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Potential advancements of nanocarriers in topical drug delivery: a mini review

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ABSTRACT

The topical route offers many attractive alternatives for the drug delivery as compared to oral administration and injection. Besides, skin provides a reservoir that delivers drug delivery for days. Nanotechnology, science at nano scale, has been emerged as a strong and potential discipline focusing on atom and molecular mechanisms that contributes to a diversity of applications in various fields such as controlled and targeted drug delivery, bio-imaging, agriculture, 3D printing, physics, mechanics, etc. Nanocarriers avoid local irritation and toxicity. The nanocarrier drug delivery system has emerged as interesting field that broaden up the use various drugs (lipophillic and hydrophilic) and provides ease of fabrication of formulations that can be efficiently delivered via topical route. The nanocarrier based delivery has been explored to deliver hydrophilic and lipophilic drug candidates through stratum corneum with local and systemic effects for the treatment of variety different skin diseases. Nanocarriers such as a nanoparticle, dendrimer, ethosome, and liposome are made up of polymers and material that differ in structure and chemical nature. These nanocarriers can deliver the drug at the target site and reduce side effects by lowering drug doses. This review covers all aspects of pharmaceutical nanocarriers related to their applications and recent advancements.

Keywords: *Nanotechnology; nanocarrier; topical delivery; skin diseases; lipophilic; hydrophilic.*

1. INTRODUCTION

Skin is the layer of soft tissues and outer covering of body and consists of dead flattened, keratin-rich cells, corneocytes and multiple layers like Epidermis, Dermis, and subcutaneous tissue. Epidermis layer is an upper layer of skin and is made up of stratified keratinized squamous epithelium. Skin has a waterproof layer that protects deeper structure. Topical drug absorption has three mechanisms i.e., transcellular, intercellular, follicular. Passages of the drug are through corneocytes and lipid bilayer of skin, barriers are in the outermost membrane of epidermis that allows a maximum amount of chemical penetration through stratum corneum or whole skin. Creams and gels are rubbed on to the skin and indicated in several pains and skin infections (local and site specific) [1]. Skin has an important feature that is bi-layered array structured. The outermost homogenous membrane of stratum corneum knows as epidermis which has thickness ranges from 10-20µm. Stratum corneum consists of a 15-25 layer of flattened, hexagonal cell joined in a matrix of lipids. It has barrier properties that have high density & low hydration rate of 15-20%. These barriers help prevent loss of internal body components, water loss from external surroundings. Epidermis is a basement membrane having 5-7 nm thick, two-layered i.e. Lamina Lucida & lamina densa. Dermis is 0.1-0.5cm thick and having collagenous and elastin fibers. In epidermal membrane, mucopolysaccharides join to peptide chain to form proteoglycans. Dermis also helps skin for nutrition, repair, and immune response for body parts. Epidermal hair follicles and sweat glands also embedded in the dermis. Topical preparation avoids first pass hepatic metabolism of the drug, which increase pharmacological activity on localized affected area and also penetration of drug can be aided by using penetration enhancer [2,3,4,5].

2. NANOCARRIERS

Nanocarrier system has micron particle size <500 nm. Nanocarrier can alter the basic properties & bioactivity of drugs. Pharmacokinetics and bio-distribution improvement also decrease toxicity and an increase in solubility and stability, targeted and site-specific delivery of actives are some important features in which nanocarrier can be used in a drug delivery system. Physiochemical properties of nanocarrier alter composition (organic, inorganic), sizes (small, large), shape and surface properties [6]. Nanocarriers are classified into various delivery systems which are represented in figure 1.

Particulate system and a vesicular system like noisome, ethosome, SLN, microsphere, liposome have got the best position in drug delivery as a colloidal carrier [7]. Lipid nanocarriers having vesicular conformation are the most convenient form to carry lipophilic and hydrophilic active agent.

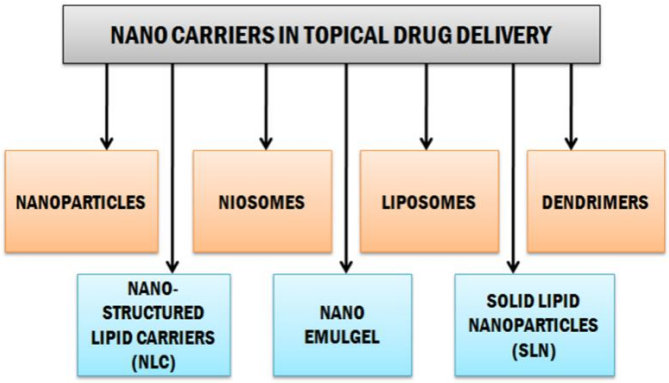

Figure 1. Types of Nano-carriers used in topical drug delivery.

Nanocarrier offers several benefits as a drug delivery system such as the delivery of a drug is decrease to non-target tissue, increase drug concentration at target site, decrease toxicity, improve stability of a drug, reduce irritation caused by active agent, taste masking of drug, and prolonged drug shelf life [8].

3. APPLICATION OF NANOCARRIER IN TOPICAL DRUG DELIVERY

Nanocarriers are first used as drug delivery in the parental and oral route of administration and still many studies are going on. The nanocarriers such as liposome, polymeric and lipoidal nanoparticles, niosomes etc. have been explored in local and systemic applications of skin. A special focus is paid to develop strategies in topical application of nanocarrier for treating alopecia, acne and transcutaneous immunization. Inflammatory skin diseases like psoriasis, atopic dermatitis, eczema, are various skin disorders are associated common efferent T-lymphocyte mediated response. Presently, lipid nanoparticles have been explored to treat skin problems like psoriasis, eczema, etc. Lipid nanoparticles with various drug candidates belonging to categories such as glucocorticoids, NSAIDs, antimycotics are under investigation for their dermal application potential in these immunity mediated skin disorders [9,10].

4. FACTOR AFFECTING TOPICAL DRUG ABSORPTION

4.1. Physiological factors

a. Lipid content of skin- act as a barrier for absorption of all drugs and minimizing the barrier property leads to increased penetration.
b. The thickness of the skin layers- high the thickness lower penetration rate.
c. Hair follicles
d. The skin pH of normal skin is ranging from 4-6 pH that is acidic & internal surrounding it is neutral usually ranged from 7-9 pH. The pH also helps maintains skin functions like enzyme regulation, involved in synthesis as well as affect percutaneous penetration.
e. Hydration of skin- Drug skin penetration can be increased by hydration of stratum corneum. In the increasing hydration of stratum corneum, there is a process in which impermeable film can lose water from the surface thereby decreasing the diffusion path length [11-13].
f. Blood flow- Blood flow can enhance the absorption of drug through dermis of skin.
g. Skin temperature- Temperature shows the direct proportional relation with skin penetration. The warmer the skin more permeable the drug will be in the dermis. The mechanism involves the heat that increases the energy of protein, lipid in cell membrane & drug particle and hence provides more absorption through the dermis.

4.2. Physicochemical factors

a. Partition coefficient- high log p-value represents high absorption. It is used to calculate distribution of drugs within the human skin. The hydrophilic drug is less absorbed due to the low partition coefficient.
b. Degree of ionization.
c. Molecular weight- molecular weight is inversely proportional to percutaneous absorption; molecular weight for transdermal drug delivery should be less than 500 Daltons.
d. Effect of vehicles [12,14].

In the literature, various reports have been published on nanocarriers using different drugs for topical and transdermal delivery and their outcomes are represented in table 1.

Table 1. Various literature reports for nanocarriers used for topical drug delivery.

Author	Year	Research	Outcome	Reference
Gannu *et al.*	2010	Studied the decrease in availability of Lacidipine based transdermal gel.	Results found that LCDP penetrate by Transdermal Route.	[15]
Azeem *et al.*	2012	Investigated the pharmacokinetics & biochemical of oil based nanocarrier for transdermal delivery of ropinirol.	Results found in gel preparation of ropinirol have improvement in penetration through skin.	[16]
El - Hadidy *et al.*	2012	Micro emulsion as vehicle for topical administration of voriconazole: formulation & evaluation.	Results found that nanoemulgel formulation (BG4-BG6) as surfactant, co- surfactant Concentration was decrease &skin permeation rate increase in two fold.	[17]
Arora *et al.*	2014	Investigation of nanoemulgel as transdermal delivery system for poor soluble drugs ketoprofen.	Results of transdermal permeation of ketoprofen from nanoemulgel were found by Franz diffusion cell, drug was used as optimized formulation.	[18]
Helena *et al.*	2015	Preparation of Deformable liposome for transdermal delivery of piroxicam	Results of entrapment of piroxicam in the aqueous compartment, through β-cyclodextrin inclusion complexes, enabled higher entrapment efficiency.	[19]
Sridevi. S. *et al.*	2003	Dendrimer Mediated Transdermal delivery: enhance bioavailability of indomethacin.	Result of phase solubility study is done by Higuchi profile. *In vivo* test steady state flux was obtained, and	[20]

Author	Year	Research	Outcome	Reference
			Cmax value is high in G_4-NH_2 and G_4-OH formulation.	
Aqil. M. *et al.*	2014	Design and optimize transdermal delivery system of PZ based on NLC.	Result is reduction in particle size of developed formulation, increase in drug loading and enhance skin permeation rate, in vivo pharmacokinetic and pharmacodynamic study is done.	[21]
Rakesh. S. *et al.*	2013	Prepared Solid lipid nanoparticle as carrier of metformin in transdermal delivery.	Result of preparation is the particle size is differing in compare to other formulation due to composition variation, zeta potential. SEM, TEM shows discrete spherical structure without aggregation.	[22]

5. TYPES OF NANOCARRIERS

Based on the size, types and nature of material used and purpose of drug delivery, nanocarriers are further categorized into following subcategories:

5.1. Nanoparticles.

The size of the nanoparticle is less than 1000 nm, Nanoparticle are classified into 2 types: nanospheres and nanocapsules. Nanosphere is a solid core structure whereas a nanocapsule is hollow core structure. Nanoparticle is used to decrease the solubility of high range hydrophobic drugs and have sustained and controlled release in topical delivery. The stability of therapeutic agents is increased by various chemical and physical methods. Nanoparticles can be synthesized using combination of polymers from synthetic as well as natural origin. Based on types of polymers, Chitosan, polysaccharides obtain from chitin (natural source) used to make nanoparticle for topical preparation It is water-soluble and bioadhesive. It can be prepared by ionic cross-linking, covalent cross-linking, precipitation, polymerization, of size 20- 700 nm [23,24]. The synthetic nanoparticles such as aliphatic polyesters, tyrosine derived polymers are some examples of this class and used for lipophilic, small drug molecules. Nanoparticles offer several advantages such as they are composed of biodegradable material, drug loading is done for both hydrophobic and hydrophilic drugs, targeted delivery can be achieved using antibodies [25].

5.2. Liposomes.

Liposome consists of bilayer of phospholipids and are spherical vesicle ranges from 10 nm to 20 mm. Liposome has the ability as a solublizing agent for poorly soluble drugs when it applies to skin, penetration enhancer and reduces the chance of side effects of the drug [26]. Liposome has many advantages in several industries such as cosmetics, industrial and medical field.

Liposomes in topical routes have good treatment in local and systematic route and have the ability for encapsulation in hydrophobic and lipophilic drugs and protect drug to be degraded [27]. Liposome interacts with skin using many mechanisms and absorbed on skin surface resulting drug release via lipid channels and forms film with high skin hydrating conditions and penetrate in stratum corneum [28].

Liposomes are drug carriers that facilitate various factors like decrease toxic effects, improved drug stability, long circulation time, site targeted delivery of drug. Liposome having a surface charge that is it can be positive, negative, neutral depends on functional groups and pH medium. Some benefits are associated with liposomes such as excellent biocompatibility, simple manufacturing, high drug loading and increased stability due to protein carriers [29,30].

5.3. Dendrimers.

They are highly branched, nanoscopic macromolecular star shaped structures basically divided into three parts: a central core, an interior dentritic structure (branches) and exterior surface with functional surface groups. They are chemically mono-dispersed and form conjugates with many functional groups depending on the nature of its branch formation [31]. Classification of dendrimer is based on the number of generations. In the creation of core, stepwise synthesis is called the first generation. Every step in addition to monomer developed the next generation. Dendrimers having a high surface charge density due to ionizable groups that helps to attach the drug to electrostatic force. These dendrimer helps drugs to better solubility, increasing the transportation of drugs to biologically membrane. Dendrimer has both positive and negative charges that allow forming complex with different drugs. It offers various benefits such as increase stability of active agents, improves bioavailability, good carriers of drugs due to better interactions, easy to functionalize and prepare [32].

5.4. Niosomes.

Niosomes are bi-lamellar vesicular colloids and subdivided into small uni-lamellar vesicles (10-100 nm size range) and multi-lamellar vesicles having 100-3000 nm size range [33]. Unlike liposomes, niosomes consists of non-ionic surfactants hence provide more stability to the system and capable of encapsulating hydrophilic and hydrophobic actives. In topical preparation, niosomes interacts with skin resulting loss of water from the skin layer that enabled good penetration of drugs [34]. Noisome absorbed on skin surface and acts as drug reservoir resulting in increase in thermodynamic activity of a drug [35,36]. Structurally, noisomes are lamellar formations (uni and multi lamellar) produce by a mixture of non-ionic surfactants of alkyl polyglycerol ether and cholesterol [37]. Method of noisome preparation is by hydration of non-ionic surfactants by hydration method. It has several techniques: pH gradient method, lipid layer hydration, EER injection, etc. [38]. The structure of noisomes contains the hydrophilic head of surfactant toward outer and innermost bilayer and hydrophobic tail toward the center of the bilayer. Niosomes are used as drug carrier because of high stability, pure variability, low cost. Also, the niosomal system provides low toxicity and biodegradability, easy fabrication, targeted drug delivery, malleability [39].

5.5. Nanostructured lipid carriers (NLC).

Nanostructured lipid carrier (NLC) is another form of lipoid nanocarrier. Preparation of NLC is usually done by blending of solid lipid with liquid lipid which makes amorphous solid in the

ratio of 70:30 at ambient temperature [40,41]. NLC are of three types based on composition, production, formulation parameter. The particle size in NLC ranges from 10-1000 nm [42]. The formulation of NLC involves the use of physiological and biodegradable lipids that are less toxic in nature [43]. NLC has biphasic drug release and has many advantages like high skin hydration, it has small particle which has the benefit of drug penetration into the skin, and they are stable in storage. NLC is an advanced generation of nanoparticle having major attention as novel drug delivery in topical preparation [44].

5.6. Solid lipid nanoparticles (SLN).

Solid lipid nanoparticle has particle size 50-1000 nm. It is made up of a single layer of shell and core. Solid lipid is present in matrix drug dissolve in a solid core matrix. These are made up of glyceride, purified triglyceride, waxes. SLNs consist of lipids that less toxic due to their physiological similarity and biocompatibility. The small size of particles facilitates deeper penetration of drug into the skin and also capable of increasing hydration of skin. The system has better stability because they are of solid nature and so mobility of active ingredients is reduced during storage [45-47].

5.7. Nanoemulgel.

Nanoemulgel consists of a mixture of nanoemulsion in a gel base, addition of nanoemulsion system in the gel matrix for good skin penetration and act as a drug reservoir by which drug release from inner to outer phase. The nanoemulsion based gel shows good adhesion for lipophilic drug having high solubility in oil phase leading to better skin penetration. When compared with cream, ointment and other conventional semisolid preparations, the nanoemulgel provides better drug permeation through skin, less stickiness and improved patient compliance. Now nanoemulgel has been used in the treatment of various skin related problems [48]. Nanoemulgel system offers benefits in controlling the release of drugs due to mucoadhesive property of hydrogel that can modulate release of drug particles through multiple layers [49,50].

Nano emulgel is usually prepared by combining nanoemulsion (o/w and w/o) with hydrogel (made of synthetic or natural polymers). By adding gelling agent, stability of topically administered drug increases by reducing surface and interfacial tension [51]. There is higher solubilization capacity & thermodynamic stability in nanoemulsion, long self-life, and fast onset of action [52]. There is a weak interaction of biocompatible with surfactants that modify the rheological behavior of nanoemulsion [53].

There are two types of nanoemulsion: oil in water (o/w) and water in oil (w/o). Nanoemulsion (o/w type) shown to have positive results on the transportation of bioactive or lipophilic drugs into the deep part of the skin [54]. The nanoemulgel of the topical route is much preferred as compared to oral route for administration due to bitter taste of drug candidate [55]. Various advantages of nanoemulgel such as quality adhesion to skin, help in poor water-soluble and lipophilic drugs, help in releasing of the drug having short half-life, non- irritant & non- toxic, and improve skin penetration and drug deposition, better loading than other formulations [56].

6. NANOCARRIER BASED MARKETED FORMULATIONS

Because of numerous advantages, nanocarriers are popular in the formulation and development of various pharmaceuticals and cosmetics. Some of the marketed formulations based on lipid nanocarriers with their brand and company's name are depicted in Table 2.

Table 2. Commercial preparations/cosmetics containing various nano-carriers for topical application [57-65]

S. No.	Marketed Products	Type of Nanocarrier	Company's Name
1	Ageless facelift cream	Liposome	I-Wen Naturals
2	Ameliox	Liposome	Mibelle Biochemistry
3	Revitalift	Liposome	Loreal
4	Mayo Niosome Base Cream	Niosome	Laon Cosmetic
5	Anti-Age Response Cream	Niosome	St. Botanica
6	Allure Body Cream	SLN	Chanel
7	Allure Perfume Bottle	SLN	Chanel
8	Cutanova Cream Nanorepair	NLC	Dr. Rimpler
9	Intensive Serum Nanorepair	NLC	Lacura
10	Nano cream	Nanoemulsion	Collonil
11	Vital Nanoemulsion A-VC	Nanoemulsion	Marie Louise
12	Lip Tender	Nanosphere	LHB
13	Nano sphere Plus	Nanosphere	Derma Swiss

7. FUTURE ASPECTS OF NANOCARRIER IN TOPICAL DELIVERY

There is lots of advancement in nanotechnology (nano-sized drug delivery) in the pharmaceutical field. In today's scenario, drugs incorporated nanocarriers provides less toxicity, fastest drug delivery, high efficacy, and high bioavailability. Currently, for nanocarrier based drug delivery, there are lots of clinical trials are going on and some product have been launched in the commercial market as well. The use of biocompatible nanomaterial for developing these carriers is of important concern to avoid cytotoxicity and hypersensitivity. The nano-size delivery enables controlled release of drugs, high drug loading and better delivery system for the drug candidates for which suitable delivery system is not yet developed. Also the system can be considered cost-effective and safe. The proper measures are there for acute and chronic toxicity of drugs on humans using nano delivery. Targeted skin drug delivery through nanosystem results in sustaining drug release & maintains a localized effect on skin by reducing skin diseases.

8. CONCLUSION

The particulate system has much advancement in topical drug delivery using nanocarrier that enhance drug penetration to skin having high efficacy and target the epidermis thus lowering the side effects. They also deliver both hydrophobic & hydrophilic drugs. Moreover, major advantages are small size, high surface energy, structured, composition. Further, future research opens up scope for various drugs, to be incorporated in nanosystem, ensuring benefits along with in-vivo and environment associated risk factors. Various topical nanoparticle cosmetic products are approved and marketed based on safety and extraordinary performance and hence nanocarriers offer potential advantage for the pharmaceuticals industries as well.

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