Skin Absorption Modulation: Innovative Non-Hazardous Technologies for Topical Formulations

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Abstract: The achievement of skin drug delivery needs to conciliate two paradoxical terms: firstly, the major barrier of permeation formed by the stratum corneum needs to be circumvented for skin drug delivery (i.e., skin absorption); secondly, the drug deposition within the skin should be ideally accomplished with a restricted percutaneous absorption. At strictly speaking, the terms of this paradox are not solvable, since Fick's laws stipulate that the rate of drug transport is not separable from the gradient of drug concentration. In this field, drug carriers as vehicle have been reported in the recent years as one of the most promising strategy to address skin drug delivery. Indeed, the passage of drug loaded particles through the stratum corneum and/or *via* the follicular ducts might (i) target the drug deposition in specific skin sites, (ii) control and sustain the cutaneous drug release, (iii) protect the drugs against substantial epidermal metabolism, and (iv) reduce the percutaneous absorption. The present paper reviews the different drug carrier systems which do not require solvent in their process, with their physicochemical characteristics, the mechanisms of drug delivery and drugs that were efficiently used as a penetrant.

Keywords: Nanotherapeutic, solid lipid nanoparticles, nanostructured lipid carriers, skin diseases.

INTRODUCTION

A wide range of nanocarriers has been developed for topical application of drugs presenting advantages in systemic treatment such as minimal side effect, absence of first-pass metabolism and in topical treatment allowing targeting specific skin layers or appendages [1]. The main barrier of cutaneous or percutaneous delivery is the non viable stratum corneum, depicted as a "brick and mortar" model [2] where corneocytes are packed in intercellular lipid matrix. This organization defines the physicochemical properties of potential drug candidates and vehicles; thus, major efforts were realized to characterize the potential universal carrier for topical drug delivery, modifying, e.g., particles size, deformability abilities, components "skin-like" without loosing sight of *la raison d'être* of nanocarriers which are drug protection and controlled release.

Liposomes were firstly developed as vesicular systems made of amphiphilic bilayers delimitating an aqueous core. Those nanocarriers are produced by different methods such as lipidic film hydration, organic solution dispersion or detergent elimination requiring solvent evaporation or detergent removal. Another nanosystems based on lipid structure are solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) obtained by hot high pressure homogenization of triglycerides, glycerides or waxes at solid state at ambient temperature. Those nanocarriers are of increasing interest due to their achievement process which does not require the use of organic solvent.

As an alternative to liposomes, polymeric nanoparticles were developed increasing storage stability and half-life; formed from polymer (i.e. emulsification – solvent evaporation, nanoprecipitation, salting out, emulsification – diffusion) or monomer polymerization (i.e. micellar polymerization, dispersed polymerization, emulsion polymerizsation or interfacial polymerizsation) allowing utilization of a wide range of polymers, selected on their biocompatibility, biodegradation and expected controlled release.

A third class of nanocarriers incorporating high amount of surfactants is described; based on non ionic surfactants (niosomes) or a mixture of surfactant and co-surfactant (microemulsions), they present different thermodynamic stability and enhance penetration through stratum corneum lipid disorganization acting like a penetration enhancer.

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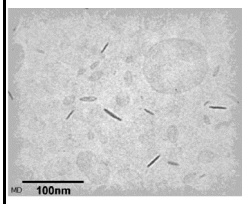
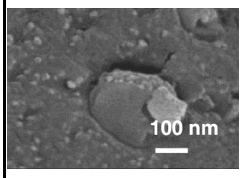
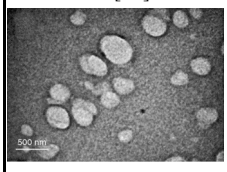
Table 1. SLN and NLC Lipid Particles Reported for Skin Drug Delivery

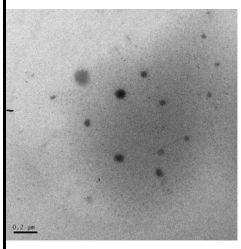
Drug Carrier Systems	Physicochemical Characteristics	Mechanisms of Drug Delivery	Penetrant
Solid lipid nanoparticles  Cryo TEM images of solid lipid nanoparticles (adapted from [5]).	Composed with solid lipids [6], surfactants, drugs. UV-blocking potential [4]. Three different models for the incorporation of active ingredients into solid lipid nanoparticles [7] : Homogeneous matrix model Drug-enriched shell model Drug-enriched core model Example of composition of solid lipid nanaoparticles (adapted from [8]): Compritol® 888 ATO 5.0% Poloxamer 188 2.5% Dynasan® 114 10.0% Poloxamer 188 1.0% Lipoid® S75 0.5% Precirol® ATO 5 10.0% Poloxamer 188 2.5% Sodium cholate 0.5% Compritol® 888 ATO: glyceryl dibehenate, tribehenin, glyceryl behenate Dynasan® 114: Glyceryl trimyristate Precirol® ATO 5: Glycerol palmitostearate Lipoid® S75: soja lecithin with 68% phosphatidyl choline.	(Reported by [4]) Occlusivity of solid lipid nanoparticles increases water content of the skin. Local depot for the sustained release of active compound in dermis. Follicular targeting.	**Anti-acneic** Isotretinoin [9] Vitamin A [10] **Anti-mitotic** Podophyllotoxin [11] **Anti-inflammatory** Triptolide [12] Prednicarbate [13] Psoralens [14] **Antifungal** Clotrimazole [15] **Anti alopecia** Minoxidil [3]
Nanostructured lipid carriers  Cryo-field emission scanning electron microscopy images of a nanostructured lipid formulation [16].  Transmission electron microscopy micrographs of nanostructured lipid carriers made with stearic acid containing 15 wt% oleic acid [17].	Nanostructured lipid carriers composed of a solid lipid matrix entrapping a variable content of liquid lipid nanocompartments [18, 19]. Blending solid lipids with liquid lipids (oils) results in matrix of the lipid particles shows a melting point depression compared to the original solid lipid but the matrix is still solid at body temperature [7]. The anamorphous state of the blended lipids in the matrix (e.g., stearic acid and oleic acid [17]) is less ordered than in a crystal of pure lipids which allows therefore to improve drug loading, to reduce drug expulsion during storage and to decrease water content in final dispersion. Three types of nanostructured lipid carriers might be distinguished: imperfect, amorphous and multiple types [7]. Example of composition of nanostructured lipid carriers (adapted from [20]). Composition is reported as % lipid in the water phase. Compritol® 888 ATO 8.0% Oleic acid 2.0% Compritol® 888 ATO 8.0% Miglyol® 812 2.0% Precirol® ATO 5 8.0% Oleic acid 2.0% Precirol® ATO 5 8.0% Miglyol® 812 2.0% Miglyol® 812: Caprylic/capric triglycerides.	Physical and chemical long-term stability, triggered release and potentially supersaturated topical formulations [7]. Occlusive capacity onto the skin surface [15]	**Antifungal** Clotrimazole [15] **Corticosteroid** Clobetasol propionate [18] **Anti-inflammatory** Indomethacin [19] Psoralens [14]

LIPID-BASED NANOCARRIERS

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLN) are submicronic particles prepared from lipids that remain at solid state at ambient temperature, with a fusion temperature close to 35–37°C for topical delivery. This technology of encapsulation seems to be promised to industrial scale-up taking account the relative easiness of lab-production. In this field, new process of minoxidil loaded SLN was recently described [3]. They have a great ability to deliver various hydrophilic or lipophilic topical agents, they

Table 2. Microemulsions Developed as Topical Delivery Systems

Drug Carrier Systems	Physicochemical Characteristics	Mechanisms of Drug Delivery	
Microemulsions  Transmission electron microphotographs of a paclitaxel emulsion. (the scale bar for all images represents 0.2 µm and ×50,000) [21].	System of water, oil and surfactants (i.e., a mixture of surfactant and co-surfactant), which is transparent, single optically isotropic and thermodynamic stable liquid solution [22]. The size of microemulsion aggregates is smaller than 150 nm [23]. Lecithins are extensively used as surfactants for topical microemulsion delivery taking account their ability of forming (i) microemulsion without co-surfactants and (ii) gels at low water content.	Solubility potential of microemulsions may be an important factor in increasing skin absorption of drugs [23]. Structural organization of the phases may contribute to additional solubility regions. Formation of super-saturated vehicles during application Ultra-low interfacial tension of microemulsion ensures an excellent surface contact between the skin and the vehicle. Potential penetration enhancer effects of microemulsions: Disruption of the lipid structure of the stratum corneum, Facilitating diffusion through the barrier, Increasing the solubility of the drug into the skin.	**Anti-inflammatory** Ibuprofen [24] Ketoprofen [25] Triptolide [12] **Anesthetic** Lidocaine [26] **Anti-acneic** Retinoic acid [27] **Hormone** Estradiol [28] **Antifolate** Methotrexate [29] **Anti-psoriasis** 8-Methoxypsoralen [30]

Example of composition of microemulsion dispersion (modified and adapted from [23])

1. Oil phase :

Fatty alcohols	*Fatty acids, their esters and derivatives*	*Alcohols*
Octanol	Oleic acid	Benzyl alcohol
Decanol	Ethyl oleate	
Hexadecanol	Glyceryl monooleate	
	Isostearylic isostearate	
	Isopropyl myristate	
	(ester of isopropyl alcohol and myristic acid)	

2. Surfactants and co-surfactants:

Non-ionic	*Amphoteric*	*Anionic*	*Miscellaneous*
Span® 20,	Lecithin	Dioctyl sodium sulfosuccinate	Labrasol®
Span® 80,	Epikuron® 200	Sodium monohexylphosphate	Plurol® oleique
Tween® 80			Plurol® isostearate
Cremophor® RH			

Lecithin is mostly a mixture of glycolipids, triglycerides, and phospholipids (e.g. phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol).

Epikuron® 200 is containing about 95% of soy phosphatidylcholine.

Labrasol : PEG-8 glycol caprylate

Cremophor RH : Polyoxyl hydrogenated castor oil

Plurol® oleique : polyglyceryl oleate

Plurol® isostearate: polyglyceryl isostearate

3. Aqueous phase:

Water

Electrolyte solution: 154 mM NaCl

Colloidal solution : gelatine, carbopol®

Propylene glycol

are biocompatible, protect drugs from oxidizing agents and may be designed to fine-tune the pharmacokinetic (i.e. burst release, sustained release). SLN are naturally UV blockers and have been found to enhance water content of the skin [4].

Nanostructured lipid carriers (NLC) correspond to solid lipid nanoparticles with an inhomogeneous structure corresponding to liquid oil inclusion in the solid lipid matrix. Those nanocompartments and the decreased lipid crystalline organization increase drug entrapment, and change the fusion kinetic of particles and thus drug delivery.

Table **1** shows some examples of SLN and NLC compositions in topical applications and drug that were used as model penetrant or developed for *in vivo* testing.

SURFACTANT-BASED NANOCARRIERS

Microemulsions

Microemulsions are clear, stable, isotropic liquid mixtures of oil, water and surfactant often in combination with a cosurfactant (Table **2**). The potential as penetration enhancer is suggested to lean on disruption of the lipid structure of the stratum corneum due to large amounts of surfactant present.

NIOSOMES AND CUBOSOMES

Niosomes are unilamellar or multilamellar vesicles wherein an aqueous core is enclosed in a highly ordered bilayer made of non ionic surfactant, exhibiting a similar behavior to liposomes [4, 31]. Niosomes represent second-generation vesicular carriers with higher chemical stability, enhanced encapsulation efficiency, intrinsic skin penetration-enhancing properties and lower cost of production as compared to liposomes. Cubosomes are bicontinuous cubic phase liquid crystals where the surfactant assembles into bilayers that are twisted into a three dimension, periodic, minimal surface forming tightly packed structure, like "honeycombed" the bicontinuous domains of water and lipid [32] (Table **3**).

Table 3. Niosomes and Cubosomes Systems for Topical Drug Delivery

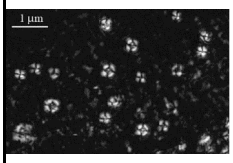
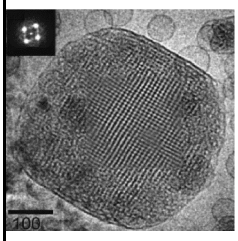
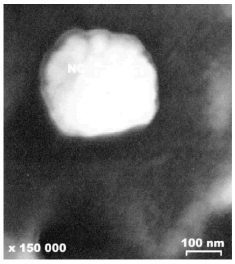
Drug Carrier Systems	Physicochemical Characteristics	Mechanisms of Drug Delivery	Penetrant
Niosomes  Light polarization optical micrograph of minoxidil loaded niosomes showing Maltese crosses (adapted from [33]).	Niosomes are unilamellar or multilamellar structures formed synthetic non-ionic surfactants entrapping hydrophilic or hydrophobic solutes [34]. Good chemical stability but physical instability with dispersion, aggregation and hydrolysis of drugs [35]. Example of composition of niosomes (reported from [36]): GDL:CHOL:POE (57:15:28) GDL:CHOL:POE:DOTAP (50/15/23/12) GDL:CHOL:POE (58:15:27) GDL:CHOL:POE (58:15:27) GDL:CHOL:POE:DOTAP (50/15/23/12) Span60:CHOL (2:1) Span60:CHOL (1:1) Span60 Span40:SoyPC:CHOH (4.5:4.5:1) GDL : Glyceryl dilaurate POE : polyoxyethylene-10-stearylether DOTAP : 1,2-dioleaoyloxy-3-(trimethylammonio)-Propane PC : Phosphatidylcholine CHOL : Cholesterol	Modification of intercellular lipid barrier [31, 37]. Adsorption or fusion of niosomes to the skin's surface with high thermodynamic gradient of drug at the interface. Non-ionic surfactant acts as a permeation enhancer.	**Anti-acneic** Tretinoin [38] **Antibiotic** Enoxacin [31] **Anti-inflammatory** Nimesulide [39] Aceclofenac [40] Diclofenac diethylammonium [41] **Antineoplastic** Daunorubicin [42] **Peptide** luteinizing hormone releasing hormone [43] **Antialopecic** Minoxidil [33].
Cubosomes  Cryo-transmission electronic microscopy micrographs of indomethacin monooleine dispersion (adapted from [44]).	Cubosomes are dispersed particles of bicontinuous cubic liquid crystalline phase [45]. Cubic liquid crystalline phase forms *via* self-assembly of certain surfactants that are combined with water in the proper ratio. One of the most common surfactants used to make cubosomes is the monoglyceride glycerol monoolein [44]. Example of composition of cubosome dispersion (adapted from [44]). Glyceryl monooleate 90 (w) Poloxamer 407 10 (w) The dispersed phase/dispersing phase ratio was 5:95 Poloxamer 407 : $PEO_{98}POP_{67}PEO_{98}$	Similarity between the cubic phase structure and the structure of the stratum corneum [46]. Formation of a mix of cubosomal glyceryl monooleate with stratum corneum lipids [44]). Formation of a cubosome depot in this layer from which drug can be released in a controlled fashion [44]).	**Anti-inflammatory** Indomethacin [44]].

Table 4. Polymeric Nanoparticles Obtained with Non Hazardous Methods for Topical Drug Delivery

Drug Carrier Systems	Physicochemical Characteristics	Mechanisms of Drug Delivery	Penetrant
Nanoparticles  Morphological appearance of 0.60% chlorhexidine base loaded PCL nanocapsules analysed by scanning electron microscopy (x 150 000, bar = 100 nm) [58].	Nanoparticles are colloidal particles ranging in size from 10 to 1 000 nm generally made of polymers (biodegradable or not). Two different types of nanoparticles may be distinguished: nanospheres and nanocapsules. Nanocapsules are vesicular systems in which the drug is confined to a cavity (an oily or aqueous core) surrounded by a unique polymeric membrane; nanospheres are matrix systems in which the drug is dispersed throughout the particles [60]. Biodegradable polymers used in the nanoparticles formulation are poly(lactic acid), poly(glycolic acid), poly(lactide-co-glycolide) [61, 62], poly-ε-caprolactone [49, 58, 63], chitosan [64]. Poly(butylcyanoacrylate) was also suggested for topical nanoparticles [56]. Example of composition of nanoparticle dispersion Polymer and additives / Size (nm) Formulation 1 [56] Poly(butylcyanoacrylate) 129 Citric acid, dextran 40 Formulation 2 [65] Poly(ε-caprolactone) ~ 300 Epikuron® 200 Labrafac hydrophile WL 1219® Tween 80® Epikuron® 200 is containing about 95% of soy phosphatidylcholine. Labrafac hydrophile WL 1219® is a mixture of caprylic/capric triglyceride PEG-4 esters.	Hair follicle penetration of nanoparticles is likely rather size than structure dependent. Taking account the rigidity of polymeric nanoparticles, stratum corneum penetration may be limited to the most superficial layers of the stratum corneum [49]. Mechanical massage of the skin would promote the penetration of nanoparticles into hair follicles [48].	**Antipsoriatic** 4, 5', 8-Trimethylpsoralen [62] **Antiseptic** Chlorhexidine [49, 58, 59, 63] **Antimetabolite** 5-fluorouracil [56]

POLYMER-BASED NANOCARRIERS

Nanoparticles

The effect of drug inclusion in polymeric nanoparticulate carriers on transdermal drug delivery was reviewed twenty years ago [47]. Since, several reports emphasized site-specific drug delivery of polymeric micro- and nanoparticles in pilosebaceous structures [48-52] and dermatoglyphs [53].

Furthermore, the uptake of polymeric nanoparticles by epidermal cells was found dependent on their size [54], whereas benzopsoralen-loaded poly(D,L-lactic-co-glycolic acid) nanoparticles were endocyted by the majority of the cells present in the rat cell exudate confirming the potential of such carriers to target cellular structures [55].

Therefore, polymeric nanoparticles were suggested to increase the skin drug concentration within pilosebaceous units, to improve the therapeutic index of certain drugs (e.g., adapalene [52], 5-fluorouracil [56] and all-trans retinoic acid [57]), to avoid degradation of drugs at the skin surface and to control the drug release onto the stratum corneum [58] and into the hair follicles [49]. Classical limitation in the choice of such system is the use of organic solvent during process (i.e., dichloro methane, ethyl acetate, acetone…). Recently, new process of solvent-free production involving hydrophilic gel as coating of hydrophobic polymer was described for industrial scale-up of so-called Nanochlorex© polymeric nanocapsules [59] (Table **4**).

CONCLUSION

Nanoencapsulation is technology presenting obvious and rising advantages for the treatment of skin diseases. Nanocarriers (e.g. liposomes, niosomes, transfersomes, solid lipid nanoparticles, polymeric nanoparticles and microemulsions) are well defined and characterized systems. Therefore, the encapsulation of drug within these carriers for topical application should be considered in term of skin tolerance, cutaneous bioavailability and industrial scale-up. Biophysically, nanocarriers open a window for the delivery of molecules considered as poor candidates in topical formulation (e.g., high molecular mass, high hydrophily) by enhancing their penetration and permeation through the skin. Furthermore, the use of drugs presenting a weak therapeutic index may be re-considered by the drug loading in colloids which reduces systemic side effects. Technologically, the straightforward production of nanocarriers avoiding organic solvents should be a relevant criterion for industrial scale-up (e.g. solid lipid nanoparticles and microemulsions) conditioning the becoming of topical formulations for the 21st century's dermatological practices.

ABBREVIATIONS

SLN = Solid Lipid Nanoparticles

NLC = Nanostructured Lipid Carriers

UV = Ultra Violet

PEG = Polyethylene Glycol

PCL = Poly-ε-Caprolactone

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