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REVIEW ARTICLE

Medicated Foams and Film Forming Dosage Forms as Tools to Improve the Thermodynamic Activity of Drugs to be Administered Through the Skin

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Abstract: Medicated foams and film forming systems are dosage forms formulated to undergo a controlled metamorphosis when applied on the skin. Indeed, due to the presence of propellant or a particular air-spray foam pump, a liquid can generate foam when applied on the *stratum corneum*, or a liquid or conventional dosage form can form on the skin a continuous film as a consequence of the solvent evaporation. Thanks to these controlled modifications, the drug thermodynamic activity increases favoring the skin penetration and, therefore, the bioavailability with respect to conventional semi-solid and liquid dosage forms. Furthermore, the available clinical data also evidence that these dosage forms improve the patient's compliance. The main formulative aspects of medicated foams and film forming systems are reviewed with the aim to underline the possible advantages in terms of biopharmaceutical performances and patient's adherence.

Keywords: Cutaneous administration, film forming system, medicated foam, skin permeation, substantivity, supersaturation.

1. INTRODUCTION

The most common dosage forms intended to be applied on the skin are solutions, suspensions, creams, gels, ointments, and lotions. They are usually perceived as safe with minimal risk of systemic exposure and associated side effects. However, to design an effective topical drug delivery could be challenging since the penetration is limited by the peculiar barrier properties of the *stratum corneum*. Indeed, being regulated by the Fick's law, the penetration is proportional to the drug thermodynamic activity that provides the driving force for the passive diffusion process [1]. Therefore, the simplest strategy to improve the drug permeation through the skin is to increase the permeant concentration in the dosage form until saturation. Obviously, the development of a supersaturated system, having a chemical potential greater than that of the corresponding saturated systems, can furtherly enhance the permeation through the *stratum corneum* [2]. The efficacy of such an approach was widely studied using solutions [3] or applied to develop patches [4], but supersaturation also spontaneously occurs in semisolid preparations containing water, *e.g.* creams and gels, in which the loss of water, due to the skin penetration or evaporation, can increase the drug concentration into the pharmaceutical form. However, the drug chemical potential in these formulations is not the only factor influencing the permeation process, but also the "water activity" (*i.e.* the thermodynamic energy status represented as the ratio of partial vapour pressure of water in the formulation and vapour pressure of pure water) has to be considered. The greater the value, the higher the flux of the permeant [5]. In other words, the drug release from topical formulations is influenced not only by the formulation viscosity and the drug thermodynamic activity but also by the physicochemical characteristics of the excipients which influence the water activity. As an example, the inclusion of small molecule humectants, *e.g.* propylene glycol, dropdown the water activity and, therefore, significantly affect the drug permeation [5]. In the case of semisolid preparations, the skin permeation is furtherly complicated by their continuous metamorphosis. Indeed, the components of the pharmaceutical dosage form can penetrate the *stratum corneum*, evaporate or mix with the lipids of skin surface. These unpredictable modifications of the vehicle composition lead to changes in drug solubility and, therefore, drug thermodynamic activity as well as water activity [3, 6]. In this framework, film-forming dosage forms and medicated foams, being appositely designed to have a controlled metamorphosis when applied on the skin, can permit a reproducible drug absorption since both the variations in water activity and the permeant thermodynamic activity are less relevant with respect to other liquid and semisolid dosage forms [5]. These systems enable to generate an (albeit transient) super-

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saturated system on the skin surface and/or in the upper *stratum corneum* since the drug concentration in the vehicle increases due to the propellant loss or solvent evaporation upon application and spreading on the skin.

In this review, we describe the main features of medicated foams and film forming systems, as well as their main permeation mechanisms. Furthermore, the published available data on the potentialities to improve the patient's adherence and/or compliance are discussed. Reviewed articles were obtained from the PubMed, SciFinder and Scopus online databases.

2. MEDICATED FOAMS

Medicated Foams (MF) are exploited to administrate several active ingredients and drug-loaded lipid nanoparticles, even if most of the commercial foams deliver corticosteroids or NSAIDs to treat psoriasis and muscle-skeletal disorders, respectively (Table **1**). Generally speaking, foams can be produced by (i) mechanical agitation of a liquid or a solution ("whipping"); (ii) injecting a stream of gas or liquid or the mixture into a liquid ("bubbling") and (iii) sudden pressure reduction [21]. The latter is typical of MF intended to the cutaneous application, which is generally prepared by adding to a canister the formulation consisting in a solution, O/W emulsion, or suspension, containing the active ingredient(s). Then, the propellant is forced, under pressure and/or at low temperature, into the container, which is sailed to make the final MF product.

After actuation, the propellant evaporates producing a liquid or semi-solid foam product that is expanded with air. As propellant(s) can also act as solvents, once applied on the skin, the concentration of the drug in the vehicle increases, thus enhancing the absorption of the active ingredient through the skin [22]. The "bubbling" approach has the advantage to avoid the environmental issues related to the use of propellants, even if the increase of drug concentration is lost. In this case, the pressure required to generate the foam is provided by an "air-spray foam pump" and surfactants are the most relevant components of the formulation [14]. Another propellant-free approach is based on the formulation of a semi-solid gel ("Bag-in-can" system), which produces a foam when it is rubbed on the body. These products usually contain a low boiling hydrocarbon, such as isopentane (boiling point ~28 °C) which evaporates after application at body temperature, forming a foam. Because of the low boiling point of isopentane, these formulations are packed in pressurized containers [23], but a barrier system separates the product with solubilized isopentane from the pressurizing gas. The external pressure is needed to dispense the product and to keep isopentane in the product. Even if a high pressure is necessary to deliver the product, it does not influence the quality of the medicated foam after actuation.

2.1. Formulation Aspects

To design an MF, propellants play a key role since they evaporate at atmospheric pressure, generating the foam, and the velocity of this process is dependent on the rate of propellant evaporation. Hydrocarbons (*e.g.* n-butane, isobutane, n-propane or mixtures thereof) at the concentration of 3-12% [23] can produce a foam of adequate quality, despite the potential safety hazard due to the high flammability and explosivity. These propellants are liquefied under pressure and their blends have a wide interval of boiling points up to -42 °C, without the metering problem of compressed gases. There are also systems containing immediately evaporating propellants and propellants which evaporate with a delay (*e.g.* n-pentane, isopentane, isobutane), causing a cooling effect on the skin surface. Hydrofluroalkanes (HFAs) have been gaining more attention for pharmaceutical application since they present a high vapor pressure without safety and environmental concerns [24, 25].

Essential components to generate and stabilize a foam are also foaming agents, namely surface-active agents (*e.g.* surfactants or certain polymers of different nature including proteins [26]) which orient themselves at the air-water interface forming micelle on valve actuation. When they are adsorbed to this interface, the surface tension decreases, and the surface pressure increases, leading to the foam formation. Higher values for surface pressure and lower values for surface tension do not always lead to an increase of foam stability, for which the concentration of foaming agent in the adsorbed layer is one of the most important factors. During foam formation, rapid adsorption of the foaming agent is desirable. However, in this phase, the concentration of foaming agents in the bulk phase decreases with the increase of the surface area, leading to the decrease of the concentration gradient and, therefore, of the diffusion rate. Therefore, to ensure a rapid diffusion of a foaming agent to the surface, high concentrations of foaming agents and low viscosity of the liquid phase are necessary. For some foaming agents, the maximum capacity of foam formation is obtained at a concentration equal or close to the critical micelle concentration [27] or when they are used in combination [28].

A viscosity-modifying agent in the concentration range of ~ 0.05 - 2.0% is required to facilitate the creation of foam with desirable texture and optimum spreading properties [8]. These excipients are often selected among natural (*e.g.* xanthan gum), semi-synthetic (*e.g.* cellulose ethers) and synthetic (*e.g.* poly(vinyl pyrrolidone)) polymers.

Besides these components, other excipients can also be incorporated, depending on the active agent and the required foam characteristics. For example, to formulate ionizable drugs (*e.g.* minoxidil), an acid can be employed to maintain the pH in the most favorable range [11].

Besides the approach to obtain the foam, an assessment of the general appearance as well as the stability are important factors for cosmetic acceptability of foams.

There are two fundamental parameters determining the structure and behavior of the foams: the gas volume fraction and the bubble diameter. Generally, the fraction of gas volume in the foam is between 0.5 and 0.9, while the bubble size is between 0.1 and 3 mm depending on how the foam is generated and the excipients used [23].

The stability of product and foam should be evaluated prior to dose application (*i.e.* inside the canister) and post-dose application, respectively. However, the former is often neglected due to practical problems related to the explosiveness

Table 1. Literature data on medicated foams *vs.* other cutaneous pharmaceutical forms.

Drug	Set-up	Main Findings	Year	Refs.
In vitro				
Clindamycin	Human skin; flow-through diffusion cells *vs.* gel	Greater accumulation after 24 h and earlier onset than clindamycin gel.	2005	[7]
Clobetasol propionate	Human skin; flow-through diffusion cells *vs.* cream, emollient cream, lotion, and solution	A faster initial permeation of clobetasol compared with the other vehicles. In the first 14 h, foam delivered a similar amount of drug (J and AUC) compared with the emollient cream and a greater amount of drug compared with the solution, cream, and lotion. The foam vehicle delivered more clobetasol than the other formulations.	2005	[7]
Clobetasol propionate	Different anatomic region of human skin *vs.* foam, cream, and emollient cream	Foam needs the least time to overcome anatomic region variations (= thickness), whereas cream and ointment take a longer time for the onset of delivery.	2005	[7]
Ketoconazole	Silastic membranes; static Franz cells	Penetration 11-fold higher *vs*. cream.	2005	[7]
Metronidazole	*In vitro* skin penetration study; excised human skin; a flow-through diffusion cell	The total cutaneous penetration of metronidazole was two- to three-fold higher than the reference cream.	2006	[8]
Vitamin E acetate	*In vitro* silicone membrane penetration study; *in vitro* skin tape stripping	The increase in Pluronic surfactant concentration after application modified the lipid nanoparticles to enable drug release and penetration into skin.	2009	[9]
Benzoyl peroxide	*In vitro* silicone membrane penetration study	Benzoyl peroxide loaded in nanoparticles was chemically stable over a 7 d period. Foams allowed to obtain a comparable flux to commercial gels and creams, but at much lower concentration.	2010	[10]
Minoxidil	*In vitro* silicone membrane penetration study	Foam delivered significantly more drugs across the membrane than the saturated aqueous solution. The cumulative permeant amount of drug depends on the surfactant concentration in the foam.	2010	[11]
Calcipotriene + betamethasone	Raman imaging	After propellant evaporation, a supersaturated environment was created, where drug crystals were absent for at least 26 h.	2016	[12]
Thiocolchicoside	Skin; Saarbruecken penetration model-based cells	At each incubation time, significant higher amounts of drug were detected for the foam formulation.	2008	[13]
Cholecalciferol + salicylic acid	Pig-ear test for irritancy potential evaluation	Incorporation of two incompatible drugs.	2017	[14]
In vivo				
Minoxidil	Caucasian male volunteers aged between 22 and 29 years. Every 10 d, 0.007±0.002 g foam was applied to the chest and the occipital region of the scalp	Hair follicles contribute to the penetration of minoxidil into the blood circulation since faster absorption of minoxidil was detected when the hair follicle orifices were open.	2010	[15]
Betamethasone valerate	A Phase II, randomised, single-centre, blinded, right-left comparison within 30 patients with mild-to-moderate psoriasis	After 3 wk, statistical significant improvement from baseline in thickness, redness, scaling, itch and global score.	2006	[8]
Tarazotene	Phase I study	Reduced systemic levels of tazarotenic acid in comparison to the marketed gel.	2013	[16]

Table (1) contd….

Drug	Set-up	Main Findings	Year	Refs.
Azelaic acid	A Phase 3 randomized, double-blind, vehicle-controlled, parallel-group, multicenter study with participants with moderate to severe papulopustular rosacea	Azelaic acid foam at 15% resulted efficient and safe in patients with papulopustular rosacea.	2015	[17]
Azelaic acid	Eight dogs with nonseasonal mild/moderate canine atopic dermatitis were treated twice weekly with either a commercial foam or a foam/mousse containing components from plant extracts, for 14 d. After a wash-out period of 14 d received the other foam in a randomized blinded study	A significant improvement in both skin lesions and pruritus was noted for both treatment groups. This method of product delivery is easy to use for owners, improving compliance in practice.	2018	[18]
Econazole nitrate	Two randomized, double-blind, parallel-group, vehicle-controlled, multicenter studies enrolled males and females ≥12 y old with a clinical diagnosis of interdigital tinea pedis and baseline fungal culture positive for a dermatophyte. Subjects applied 1% econazole nitrate foam (n=246) or foam vehicle (n=249) once daily for 4 wk	The drug-loaded foam exhibited superiority over foam vehicle with a high mycologic cure rate for all pathogens evaluated. Econazole nitrate foam 1% was safe and well tolerated with a safety profile comparable with the foam vehicle.	2014	[19]
Tazarotene	Two randomized, double-blind, vehicle-controlled, parallel-group studies were randomly treated with either0.1% tazarotene foam or vehicle foam once daily for 12 wk	Tazarotene foam significantly reduced the number and severity of acne lesions after 12 wk and had a safe and acceptable tolerability profile.	2013	[20]

and flammability of certain propellants. The latter is related to three main factors, which can occur concurrently: Ostwald ripening (disproportionation), drainage and film rupture. Ostwald ripening involves the transport of gas from small to large bubbles, so that the smaller air bubbles dissolve, while the larger bubbles increase in size. The liquid drainage is the flow of liquid through channels between the bubbles, which is usually driven by capillary (surface tension) forces and is resisted by viscous forces. It depends on the individual channels and on the type of surfactant used to create the foam. The consequent thinning of the channels that separate the foam bubbles, and the elasticity of the lamellae (*i.e.* the thin layer of the continuous liquid film separating the faces of two adjacent polyhedral bubbles), increases the occurrence of Ostwald ripening and film rupture. The rupture of the liquid film separating the bubbles leads to their coalescence and complete collapse of the foam structure. Generally, foams with a higher fraction of gas volume are more stable because liquid drainage is delayed. However, it is difficult to develop a general theory concerning the stability of foams, since many dynamic and static factors are involved [23]. Instability can be also increased by some excipients added to improve the drug solubility or to obtain a peculiar formulation. As an example, oils, alcohols or organic solvents, which are normally not very soluble in water, diffuse at the level of the lamellae, increase the drainage of the liquid and consequently make them thin, increasing the fragility of the foam [29]. Moreover, the failure of the structure for hydroethanolic foams, when a critical temperature is attained, is rapid and occurs at lower temperatures compared with emulsion foams. Aqueous foams showed higher temperature stability than hydroethanolic or emulsion-based foams [30].

There are several excipients that can be added to improve the foam stability: surfactants at the interfaces can form a strong and elastic interfacial film around the foam bubbles and thus retard coalescence; hydrophilic polymers with high molecular weight can increase the viscosity reducing the drainage; electrolytes can cause the electrostatic stabilization of the bubbles. Moreover, both temperature and pressure influence the drainage speed by altering the liquid bulk viscosity [23].

Despite stability is an important factor for the cosmetic acceptability of foams, the main pharmacopeias do not report any information on these aspects. For example, the European Pharmacopoeia 9th Edition suggests two characterization methods in the monograph "Medicated Foams" (*Musci medicati*). The former is based on the estimation of the relative foam density as an indication of the foam firmness; the latter is related to the foam expansion time as a parameter for the foamability of the formulation. Density of the produced foam is determined by weighing a predefined volume of foam compared to the weight of the same volume of water. For determination of foam expansion time, a foam volume is fed in a burette and foam expansion is followed within a defined time.

The problems of measuring the foam stability depend mainly on the insufficient characterization of the microscopic processes involved, essentially the collapse of the foam through the loss of solvent. In this view, the General Chapters Dosage Forms Expert Committee [31] is investigating the inclusion in the USP of a general chapter on pharmaceutical foams providing guidance on important quality and performance attributes of this dosage form. The rate of foam

liquid drainage and collapse can be observed by dispensing a foam into a graduated cylinder. Observations are made of the volume occupied by the freshly dispensed foam and after a defined period, *e.g*., 30 min, of the aged foam and the drained liquid.

3. FILM FORMING SYSTEMS

A Film-Forming System (FFS) is defined as a liquid or semi-solid dosage form which produces a polymeric film after application on the skin due to the rapid evaporation of the solvent [32]. Upon evaporation, the polymer chains interpenetrate to form a continuous film. This event occurs at a well-defined polymer concentration [33-36], which is dependent on the molecular volume of the macromolecules in the solvent, usually expressed as intrinsic viscosity [37]. In the case of polymeric latex, the solvent evaporation causes coalescence of the polymer particles and, therefore, the interpenetration of the polymer chains.

This process is strongly linked to the dimensions of the polymeric particles involved, but perhaps the most critical point is the temperature. In fact, the nature of this process provides that there is a Minimum Film-Forming Temperature (MFFT), below which the dispersion, once in contact with the skin, forms an opaque and slightly homogeneous film. It is, therefore, necessary that the solvent evaporation occurs at a temperature higher than that of the MFFT, to guarantee the coalescence of the particles. The value of MFFT depends strictly on the polymer type and particle size.

Because of the metamorphosis of such dosage forms, there is a considerable increase in the concentration of the drug in the residual film left on the skin surface, leading to the possible drug supersaturation on the skin or in the *stratum corneum* [38]. Therefore, the drug permeation profile usually comprises a rapid uptake of drug when solvent(s) evaporate(s) or penetrate(s) the skin, followed by a slower profile governed by release from the residual film. In addition, some of these formulations can also determine the formation of a drug "reservoir" in the *stratum corneum* [39] allowing to obtain a greater and more prolonged absorption with only one application per day [40, 41]. Efforts carried out to design FFS for the transdermal administration of different classes of drugs (*e.g*. steroid hormones, local anesthetics, NSAID, analgesics and antiemetic agents, Table **2**), evidence that the optimal formulation should quickly dry on the skin; the formed film should not adhere to the patient's clothes, and its mechanical properties should overcome the tangential stress due to the body movements.

3.1. Formulation Aspects

Independently of the formulations to be applied on the skin, namely solutions, sprays, gels and emulsions, a broad range of film-forming materials, both of synthetic and natural origin, has been tested to design FFS (Table **2**). Among those of synthetic origin, there are cellulose derivatives, polymers or copolymers of acrylic acid, polymers or copolymers of methacrylic acid, vinyl polymers and silicones [42]. Instead, those of natural origin are less used, even though recently the research was focused to the exploitation of biodegradable natural polymers [43], *e.g*. regenerated silk fibroin [44] and chitosan [45]. Besides polymers, two other main components have to be considered and balanced to design an efficacious and safe FFS: solvent(s) and plasticizer(s). Indeed, the dosage form should quickly dry on the skin and the MFFT should be below the skin surface temperature (~32 °C). After formation, the formed film, consisting of a thin layer of polymer perfectly transparent, should adhere to the skin, but not stick to clothes [46].

The mechanical properties of the formed film should overcome the tangential stresses due to the body movements ensuring a strong and total adhesion to the skin for the entire time of application, as in the case of patches [47]. The substantivity is also one of the main attributes enabling the film to resist removal, for example by clothing, or following cleansing of the skin surface [38].

To assure the drying of the film forming formulation in a rather short time, the volatility of solvent(s) has to be evaluated. Organic solvents, *e.g*. short-chain alcohols, are generally preferable also because they guarantee the complete solubilization of the most used film-forming polymers. Among them, ethanol is the solvent of choice as the main regulatory agencies allow its use for topical application in concentrations higher than 95% [48, 49] and it can also act as a permeation enhancer [50]. In literature, there are numerous examples of formulations containing different organic solvents (*e.g*. ethanol, isopropanol, ethyl acetate, acetone) alone or in mixture. However, the choice does not significantly influence the release profile from the FFS [43], even if they rapidly distribute in the *stratum corneum* [51]. Nevertheless, in some cases, a non-volatile component is also added to avoid drug precipitation during the formation of the film [51].

The mechanical properties of the formed film are deeply influenced by the type and amount of polymer. An excessively low concentration can lead to the formation of discontinuous films or with poor mechanical resistance, while a high concentration solution produces thick and rigid films on the skin, which are uncomfortable and could delay the drug release [38]. A plasticizer is often added to increase the free volume between the polymer chains and, thus, increasing their mobility. These small molecules play a dual role not only assuring that the formed film completely adapts to the skin movements, but also decreasing the film forming temperature below the skin surface temperature.

The creep compliance should be directly or indirectly measured to assure that the film overcomes the tangential stress due to the body movements. Gennari *et al*. proposed the evaluation of the tensile properties of the formed film to verify that its elastic modulus did not exceed that of the *stratum corneum*, in order to assure its intimate and prolonged contact [32]. Garvie-Cook *et al*. determined the elastic moduli of films based on Eudragit® RS by nanoindentation [52]. Despite the elastic moduli determined by AFM (Y=0.3 GPa) [53] were different an order of magnitude to those determined by texture analysis (Y=55 MPa) [32], the minimum plasticizer concentration needed to obtain a flexible formulation was comparable, independently of the technique used to evaluate the film mechanical properties. Generally speaking, very few methods exist to probe the substantivity of dermal formulations and none of them is set-up for FFS. Clinical studies evidenced that films constituted of hydrophilic poly-

Table 2. Dosage forms and main components of film forming systems.

Dosage Form	Active Ingredient	Polymer	Solvent	Refs.
-	Betamethasone valerate	Klucel™ LF; Kollidon® 12 PF/17 PF/25/30; EC; CH; PAMA+; PME; PAOC	Ethanol	[54]
	Betamethasone valerate	HPC, PAMA+, PAOC	Ethanol	[52]
	Betamethasone valerate	HPC, PAMA+, PAOC	Ethanol	[53]
	Ethinylestradiol	PAMA+, HPC, PU	Ethanol or ethanol/water	[56]
	Flurbiprofen Ketoprofen Ibuprofen	PAMA+	Isopropyl alcohol/acetone	[32]
	Ketorolac	PAMA+, Eudragit E, PVP K30	Ethanol	[57]
	Mupirocin	PAMA	Ethanol/acetone	[58]
	Oxybutynine	Carbopol 940, Lutrol F127	Ethanol/acetone/methylal	[59]
Metered dose spray	Methylphenidate	PAMA, PAMA+	Ethanol; isopropyl alcohol	[60]
	Ropivacaine	PAMA+, PAMA, PAA, HPC, polaxamer, PVA, PVP	Ethanol; isopropyl alcohol	[61]
	Betamethasone valerate	PVP K90	Ethanol	[62]
	Testosterono	PAMA+, Eudragit E, PVPS630, PVP K30	Ethanol	[41]
	Dexketoprofen	PAMA+, PVP K12, PVPS630, PVP K30	Ethanol	[63]
	Fluconazole	EC, PAMA+	Alcohol-acetone	[64]
Lotion	Testosterone	PVP	Isopropyl alcohol	[65]
Emulsion	Nonivamide		Water	[66]
	Nonivamide	PAMA+	Water	[67]
	Nonivamide	PME, PAMA+	Water	[68]
Gel	--	PVA	Water	[69]
	Caffeine	Fibroin	Water/ethanol	[44]
	Ketoprofen	CH	Water/ethyl alcohol	[70]
	Rotigotine	HPC and Carbomer 934	Water/ethanol	[71]
	Tolterodine	Carbopol 980 (neutralized by triethanolamine), HPC, HPMC	Water/ethyl alcohol	[72]

Abbreviations: PAMA+ poly(ammoniummethyl methacrylate) (Eudragit®RL or Eudragit®RS); PAMA poly(aminomethyl methacrylate) (Eudragit®E); PAA poly(methylmethacrylic acid) (Eudragit®L); HPC hydroxypropyl cellulose; polaxamer; PVA poly vinyl alcohol; PME polymethylethylacrylate (Eudragit NE); PVP polyvinyl pyrrolidone; EC ethyl cellulose; CH chitosan; HPCH hydroxypropyl chitosan; PAOC Acrylates/Octylacrylamide Copolymer (Dermacryl 79); PU polyurethane; HPMC hydroxypropyl methyl cellulose.

mers hardly guarantee the necessary substantivity to act as external drug reservoir [39] because they are easily removed by washing or sweating. Some Authors proposed an *in vitro* method to simulate the skin-to-skin or clothing-to-skin contact and to determine the amount of formulation removed from the skin [53]. According to these preliminary data, FFS presented the highest substantivity with respect to the semi-solid preparations, such as creams and ointments [53].

The ability of a film to remain attached to the skin also depends on the interactions it establishes with proteins and lipids present on the skin surface. Since, at physiological pH, the skin has a net negative charge, the films formed by cationic polymers show a greater substantivity than those formed by neutral or anionic polymers. Furthermore, also the possibility of forming hydrophobic interactions (such as hydrogen bonds or Van der Waals bonds) must be considered to evaluate the adhesive capacities of the film [38].

To avoid the adhesion to clothes, the film stickiness can be qualitatively tested by pressing cotton wool on the dried film under low pressure. Depending on the quantity of cotton fibers retained by the film, the stickiness can be rated as high (dense accumulation of fibers on the film), medium (thin

fiber layer on the film) or low (occasional or no adherence of fibers). Similarly, adhesive properties can also be evaluated by a thumbtack test on the dried film [47]. On the other hand, a probe-tack test allows obtaining a quantitative and controlled measurement of the stickiness: a flat, solid punch, called probe, is brought into contact with the film deposited on a rigid substrate. The detachment force is then recorded while the probe is being pulled away [32].

The ability of the formulation to guarantee or enhance the skin penetration of drugs depends on the solvent(s), polymer and eventually plasticizer used to tune the mechanical properties. Not only the drug thermodynamic activity but also the solvent evaporation rate can significantly influence the skin permeation from FFS. The relevance of both parameters is strictly related to the loaded drug, even within the same class of compounds [32]. In particular, the vehicle composition, apart from its function to solubilize both excipients and drugs, can influence the initial delivery of the latter into the skin, according to the solvent evaporation rate: the lower the evaporation rate, the higher the "burst" effect and the flux in the initial hours following drug application. The type and amount of polymer used can affect the ability of the formed film to control the drug release. For example, films made of hydroxypropyl cellulose assure a zero-order kinetic for a prolonged period; while those obtained from acrylic and methacrylic polymers, more hydrophobic, can produce a more rapid burst effect, with the possibility of forming a drug reservoir in the *stratum corneum* [54]. The use of methyl methacrylate copolymers appears of interest [42, 52, 54, 57, 68], even if the literature reports contrasting results on Eudragit® RL (EuRL) when it was compared to hydroxyethyl cellulose. As an example, the skin permeability of estradiol from EuRL based films resulted significantly lower than that obtained with the cellulose ether [39].

A second aspect influencing the skin permeation is the drug concentration and the applied amount of dosage form. In this case, the main criticism is related to drug crystallization that can occur also in a relatively short period of time, affecting the whole permeation process through the skin. However, some polymers can act as anti-nucleating agents, inhibiting the drug crystallization over time [2, 52].

A plasticizer can influence the drug release whether the film-forming formulation is a dispersion or a solution. In the first case, the plasticizer facilitates the coalescence of the polymer particles leading to the formation of a continuous and thick film, with a typically prolonged release profile. In the case of solutions, the presence of a plasticizer increases the mobility of the polymer chains, the diffusion capacity of the drug and its release profile [54, 73].

The drug diffusion and release can be also influenced by the environmental moisture, which can act as a plasticizer of hydrophilic polymers.

FFS can eventually include various other excipients, such as permeation enhancers and lipid excipients (medium-chain triglycerides), which can contribute to increase and prolong the drug release [54, 55].

FFS can be formulated as solutions, sprays, gels and emulsions, the choice depending on the nature of the drug itself and the biopharmaceutical performance required. Gels generally facilitate and assist skin wound healing, since the formed film is more resistant to insults due to the movements of the skin. Interestingly, different topical gels present on the market can be considered as FFS, since polymers contained in these formulations show film-forming properties, even if the drying is slower than that of solutions. Some of these gelling agents are, for example, gellan gum (an anionic polysaccharide with high biocompatibility and reduced toxicity), carboxymethyl cellulose (in concentrations between 4 and 6%), Carbomer, hydroxyethyl cellulose and hydroxypropyl methylcellulose. In case of emulsions, the W/O emulsion based FFS promoted the absorption of Ethylhexyl methoxycinnamate, a lipophilic solar screen, as the oily component seems to have an occlusive effect on the skin. However, further studies showed that other lipophilic compounds, such as parabens, appear to cross the cutaneous layers better when administered in O/W emulsions probably because of their greater affinity for the skin surface with respect to formulation [74]. The selection of the dosage form influence also the application device to be selected. For instance, solutions are delivered to the skin through appropriate applicators or predosed pump dispensers thus allowing the control of the administered dose. Gels are applied directly to the skin, especially in body regions such as arms, shoulders, abdomen and inner thigh.

4. BIOPHARMACEUTICAL ASPECTS

The advantages of the MF and FFS compared to conventional formulations concern also biopharmaceutical aspects, since both have certainly demonstrated an improvement of bioavailability. Indeed, the metamorphosis to whom they undergo allows to generate a metastable supersaturated system. The consequent increase of drug thermodynamic activity appears a safer strategy with respect to chemical skin penetration enhancers usually used in the formulations of ointments, creams or gels. The literature data reports several *in vitro* studies aimed to compare the impact of these dosage forms on drug delivery, penetration and permeation through the *stratum corneum*.

When thiocolchicoside was formulated as foam, to avoid contact with the afflicted areas during the spreading phase, the drug accumulation into full human skin thickness was promoted in comparison with the simple drug solution [13]. Furthermore, the comparison among the *in vitro* permeation behavior of the foam, the commercial ointment and a control gel evidenced that the best permeation profile was obtained from the foam which allowed to increase the thiocolchicoside flux about 2- and 3-fold compared to ointment and gel, respectively [75].

The *in vitro* application onto the skin of clobetasol propionate (0.05%) formulated as a low-residue foam [76] improved the permeation rate with respect to other conventional semi-solid formulations [7]. Moreover, the *in vitro* application of clobetasol propionate foam to donor skin resulted in 5.9±1.1% drug accumulation after 12 h, compared with 2.8±0.3% with a solution, 2.7±0.3% with emollient cream, 2.1±0.2% with cream and 1.3±0.1% with lotion [77]. The same technology was also exploited to formulate a foam containing 2% ketoconazole for the treatment of mycoses and dermatological diseases, particularly seborrheic dermati-

tis. The foam allowed to accumulate in the epidermis a 2-fold higher amount of ketoconazole compared with a conventional cream [78]. Again, the use of a 0.12% betamethasone valerate foam for the treatment of psoriasis affecting the scalp and non-scalp regions of the body [70] improved the drug skin penetration both in terms of time and amount with respect to a lotion [79].

FFS can be used to obtain both local and systemic effect. A very important application is the treatment of chronic dermatological diseases, such as atopic dermatitis and psoriasis, which require daily treatments preferably with topical action. This type of therapy, however, provides a large number of related adverse effects, such as toxicity caused by the application of corticosteroids, which, failing to permeate the skin layer, form depots on the surface of the skin. With the use of polymeric FFS, the permeation of these molecules through the *stratum corneum* was greatly increased: in a study carried out with an FFS based on betamethasone valerate, a drug depot in the skin was detected, about six times greater than that obtained with traditional topical dosage forms. It follows that increasing the depot of the drug in the skin, the permeation is increased through the upper layers of the epidermis [62].

Regarding FFS, estradiol was one of the first molecules to be loaded in the attempt to reach the systemic circulation after application of a spray on the skin [39]. As the results were immediately satisfactory, in the last years several FFS have been placed on the market for the administration of estradiol, terbinafine (human) and fentanyl (veterinary) and many others are in planning or in experimental phases.

FFS are able to enhance skin penetration also in comparison with transdermal patches as demonstrated in the case of ethinyl estradiol [56].

Several studies were carried out with the intent of evaluating the function of the drug "reservoir" on the skin surface. For example, when a formulation based on fentanyl in a volatile solvent was applied topically, more than 50% of the initial dose remained on the skin surface as a residue, while only 20% permeated through the *stratum corneum*, in a 24-hour period [80]. Hence, despite the large amount, the drug on the skin surface has only minor importance in the maintenance of therapeutic effects. As an example, Evamist®, a film-forming formulation currently on the market for the delivery of estradiol, delivers 21 μg of estradiol, while the applied dose is 1.53 mg. The washing, performed after 30 min from the application to remove the excess of drug deposited on the skin surface, does not drop down the estradiol bioavailability [81]. However, the poor efficiency, intended as the dose absorbed by the skin with respect to the applied dose [82], is typical of all topical dosage forms including patches, since the absorption is governed by the chemical potential.

In addition to estradiol, testosterone and some progestins were also included in FFS for the treatment of androgen deficit in men [65] and contraception [83]. In particular, nestorone (a 19-norprogesterone derivative) was formulated in a pre-dosed polymeric FFS and applied three times a day to the forearm of six postmenopausal women. Clinical data evidenced that the concentrations reached through this route of administration and the obtained pharmacokinetics have effectively led to a blockage of ovulation and, therefore, to the desired contraceptive effect.

5. ADHERENCE TO TOPICAL TREATMENTS

"Adherence to medications" is defined as "the process by which patients take their medications as prescribed" [84] and "non-adherence to medications" is thus defined as "late or non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen or early discontinuation of the treatment" [61, 84]. Poor medication adherence is a worldwide problem associated with negative health outcomes and increased health care costs.

The issue of patient adherence to topical drugs is particularly significant in relation to chronic skin diseases, including psoriasis, atopic dermatitis, and acne, which require long-term use of topical medications. Several factors make adherence to topical treatment of skin disease different from other medication adherence issues. Patients with skin disease may be more likely to adhere to their treatment regimens because dermatological diseases are more visible and highly symptomatic and because topical treatments have few systemic side effects. On the other hand, patient adherence may suffer as topical treatments are more time-consuming and complicated to use than oral treatments. Indeed, ambiguous and subjective usage and dosing instructions (*e.g*. "apply sparingly") may lead to incorrect use of topical drugs. Complicated application instructions may be more difficult to understand or remember, and result in more frequent misuses compared to oral therapy (*e.g*. 'take one tablet daily'); patients may be put off by topical treatments' non-aesthetic and galenic nature (*e.g*. messiness, smell, spreadability, and discoloration), or side effects such as irritation, burning, and dryness [85].

Formulations or dosage forms to be applied to the skin could contribute to greater medication adherence and better treatment outcomes. As an example, patches do not always have excellent esthetic properties, since, under certain conditions, they can be clearly visible, thus reducing patient compliance. Semi-solid formulations (gels and ointments) may result, in some forms, more discreet than patches, but they cannot always guarantee a prolonged adhesion to skin surface, also because they are easily removable in contact with clothing. Moreover, ointments leave sticky and oily skin surface after application, further decreasing patient compliance [62, 86]. Another problem related to wear and tear is the time needed to dry these formulations, which can be quite long, and often they require rather large areas of application, making the administration even more uncomfortable.

Despite many reports underline that patient's preferences for the various topical formulations are highly variable [87], both medicated foams and FFS could solve, or at least reduce, some of these problems and, therefore, improve the adherence. Indeed, these dosage forms can reduce the frequency of administration and the duration of the treatment period. As an example, FFS containing the antifungal terbinafine allows a once-a-day administration to overcome the issues related to multiple administrations required by traditional formulations (gels or ointments) [88, 89]. For patients who prefer a less messy vehicle, adherence and outcomes are

likely to be better with these formulations compared with the traditionally recommended ointment. Moreover, due to evaporation of the propellant or volatile solvent(s), both formulations can leave a fresh sensation on the inflamed skin [90]. Furthermore, the design of low viscosity formulations can facilitate their application on the skin. Recently, a fixed-combination calcipotriene 0.005% and betamethasone dipropionate 0.064% formulated as a foam was proposed as an alternative to the corresponding ointment and gel in the treatment of psoriasis vulgaris. In such formulation the use of dimethyl ether and butane mixture used as propellant allows formation of a stable supersaturated system which enhances skin penetration of both loaded active substances compared to an ointment. Following once-daily topical application, preference data indicated that younger patients (aged 18-39 years) receiving the foam thought it was more effective and easier to apply than the gel [91]. After 15 days of use, 94% patients with mild to severe psoriasis would recommend foam to other patients with psoriasis, with 73% being very likely to do so [92].

CONCLUSION

In case of FFS, the appreciation of patients is related to the discretion of the film applied on the skin so that, thanks to their transparency, FFS are often referred as "transparent patches". This feature was demonstrated to improve the patient compliance, above in case of some treatments, such as hormone replacement therapy and smoking cessation, for which privacy is one of the main concerns of the patients. Therefore, dosage forms simple to hide and almost invisible after application, such as FFS, are very attractive.

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