The potential of polymeric film-forming systems as sustained delivery platforms for topical drugs

Abstract

Introduction: Dosing regimens requiring multiple daily applications frequently result in poor patient compliance, especially in the treatment of chronic skin diseases. Consequently, development of sustained delivery systems for topical drugs permitting less frequent dosing is of continuing interest for dermatological therapy.

Areas covered: This potential of polymeric film-forming systems (FFS), created *in situ* on the skin, as sustained delivery platforms for topical drug delivery is reviewed. Key formulation parameters that determine delivery efficiency are considered focussing on those that permit a drug reservoir to be established in the upper layers of the skin and/or on the skin surface from which release can be sustained over a prolonged period. The advantageous and superior cosmetic attributes of FFS (compared to conventional semi-solid formulations) that offer significantly improved patient compliance are also addressed.

Expert opinion: The promise of polymeric FFS as convenient and aesthetic platforms for sustained topical drug delivery is clear. Manipulation of the formulation allows the delivery profile to be customised and optimised to take advantage of both a rapid, initial input of drug into the skin (likely due to a transient period of supersaturation) and a slower, controlled release over an extended time from the residual film created thereafter.

Keywords

Dermal drug delivery; polymeric film-forming systems; supersaturation; topical formulations; sustained delivery.

Article highlights

- Optimisation of the formulation of polymeric film-forming systems (FFS) permits sustained drug delivery to be achieved via the formation of a drug reservoir in or on the skin.
- The initial metamorphosis of the formulation, and consequent increase in the degree of drug saturation, enables the establishment of a drug reservoir in the upper skin layers.
- FFS prepared with hydrophobic polymers have greater skin substantivity, facilitating formation of an external drug reservoir from which sustained delivery may be achieved.
- Realisation of the long-term potential of FFS as sustained, topical drug delivery systems requires proof-of-principle to be demonstrated conclusively *in vivo*.
- A key issue is to accomplish the desired therapeutic effect with a FFS formulation that creates an aesthetically acceptable residual polymeric film on the skin.

1 Introduction

The topical treatment of skin diseases is desirable for obvious reasons: the drug product is applied directly at the affected site, achieving levels at the local target that are at least as high as those possible by (e.g.) oral administration, but with very limited systemic exposure and associated side-effects. However, topical delivery can be challenging due to the efficient barrier properties of the stratum corneum (SC). Typically, only a small percentage of the applied drug reaches the target site, the remainder being left in a non-diffusible (i.e., solid) form in the residual film post-application and unavailable for delivery (1, 2).

Patient compliance to the repetitive daily application of conventional, cosmetically sub-optimal topical dosage forms (ointments, etc.) is often poor (3-5), compromising the efficacy of the treatment of chronic skin diseases in particular (3). The development of topical, sustained delivery formulations permitting prolonged therapeutic effect and less frequent dosing would offer great benefit, therefore, in dermatological therapy. How can this be achieved? Two strategies that almost certainly overlap in practice are envisaged involving formation of drug "reservoirs" on and in the skin. The former requires creation of a residual film of formulation, in which the drug maintains at least some solubility, with good substantivity and resistance to washing and wear (6). The latter depends on manipulation of the formulation's metamorphosis post-application to relatively rapidly transfer sufficient drug into the outer layers of the SC, the slow diffusion from which can subsequently control delivery of the active to the underlying tissue. This so-called "reservoir" function of the skin (7) has been recognised for many years (8).

Clearly, therefore, the objective of sustained topical delivery will depend on those formulation characteristics that (a) comprise the residual surface film, (b) the volatile excipients, the evap-

orative loss of which drives drug into the SC upon initial application (possibly resulting in transient supersaturation), and (c) the physicochemical properties of the drug that governs its affinity for, and ability to diffuse through, the SC (9).

2 Film-forming systems for topical application

The use of polymeric FFS created *in situ* for topical application is relatively new, although such systems are well-known as controlled-release film coatings of solid oral dosage forms and have been investigated for transdermal delivery as well (10-13). In the latter case, the product Axiron® topical solution (Eli Lilly and Co., Indianapolis, IN), a polymeric FFS developed by Acrux, Inc. (Melbourne, Australia), for the transdermal delivery of systemically active testosterone was approved by the U.S. Food & Drug Administration (FDA) in 2010 (14).

The disadvantages of conventional topical dosage forms, especially ointments, include their poor cosmetic attributes (visual appearance and perceived skin feel) and long drying time, making application of medication inconvenient and time-consuming for patients (4, 15) and resulting in poor compliance (16-18). A better and more patient-friendly formulation would be fast drying, aesthetically pleasing, and able to deliver the drug over longer periods of time, (≥ 24 hours, for example). FFS have displayed good tolerance *in vivo* (11, 19), and fulfil many of these requirements supporting the rationale for their study and development. These attributes have been reinforced in a more recent study (20), in which the efficacy of a clobetasol spray was associated with factors beyond simple patient compliance.

The use of FFS technologies for topical application has been examined over the last decade both directly and indirectly. Indeed, some topical gels, already on the market, can be considered as FFS given that the gelling polymers used also display film-forming properties. After their application, a film is eventually formed on the skin, albeit more slowly than from a polymeric solution due to the higher viscosity. For example, DuraPeel™ (Nuvo Research Inc., Mississauga, Ontario, Canada) incorporation into a cream or a gel facilitates formation of clear films on the skin from which the drug substance may then be released for up to 12 hours

(21). A FFS based on PharmaDur® (Polytherapeutics, Inc., Bridgewater, New Jersey) graft polymers also enables imperceptible and invisible films to be created *in situ* from gelling topical solutions (22).

With respect to the treatment of skin disease, an example of a FFS for drug delivery to the SC is Lamisil® Once (Novartis Consumer Health SA, Nyon, Switzerland) which contains the anti-fungal agent terbinafine for the treatment of dermatophytoses. The increased residence time of the product on the skin has permitted the daily applications of the conventional cream or gel formulations to be replaced with a single administration (23, 24). Another illustration is provided by the MedSpray™ (Patch in a Can®) technology (MedPharm, Ltd., Guildford, U.K.), an aerosol, propellant- and solvent-based polymeric FFS for topical, dermal and transdermal drug delivery (25) that aims to create *in situ* a supersaturated, residual drug film. The performance of the approach has been studied using various corticosteroids (26-29), and a comparative clinical study of MedSpray™ 1% w/w terbinafine and Lamisil® Once (topical solution), both dosed only once, has demonstrated comparable anti-fungal activity and positive consumer acceptability (Figure 1) (21).

2.1 Film-formation mechanism

FFS can be either dispersions or solutions of film-forming polymer, depending on the solubility of the polymer in the selected solvent; this difference in starting vehicle will influence the film-formation mechanism (Figure 2) and the mechanical properties of the resulting film (30-32). Films formed from dispersions, especially emulsions, tend to appear cloudy and are less cosmetically acceptable as compared to the generally preferred transparent films formed from solutions.

In solution, the polymer chains are highly mobile but come into closer contact as the solvent evaporates, eventually forming a film. From a polymer dispersion, the film is created via the physical process of polymer particle coalescence, the particles deforming as capillary forces increase with solvent evaporation. Incorporation of a plasticiser is often required in this case to lower the minimum film-forming temperature (thereby softening the polymer particles and facilitating their coalescence) (31). For both types of film, the rate of film-formation and the microstructure of the film depend on the rate of solvent evaporation that can, in turn, give rise to differences in drug release profiles (30).

3 FFS vehicle

Drug release from all topical delivery systems, and the rate and extent of the compound's subsequent skin uptake and penetration (i.e., local bioavailability and efficacy) depend sensitively on the composition of the applied formulation (15, 33-36). Interactions between drug, vehicle and skin are complex and determine how the active partitions into, and subsequently diffuses through, the barrier (18). Formulation optimisation is typically directed at maximising the penetration of the drug to its site of action, and this means maximising the thermodynamic activity (37, 38). Classically, the approach has been to develop formulations in which the drug is either at a concentration close to its saturation solubility, or is present as a suspension. For polymeric FFS, of either the solution or dispersion type, there is transformation of the formulation post-application as volatile excipients evaporate to leave a residual film. The delivery profile likely comprises at least two phases, therefore: a rapid uptake of drug as it concentrates in the FFS when solvent(s) evaporate(s), followed by a slower profile governed by release from the residual film. A clear challenge, as a result, is not only to formulate effectively for the initial delivery of drug into the skin, but also to ensure that sufficient drug is left in molecular (as opposed to solid) form in the residual film since only the dissolved compound is capable of diffusing (33). Because of these constraints, it is self-evident that the optimal vehicle will depend on the specific drug and perhaps on its intended concentration too (18, 33, 39).

Table 1 lists properties of the FFS vehicle and the drug substance that may affect release and delivery into the skin. Many factors are interrelated and knowledge of their interactions is essential in understanding the mechanism(s) of drug delivery from FFS and its optimisation.

3.1 Metamorphosis of FFS vehicles

Post-application to the skin, the quantitative composition of a FFS changes significantly, in particular through the loss of volatile excipients (18, 33), resulting ultimately in the creation of the residual polymeric film. In this process, the drug concentration increases, quickly reaching saturation, and with the distinct possibility of (albeit transient) supersaturation on the skin surface and/or in the upper SC (18, 40-42). Enhanced drug flux is therefore anticipated, even greater than the theoretical maximum for the period of supersaturation (25, 27, 37, 41, 43-47). The latter phenomenon also supports the idea that FFS application enables a drug reservoir to be established in the skin from which sustained delivery can be subsequently achieved. Figure 3 schematically outlines the drug delivery consequences of this 'metamorphosis' of a FFS.

Supersaturating formulations (i.e., those which result in the degree of saturation of the drug exceeding 1.0) are inherently thermodynamically unstable, and it is only a matter of time before crystallisation of the drug occurs within the residual film (48). If the solubility of the compound in this film is low, then further delivery is compromised because only drug in molecular form can diffuse (and re-dissolution is likely to be slow or negligible due to the low solubility) (28, 44, 49, 50). To mitigate against this challenge, and to inhibit crystallisation during storage (28, 29), anti-nucleating polymers have been a focus of research in the FFS area, as discussed further below in section 3.2.3.

3.2 Formulation parameters and modulation of release

The drug delivery characteristics of FFS are dependent, at the very least, on the following: solvent (30, 51), polymer type and concentration (10, 11, 52), plasticiser type and concentra-

tion (16, 52-55), other incorporated excipients (e.g., penetration enhancer, lipid component) (11, 56-59), and the drug (39, 60-64). Each is now considered in turn.

3.2.1 Drug

Drug penetration across the skin is primarily determined by solubility, molecular structure, and lipophilicity (60, 64). In general, smaller compounds diffuse more readily across the SC than larger ones, and maximum fluxes of drugs with molecular weights greater than 500 Daltons are very low (61, 65). Broadly speaking, skin permeability increases with increasing lipophilicity (the SC being a lipophilic barrier, consistent with its principal role of retarding water loss), at least up to a point (60). For very hydrophobic compounds, however, their very low water solubilities mean that uptake into the viable skin becomes the rate-limiting step (as opposed to diffusion through the SC). Consequently, it appears that a modest level of lipophilicity, corresponding to an octanol-water partition coefficient (P) of 10-1000 (log P = 1-3) (65, 66), coupled with finite oil and water solubilities, are ideal characteristics for good skin penetration. With respect to FFS, while skin permeation remains dependent upon the nature of the drug, the type of polymer used differs also has an impact upon the release and percutaneous absorption of the active thereafter (39). In terms of the skin 'reservoir' effect mentioned earlier, it is evident that drugs, which are more lipophilic than the 'ideal' candidates for rapid penetration, would be more suitable for achieving the sustained delivery profile sought from the FFS residual film (63, 67, 68). It is also worth noting that other molecular structural features have been linked to skin penetration, including the drug's ability to accept or donate hydrogen bonds (factors that impact already, of course, on log P); with respect to FFS, it has

been reported that hydrogen-bonding between the drug and the film-forming polymer is a mechanism by which crystallisation of the former can be inhibited (45, 69).

3.2.2 Solvent

Polymeric films formed from solutions are more mechanically resistant than those created from dispersions (30, 51). This difference may be ascribed to differences in film microstructure (Figure 2) with a higher degree of polymer-polymer chain inter-penetration in films formed from solutions (30). With respect to the drug, the casting solvent in FFS can affect the crystalline state of the drug in the residual polymer film (70).

Obviously, the FFS solvent must be volatile to allow formation of the film and, for this reason, organic solvents, such as the lower alcohols (ethanol, isopropanol), are preferred. Polymer solubilities in organic solvents are typically high and, although less environmentally friendly than aqueous-based solvents, for example, the fast evaporation of volatile organic solvents leads to short FFS drying times and better convenience for the patient. Ethanol is the solvent of choice (71), and despite reports of it provoking skin irritation when used at high levels in dermal formulations, the FDA accepts >95% of the dehydrated solvent in topical solutions (72). Ethanol has also been described as a penetration enhancer (58) and there is no question that it facilitates the initial partitioning and uptake of lipophilic drugs into the SC upon application of a FFS. However, on the whole, the literature is limited in terms of the effect of the organic solvent used to create a topical FFS delivery system; indeed, when FFS were tested for transdermal delivery, little or no difference in delivery could be associated with the specific organic solvents used (ethanol, isopropanol and ethyl acetate, including binary mixtures thereof) (39).

3.2.3 Film-forming polymers

Various polymers are potential film-formers, such as cellulose derivatives (11, 31, 73-75), acrylate polymers or copolymers (11, 31, 73, 74), methacrylate polymers or copolymers (11, 12, 31, 59, 73, 74, 76, 77), silicones (11, 73), and vinyl polymers (12, 29, 59, 73-75) (Figure 4). The nature and the concentration of the polymer affect the mechanical properties and cosmetic attributes of the formed film (12, 31, 73, 75-78), as well as its ability to deliver the drug (10-12, 31, 39, 52, 76, 79). Personal experience demonstrates that the film formed on the skin is thick and rigid when the polymer concentration used is too high. Such non-flexible films are uncomfortable to wear, and show clearly that the sensorial, cosmetic attributes of the film should be considered during their development. As far as drug delivery is concerned, while hydroxypropyl cellulose films display long-term, zero-order drug release, for example, those formed with the more hydrophobic polyacrylate and polymethacrylate polymers produce an initial 'burst' release of the compound with the potential to establish a drug reservoir in the SC (Figure 5) (79). Differences in release kinetics can be attributed to factors such as the diffusivity of the drug in the polymeric network and the physical state of the drug (crystalline, amorphous or dissolved) in the film, which in turn depend on the physicochemical properties of the polymer and drug and the interactions between them.

The moisture sorption of polymeric films increases with increasing hydrophilicity of the polymer (53, 76). The plasticising effects of water on the polymer network (80, 81) can increase drug diffusivity and release. The water-solubility of hydrophilic films makes them less resistant to removal (e.g., by washing or in perspiration) and unlikely therefore to have sufficient skin substantivity to function as an external drug reservoir. As with hair care products, substantivity is not only determined by the water solubility of the polymer, but also by its net

charge and interaction with skin surface protein and lipids (82). As the skin surface has a net negative charge at physiological pH, films created with cationic polymers display higher substantivity than those formed from neutral or anionic polymers. Furthermore, attractive forces such as hydrogen bonding and van der Waals forces suggest the use of lipophilic and protein-like polymers (83, 84).

The concentration of the film-forming polymer is crucial. If it is too low, then the film formed can be rather weak (39). On the other hand, a higher polymer content (resulting in a denser film network) may retard drug release (10, 28, 52). A higher polymer concentration also increases the FFS viscosity and increases its drying time, upon application to the skin (28).

Polymer blends have been used to design controlled-release coatings for solid oral dosage forms. Blending hydrophobic and hydrophilic polymers has proven effective, with the hydrophilic polymer component forming pores upon hydration (30, 31, 55, 85). A similar approach has been demonstrated for topical polymeric films as well, to achieve a wide range of release rates and also, in some cases, a different release mechanism (10, 76, 77, 86, 87). However, polymer blend systems are more complex, and phase separation and plasticiser redistribution between the polymers, can occur leading to inconsistent performance (31, 88).

Some film-forming polymers display anti-nucleating properties, i.e., they prevent or inhibit nucleation and crystallisation of the drug (43, 50, 70, 89, 90). Figure 6 illustrates the anti-nucleating effect of hydroxypropyl cellulose and polymethacrylate copolymer on betamethasone 17-valerate (BMV). Mitigating against drug crystallisation is an obviously desirable feature of film-forming polymers, which can lengthen the period that supersaturation is maintained, and possibly permit a higher degree of supersaturation to be achieved. Because of the importance of maintaining solubilised drug in the topical film, inhibition of crystallisation is

key to the establishment of a drug reservoir for sustained delivery. The mechanism of anti-nucleation involves preferential interaction of the polymer chains with the drug in molecular form thereby hindering solute-solute interactions that otherwise lead to formation of crystals (50, 86). Although other mechanisms of anti-nucleation have been suggested in the literature, the inhibition of crystallisation of the corticosteroid, hydrocortisone acetate, has been explained by its association with the polymer via hydrogen bonding(90). It follows that the anti-nucleation efficiency of a polymer may depend sensitively upon the manner in which it interacts at a molecular level with the specific drug of interest (Figure 6) (91, 92).

3.2.4 Plasticiser

Plasticisers are typically low molecular weight additives that impart flexibility to a polymer. Organic esters, phosphate esters, fatty acid esters, and glycol derivatives are examples of commonly used plasticisers (53, 73, 76, 93, 94). Incorporation of a plasticiser results in a less brittle, stronger, and more flexible film (94, 95). This improvement in mechanical properties is a consequence of the plasticiser increasing the free volume between the polymer chains, and thereby increasing their mobility (95). Plasticisation reduces the polymer glass transition temperature (T_g), above which the chains are mobile (95) and the formed film is flexible. Ideally, this desirable feature is achieved below the skin temperature (~32°C) (96) allowing the film to adapt to the movement of the skin with improved substantivity. Furthermore, incorporation of plasticiser reduces the minimum film-forming temperature and facilitates polymer coalescence and film-formation.

The nature of the plasticiser and its concentration determine its impact on film formation (53-55, 97). Examples of plasticisers of varying lipophilicity are shown in Table 2. Generally, the

most efficient plasticisers have structural features in common with the polymer(s) into which they are incorporated. The impact of a plasticiser on drug release and delivery depends on whether a dispersion or solution FFS is being used. In the former case, the plasticiser-facilitated coalescence of polymer particles results in a more complete and dense film, from which slow drug release has been shown (30, 54). In contrast, plasticisation of solution FFS does not affect film formation to the same extent, but generally increases both polymer chain flexibility, and drug diffusivity and release (27, 76, 79, 88, 93). Further, the compatibility of plasticiser and polymer can have an important effect on drug release as well (55); for example, the lipophilic plasticisers, tributyl citrate (TBC) and dibutyl sebacate (DBS), incorporated into a hydrophobic, polyacrylate copolymer-based FFS, enhanced BMV release more than was observed when the polymer was the hydrophilic, hydroxypropyl cellulose (Table 3) (79).

3.2.5 Other excipients

The incorporation of penetration enhancers (58) into FFS can increase drug delivery (7, 11, 98) and establish a larger reservoir in the SC (9). The extent of enhancement depends on a number of factors (including concentration), and binary mixtures of enhancers can induce synergistic effects (11). However, it is recognised that there is always the risk of skin irritation when enhancers are used (99, 100).

The incorporation of a lipid excipient, such as medium chain triglycerides (MCT), into a FFS has been shown to result in a structured, two-phase polymeric film (Figure 7). The softer lipid-enriched inclusions provide an environment in which the solubilised drug is released quickly in an initial phase (59, 77, 92) and then in a sustained fashion thereafter (79, 92).

4 Expert Opinion

Polymeric film-forming systems (FFS) created *in situ* are promising sustained delivery platforms for topical drugs. With an appropriate vehicle composition, FFS can facilitate an initial 'burst' release of drug, establishing a reservoir on and/or in the stratum corneum, from which a sustained, slower delivery to target sites in the lower skin layers can subsequently occur. Evaporation of the volatile solvent component of the FFS causes a 'metamorphosis' of the formulation that results in a residual polymeric film. A transient period of drug supersaturation, perhaps extended by the judicious use of anti-nucleant polymers, during the transformation of the vehicle can be exploited to optimise the delivery profile.

The current literature does not identify a unique "recipe" for an ideal FFS formulation. Rather, it is clear that the selection of polymer, plasticiser, volatile solvent(s) and other excipients must be tailored to the properties of the drug being delivered. Open questions pertaining to the pros and cons of hydrophilic versus hydrophobic polymers, the benefits of plasticiser/excipient incorporation, and strategies to inhibit drug crystallisation as the organic solvent evaporates, demand further research work at this time.

In terms of the specific aim to use FFS as sustained drug delivery platforms for topical drugs, it is clear that the water solubility of films based on hydrophilic polymers limits their residence time on the skin and undermines their perceived utility. For the moment, hydrophobic polymer-based FFS show greater potential, their water-resistance permitting increased substantivity and a prolonged residence time on the skin, with the consequent formation of a drug reservoir both on and within the outer SC. The metamorphosis of the FFS is crucial for the formulation's ultimate utility as a drug delivery platform: Is a supersaturated state achieved and for how long? Are the anti-nucleant properties of the polymer sufficient to retard/inhibit

drug crystallisation significantly? How can drug and polymer characteristics be matched to maximise favourable interactions to retard/inhibit crystallisation? What are the roles of plasticiser and (for example) lipid excipients in an optimised FFS formulation?

With respect to the selection of appropriate drugs for delivery with the FFS approach, it is logical that more lipophilic compounds have been studied in more detail. Their obvious affinity for the lipophilic SC makes the establishment of a drug reservoir therein, and sustained release therefrom, more likely. The extent to which the delivery approach might be extended to more hydrophilic drugs is unknown.

Although FFS have been shown capable of maintaining drug release *in vitro* over several days, there is a pressing need for long-term *in vivo* investigations, to fully clarify the potential of these formulations to sustain delivery to pharmacological targets in deeper skin layers and to achieve a prolonged therapeutic effect. At the same time, such studies can address optimisation of the practical use of FFS, including identification of convenient and fool-proof application methods and dose control (e.g., via the use of aerosols or sprays).

In conclusion, it appears that polymeric film-forming systems do have a positive role to play in the next generation of topical formulations designed to offer sustained drug delivery to and into the skin. The superior cosmetic attributes of FFS, compared to conventional semi-solid topical products, coupled with the potential for less frequent dosing regimens, are attractive features in terms of patient compliance and therapeutic outcome, especially for the treatment of chronic skin diseases.

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Figures and Tables, plus legends

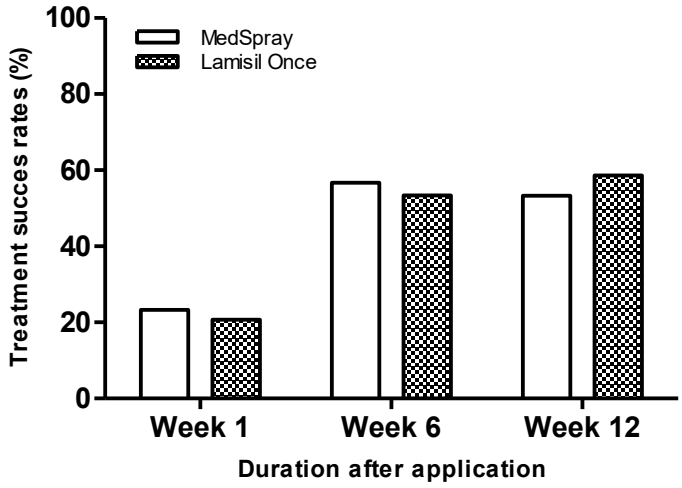

Figure 1. *Treatment success rates after a single application of either MedSpray™ 1% w/w terbinafine or Lamisil® Once (topical solution). Redrawn from data in reference (19).*

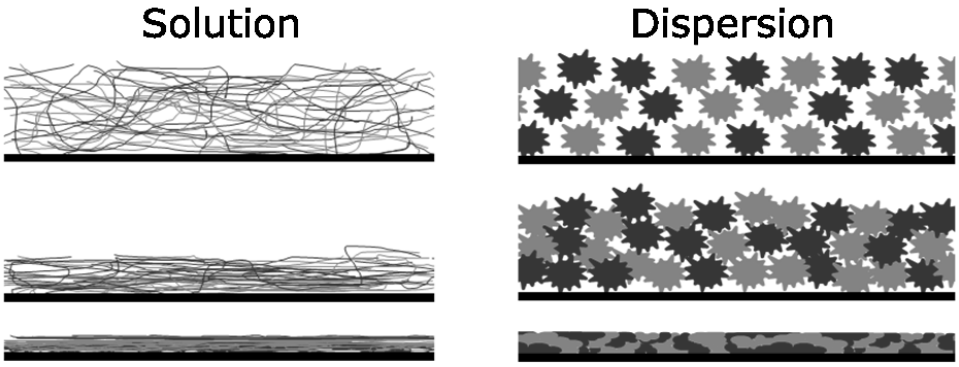

Figure 2. *Schematic illustration of the mechanism of polymeric film-formation from a polymer FFS solution (via interaction between mobile polymer chains) and dispersion (deformation and coalescence of polymer particles).*

Table 1. *Key properties that influence drug delivery from polymeric film-forming systems.*

FFS	**Drug**
Solvent	Solubility
Co-solvent	Physical state of drug in the formed film
Drying time	Molecular weight
Film-forming polymer	Chemical structure
Film-formation mechanism	Hydrogen bond donating/accepting groups
Supersaturation	Log P
Anti-nucleation	Diffusivity
Plasticiser	Drug load
Penetration enhancer	Drug-vehicle-skin interactions
Water-resistance	
Skin substantivity	
Residence time	
Film flexibility	
Contact surface area	
Surface energy of film	
Film diffusivity	
Moisture sorption	
Swelling	

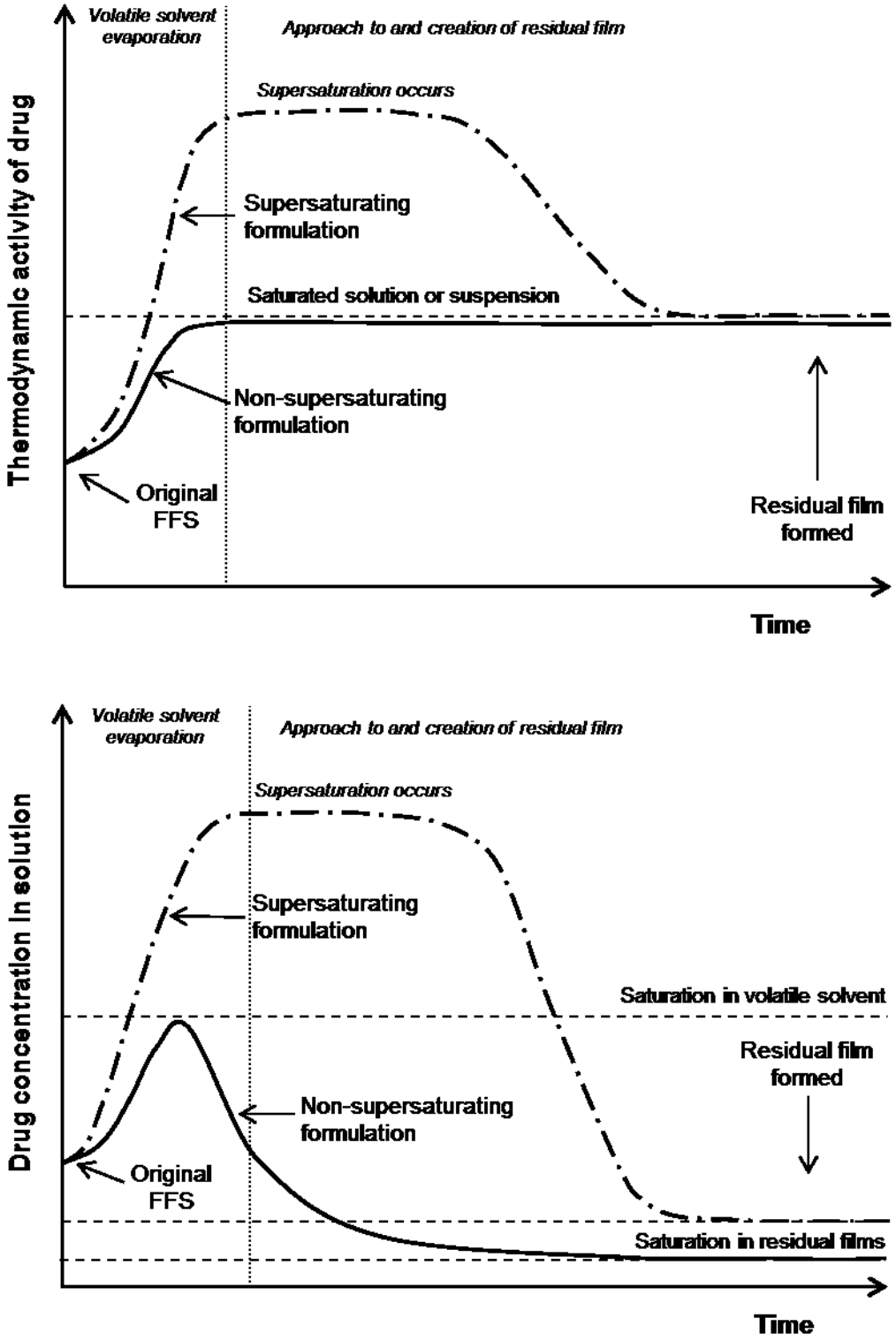

Figure 3. *Schematic representation of drug thermodynamic activity (upper panel) and concentration in solution (lower panel) during the 'metamorphosis' of a FFS. Initially, both*

thermodynamic activity and solubilised concentration increase as volatile excipients evaporate. Drug then either reaches its limiting solubility (activity maximises, solubilised concentration peaks and then begins to fall precipitately), or transient supersaturation occurs creating a thermodynamically metastable state of relatively high solubility. Ultimately, however, this situation cannot be sustained and the system evolves to a residual film in which drug solubility is markedly reduced (but optimally sufficiently finite to continue to provide continued input of the compound into the skin).

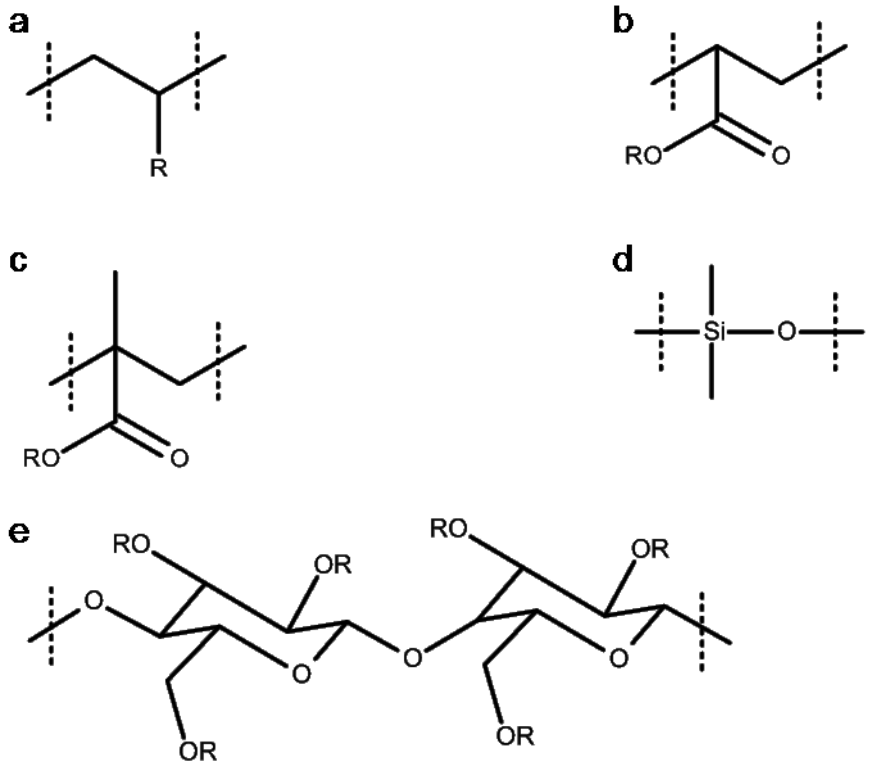

Figure 4. *Chemical structures of the repeating units of selected film-forming polymers: (a) simple polyvinyl polymers, (b) polyacrylates, (c) polymethacrylates, (d) silicones, and (e) cellulose derivatives.*

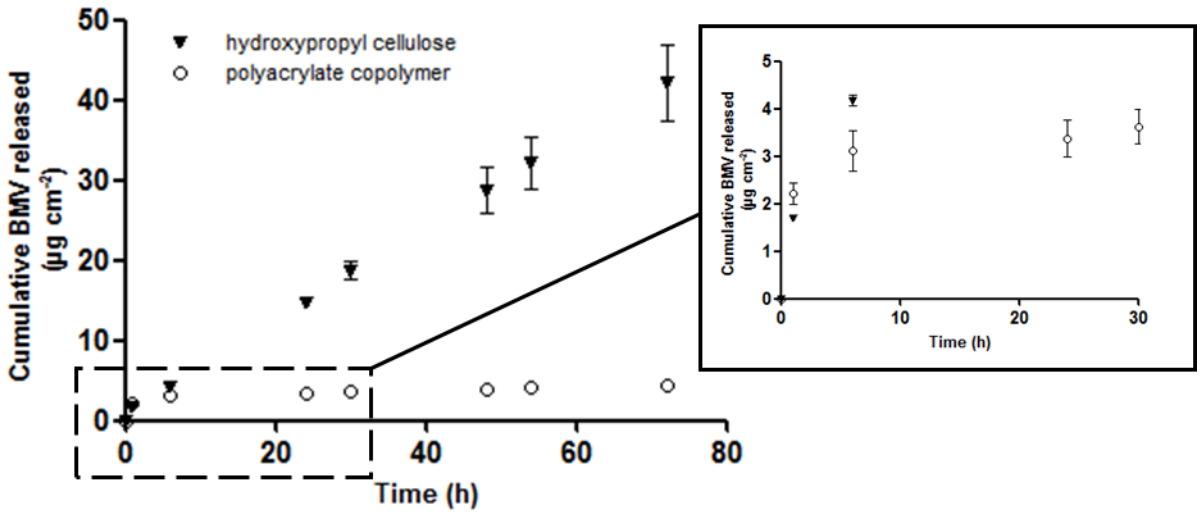

Figure 5. *In vitro release of betamethasone-17-valerate from a hydroxypropyl cellulose and polyacrylate copolymer film (mean ± standard deviation; n=3). The inset is a zoom of the initial burst release from the film. Redrawn from data in reference (79).*

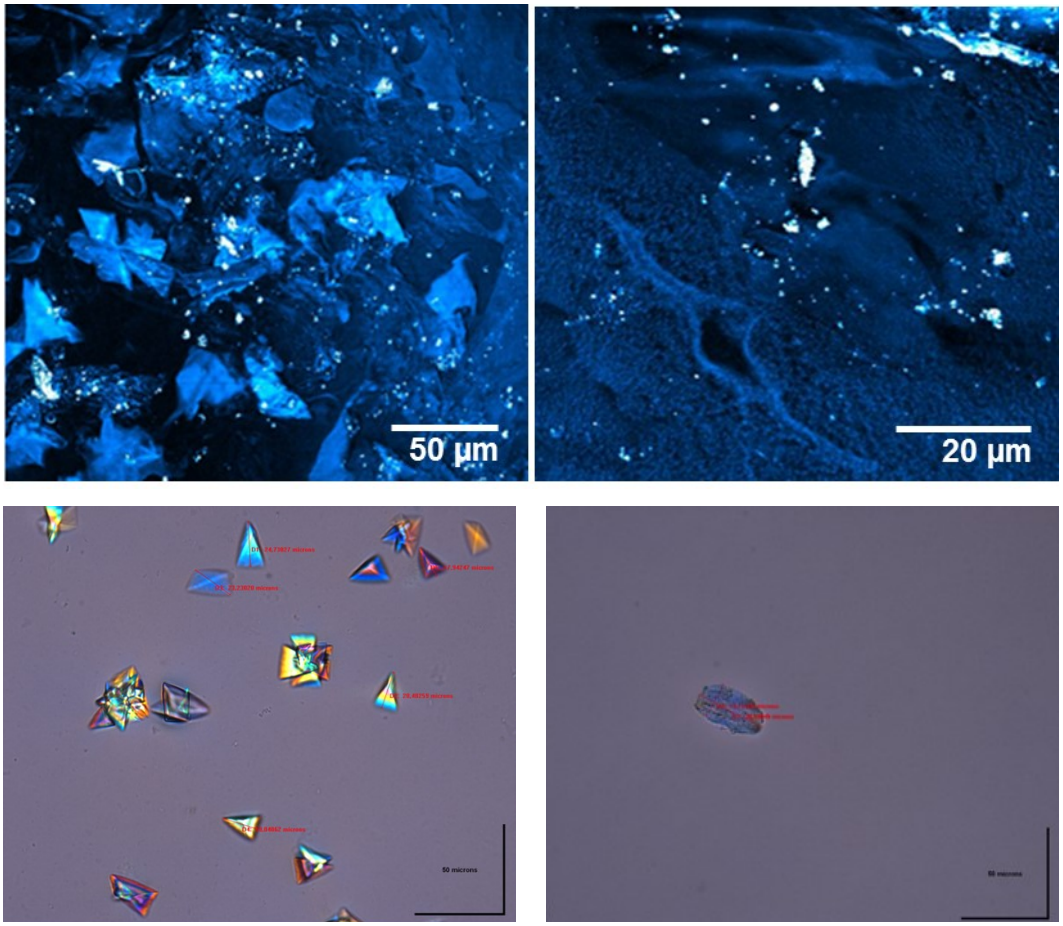

Figure 6. *<u>Upper panels</u>: Stimulated Raman scattering (SRS) images of deuterated BMV crystals formed in/on the skin within 30 minutes post-application in either ethanol (left image) or in a FFS based on hydroxypropyl cellulose (right image). SRS contrast is obtained at 2120 cm^{-1} corresponding to the $–CD_2$ stretching vibration. <u>Lower panels</u>: Micrographs illustrating the differential anti-nucleation efficiency of FFS prepared with BMV and either hydroxypropyl cellulose (left image) or polymethacrylate copolymer (right image).*

Table 2. *Examples of plasticisers used in polymeric film-forming systems.*

Plasticisers
Acetyltributyl citrate, acetyltriethyl citrate
Dibutyl phthalate, diethyl phthalate, dimethyl phthalate
Dibutyl sebacate, diethyl sebacate
Triacetin
Tributyl citrate, triethyl citrate

Table 3. *Enhancement ratios of the cumulative release of BMV in 72 hours from hydrophilic and hydrophobic polymer-based FFS when plasticised with either TBC or DBS (data taken from (79)).*

	Plasticiser	
FFS polymer	**TBC**	**DBS**
Hydroxypropyl cellulose	2.1	2.8
Polyacrylate copolymer	2.6	3.4

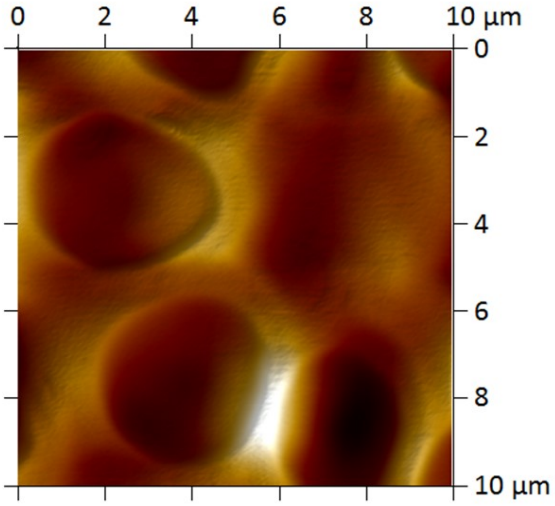

Figure 7. *Atomic force microscopy image showing the two-phase structure of a hydroxylpropyl cellulose film incorporating MCT.*