactions by interfering in the growth of T cells.

Avramoff *et al.*[33] performed a work on prodispersion liposphere for the delivery of lipophilic drug Cyclosporin. In this formulation, a homogeneous solution was prepared containing Cyclosporin, surfactants, ethyl lactate and lipids. When this solution was added into aqueous media, the whole system converted into dispersion which could be used for the delivery of Cyclosporin. The main advantages of this formulation were the achievement of improved bioavailability for water insoluble drugs and stability under normal conditions for about 2 years.[33]

Liposomes

Liposomes are vehicles widely used as topical delivery systems which are varied in their membrane composition, vesicle size and cholesterol content. There are many factors that can enhance the dermal delivery of liposomes through skin such as size, charge, fluidity etc. Surfactants have important role in the permeation of drug through SC. Surfactants present inside the liposome have the ability to break the bilayer and the drug can easily permeate through skin.

Liposome was used to reduce the solubility difficulties of temoporfin.[34] Enhanced temoporfin could be obtained from surface modified liposomes. Major drawback associated with this formulation was its poor colloidal stability. Among surface modified liposomes, PEGylated liposomes showed better activity in delivering drugs to epidermis.

PEGylated liposomes

PEGylated liposomes are novel drug delivery systems commonly used for systemic as well as transdermal delivery of drugs. Calcipotriol is a potent drug used to treat psoriasis by inhibiting the proliferation of keratinocytes. Since this drug is an analogue of vitamin D_3, it undergoes conjugation with D-vitamin receptor present in the epidermis of skin. This specific action of Calcipotriol can be done only with an efficient drug delivery system such as PEGylated liposomes that can target the drug to lower layer of epidermis.

Stability of PEGylated liposomes was achieved with hydrophilic polymers *i.e.*, poly ethylene glycol (PEG). PEGylated liposomes could increase the *in vivo* stability by restricting interaction with plasma proteins. Some alterations in the drug release profile could be obtained due to the presence of polymer. One of the major applications of PEGylated liposomes was its active targeting through receptor-ligand conjugation to specific tissues.[35]

Deformable liposomes

In 2012, Pathomthat *et al.*[36] have come with a discovery of methotrexate-entrapped oleic acid containing deformable liposomes. Improved skin delivery of drugs by this novel drug delivery system was the major advantage, which was influenced by enhanced penetration and permeation of vesicles into SC under non occlusive conditions. Also, it was highly useful for the formulation of lipophilic cosmetic products.

In the study, the physico-chemical properties and *in vitro* release characteristics of this formulation have been investigated. Phosphatidylcholine and oleic acid were the two main substances used for the preparation of deformable liposomes. Oleic acid was used as skin penetration enhancer and the enhanced permeability of liposomes was due to the elastic nature of oleic acid.[36]

Hydrophilic ointment

Nail psoriasis is a special category for which specific treatment is required. About 10 to 50% of psoriatic patients suffer from nail psoriasis and has a psycosocial impact on the quality of life. Tazarotene is newly synthesized drug which is known to be retinoid analogue derived from vitamin A. It helps to modulate the proliferation of keratinocytes and thus reduces inflammation. This drug has better effect on skin, especially matrix, bed and periungual parts of nail. Higher dose of this drug may cause toxicity and so application of lower dose is recommended. Hydrophilic ointments are used recently for administering Tazarotene to the skin. This formulation could help in the controlled release of Tazarotene and enhanced bioavailability of drug was achieved.[37]

Solid-lipid nano particles

Tretinoin is a well employed drug in the treatment of several skin diseases such as photoaging, acne, and psoriasis. Tretinoin will

come under the category of retinoic acid. High dose as well as prolonged action may cause skin irritation. Application of Tretinoin directly to the skin may lead to some adverse effects. Encapsulation of drug in vehicles is a better way to reduce such drawbacks. Encapsulation will increase the stability of the drug as well as make convenient way to deliver the drug.

Incorporation of Tretinoin in solid lipid nano particles provided stability, sustained release and protection from degradation. Easy scale up of the production process was one of the major advantages of solid-lipid nano particles. Researchers have used chitosan solid lipid nano particles, which was highly compatible with Tretinoin and possessed a lot of advantages like wound healing, bio adhesion, anti bacterial activity etc. The anti bacterial activity of chitosan combined with effects of Tretinoin resulted in the efficient topical treatment for psoriasis.[38]

Semisolid nano medicine (nano capsule)

Aline Ferreira Ourique *et al.*[39] have done some experiments on nano medicine (nano capsule) to modify the penetration and photo stability of Tretinoin by nano encapsulation. Among all nano particles, nano capsules and nano spheres were excellent carriers of the drug. Evaluation of skin care formulations such as ointments and creams are difficult since these drugs could be removed easily by contacting, wetting and much other process where as nano capsule suspensions act as reservoir systems and after application, it has the capacity to accumulate on the skin surfaces for long period. Here, the drug could then reach to deeper layers of skin and provide the prolonged effect. The specific surface offered by nano particles were relatively more and so, encapsulation and homogenous release of drugs were major advantages of these nano medicines.[39]

Conclusions

Psoriasis is a chronic skin disease affecting around 2% of the US and European population and a lot of care should be taken to minimize the severity of this disease. There is a list of drugs used to treat psoriasis which include Methotrexate, Cyclosporin, Clobetasol propionate, Calcipotriol, Betamethasone, Tazarotene, Temoporfin, Tretinoin etc. Application of high dose of these drugs using conventional formulations creates toxicity and other difficulties so that to minimize these hazards and to improve the targeting effects, novel drug delivery systems (NDDS) are preferred especially for mild and moderate psoriasis. Apart from these topical therapies, some other second and third line treatments are used nowadays which include phototherapy, Psoralen and Ultraviolet A Radiation (PUVA) therapy, Broadband Ultraviolet B (UVB) therapy, Narrowband Ultraviolet B (NB-UVB) radiation, laser treatments etc. All these therapies are based on different radiations emitted from sunlight. In these treatments, the radiations would bombard with skin cells emerged due to psoriasis and thus destroy them. Since most of the novel drug delivery systems are on progress, the clinical studies could not extend more which makes a gap between the two main domains *i.e.*, clinical phase and pharmaceutical phase.

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