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Research paper

Comparison of rheological properties, follicular penetration, drug release, and permeation behavior of a novel topical drug delivery system and a conventional cream

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ABSTRACT

A novel adapalene-loaded solid lipid microparticle (SLMA) dispersion as a topical drug delivery system (TDDS) for follicular penetration has been introduced. The objective of the present study was to investigate the rheological properties, the follicular penetration with differential tape stripping on porcine ear skin, the drug release in sebum and stratum corneum (SC) lipid mixtures, and the permeation behavior across human SC in comparison with a commercially available cream as standard. Physicochemical characterization reveals that adapalene is homogeneously distributed within the SLMA dispersion and chemically stable for at least 24 weeks. The SLMA dispersion shows a lower complex viscosity at 20 °C and a higher one at 32 °C than the cream, while the phase angle of the dispersion is always larger at both temperatures. Both formulations feature an equivalent potential for follicular penetration and deposition. However, the superiority of the SLMA dispersion is based on the preferential drug release in sebum while there is no or just a slight release in SC lipids and no permeation for both formulations. Due to the similarity of the glyceride matrix of the SLMA to sebum components, a targeted drug delivery into sebum and thereby an increased follicular penetration may be facilitated.

1. Introduction

Potent topical drug delivery systems (TDDS) need to penetrate into the skin segment where the incorporated active pharmaceutical ingredient (API) exhibits its pharmacological effects. An efficient dermal therapy accompanied with drug targeting, reduction of local adverse effects, and circumvention of systemic exposure by a negligible permeation rate are distinguished benefits brought to the patient via topical drug delivery. Key parameters of TDDS are their physicochemical properties, microstructure [1], and inactive ingredients that may favor a drug delivery into skin compartments particularly if they resemble the skin composition or even mimic the microstructure of the skin [2].

For instance, microemulsions loaded with stratum corneum (SC) lipids such as ceramides enabled a deeper penetration into the SC compared to a hydrophilic cream and might be a suitable system to supplement these lipids in disorders such as psoriasis and atopic dermatitis [3]. Skin lipid liposomes comprising cholesterol, palmitic acid, ceramides, and cholesterol sulfate were formulated with corticosteroids for various skin diseases and displayed a higher drug accumulation in the epidermis and dermis than common phospholipid-based liposomes [4]. Liposomes modified with the SC lipid oleic acid showed a high deposition of methotrexate in the skin assigned to the flexibility of these vesicles and the enhancing performance of oleic acid for a resulting increase in anti-psoriatic activity [5]. Cubic nanoparticles based on glycerol monooleate enhanced the permeation of radiolabeled corticosterone due to the potential entry of monooleate into the lipid domains of the SC, while only an adhesion to and occlusion of the skin is ascribed to fat emulsions, smectic nanoparticles, and solid lipid nanoparticles (SLN) all made of lipids differing from SC lipids in their structure and polarity [6]. A penetration-enhancing effect for betamethasone-17-valerate was described for the polar

Abbreviations: API, active pharmaceutical ingredient; DSC, differential scanning calorimetry; DoE, design of experiments; HPLC, high performance liquid chromatography; LM, lipid matrix; LOD, limit of detection; LOQ, limit of quantification; LVR, linear viscoelastic range; MPS, mean particle size; P407, poloxamer 407; PBS, phosphate-buffered saline; PEG12000, polyethylene glycol 12000; SC, stratum corneum; SLM, solid lipid microparticle; SLMA, adapalene-loaded solid lipid microparticle; SLN, solid lipid nanoparticles; TDDS, topical drug delivery systems.

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distearate SLN as the outcome of a more pronounced association with the skin lipids compared to the investigated hydrophobic cetyl palmitate and tripalmitate SLN [7].

Thus, apart from structural properties of the TDDS such as particle size, viscosity, surface tension, thermal behavior, pH value, and charge the incorporation of inactive ingredients that resemble skin lipids may apparently increase penetration and/or permeation not only due to enhancing effects but also even to constituent analogy and affinity. This approach can be exerted for the lipid matrix of the SC as the main barrier for dermal drug delivery as well as for sebum lipids within the hair follicles as shunts for topical drug carriers. SC lipids consist of approximately 50% ceramides, 25% cholesterol, 10–15% free fatty acids, 5% sterol esters, and traces of glycerides and thereby represent a more amphiphilic lipid domain packing [8], whereas sebum lipids feature 15% squalene, 25% wax esters, 45% glycerides, and 15% free fatty acids and are apparently a more hydrophobic semisolid medium [9].

Hence, sebum lipid-like drug carriers such as squarticles based on squalene and Precirol® ATO 5 and loaded with diphencyprone and minoxidil enhanced the targeting of and penetration into the hair follicles and to the dermal papilla cells for contemplated treatment of hair loss [10]. Inulin-containing water-in-oil nanoemulsions based on olive oil [11], and also oil-in-water emulsions with lipophilic phases such as soybean oil, isopropyl myristate, or oleic acid, and salicylic acid as the API [12] favored follicular drug delivery. Vehicle–sebum interaction is regarded as a benchmark feature for drug delivery into sebum and the hair follicles [13,14].

Recently, a novel adapalene-loaded solid lipid microparticle (SLMA) dispersion composed of hydrogenated palm oil, lecithin, poloxamer 407 (P407), polyethylene glycol 12000 (PEG12000), potassium sorbate, citric acid, and double-distilled water has been introduced for follicular penetration [15]. An initial stability study, a preliminary penetration study on porcine ear skin as well as an interaction study with artificial sebum lipid and SC lipid mixture delivered promising results. The signal of the API was clearly allocated to the hair follicle and an exclusive depletion of the glyceride matrix of the lipid particles in sebum but not in the SC lipid mixture was detected via differential scanning calorimetry (DSC). This innovative composition might consequently increase the local bioavailability of teratogenic drugs such as retinoids at their drug target namely the hair follicle orifice and sebaceous gland. However, the evaluation of quantitative follicular penetration, drug release particularly into sebum, and permeation of the SLMA dispersion compared to a commercial product as a standard preparation was still lacking. Therefore, the comparison of these biopharmaceutical endpoints and the rheological properties to Differin® cream as a conventional topical dosage form are the objectives of the present study.

Since rheological attributes are the key parameters within a target product profile for novel dermal drug formulations in pharmaceutical development and also an important part of generic topical drug formulations but not a critical one [16], rotational and oscillation viscometry were employed to determine characteristics such as the flow behavior, yield stress, dynamic viscosity, complex viscosity, and the phase angle. In order to guarantee product quality, to pave the way for the implementation on larger scale, and to enable quality by design knowledge of the design space is inevitable [17]. The question whether the design space is regulatory admissible was addressed via a design of experiments (DoE) for critical material attributes.

Differential tape stripping on porcine ear skin was utilized to determine the penetrated amount of the API into the hair follicles. This method is considered as the most established tool for the assessment of follicular deposition of APIs from various topical dosage forms [18–20]. Drug release studies were carried out on the artificial sebum lipid mixture as previously described [15]. Release in sebum generally depends on the diffusion and partition characteristics of the drug [21] but also of the vehicle system [22]. In addition to that, the artificial SC lipid mixture based on the composition as recently reported [15] was selected as the model to study the potential diffusion and penetration of the API from the SLMA and cream formulation since SC lipid model systems are commonly useful to analyze the effect of compounds on these processes [23]. DSC was used in order to analyze the potential interferences of the formulations with sebum which might be identifiable in the case of any shifts of the phase transition temperature of the skin lipid mixture [24].

Permeation studies across isolated human SC which are mainly performed to evaluate topical drug therapies [25] were run in order to exclude any potential systemic teratogenic side effects [26]. Infinite dosing for skin absorption prediction [27] was assured with a receiver solution of Brij® 98 as an established composition for maintaining sink conditions [28,29]. However, the systemic availability of retinoids from dermal therapy is commonly low [30], yet it needed to be proven that no or a negligible absorption is present.

2. Materials and methods

2.1. Materials

Adapalene (Glenmark Generics, Mumbai, India), hydrogenated palm oil (Softisan® 154, Condea, Witten, Germany), purified lecithin (Phospholipon® 90G, Lipoid GmbH, Ludwigshafen, Germany), poloxamer 407 (Kolliphor® P407, BASF, Ludwigshafen, Germany), polyethylene glycol 12000 (Sigma–Aldrich, Seelze, Germany), potassium sorbate, citric acid (both Caelo, Hilden, Germany), and double-distilled water are the ingredients of the SLMA dispersion. The solid lipid microparticle (SLM) dispersion without adapalene has the same composition. Differin® cream (Galderma, Sophia Antipolis, France) is made up of 0.1% (w/w) adapalene, carbomer 934 P, polyoxyethylene-20-methyl (D-glucopyranoside)sesquistearate-ether, glycerol, squalane, methyl-4-hydroxybenzoate, propyl-4-hydroxybenzoate, sodium edetate, methyl (D-glucopyranoside)sesquistearate, phenoxyethanol, cyclomethicone, sodium hydroxide solution (10%), and purified water. Squalene (Alfa Aesar, Karlsruhe, Germany), cetyl palmitate, olive oil (both Caelo, Hilden, Germany), oleyl oleate (Cognis, Monheim, Germany), palmitic acid (Hüls, Marl, Germany), coconut oil, oleic acid, cholesterol, cholesterol oleate (all Sigma–Aldrich, Seelze, Germany), ceramide IIIB (NP), and ceramide VI (AP) (both Franken Chemie, Wendelstein, Germany) were applied for the artificial skin lipid mixtures. Trypsin (Carl Roth GmbH, Karlsruhe, Germany) and trypsin inhibitor type II-O chicken egg white (Sigma–Aldrich, Steinheim, Germany) were the reagents for trypsination. Polyethylene glycol-20-oleyl ether (Brij® 98, Uniqema, Emmerich, Germany) and phosphate buffered saline pH 7.4 (PBS, MP Biomedicals, Illkirch, France) were used for the receiver solution in the drug release and permeation studies. Acetonitrile, tetrahydrofuran (both VWR Chemicals, Darmstadt, Germany), acetic acid (Carl Roth GmbH, Karlsruhe, Germany), and purified water generated with an EASYpure® LF (Barnstead, Dubuque, United States) were the solvents of the mobile phase for drug quantification via high performance liquid chromatography (HPLC).

2.2. Preparation of the SLMA and SLM dispersions

The SLMA and SLM dispersions were manufactured according to the previous report [15]. In brief, the lipid matrix (LM) of 70% hydrogenated palm oil and 30% purified lecithin (both by weight) was stirred until transparency at 70 °C and subsequent solidification at