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# **Formulation considerations in the design of topical, polymeric film-forming systems for sustained drug delivery to the skin**

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## Graphical abstract

Polymeric film-forming systems (FFS) are potential drug delivery systems for topical application to the skin. The FFS form thin and transparent polymeric films *in situ* upon solvent evaporation. Their application convenience and cosmetic attributes, superior to conventional semi-solids, may offer improved patient compliance. This study represents the first phase of an investigation into the use of FFS for prolonged dermal drug delivery. FFS formulations were distinguished based on their ability to sustain the release of betamethasone 17-valerate (BMV) *in vitro* over 72h. The effect of film-forming polymer (hydrophilic: hydroxypropyl cellulose (Klucel™ LF); hydrophobic: polymethacrylate copolymers (Eudragit® NE and Eudragit® RS), and polyacrylate copolymer (Dermacryl®79) was first determined, and then the impact of incorporation of plasticisers (triethyl citrate, tributyl citrate, and dibutyl sebacate) was examined. The Klucel film released a significantly higher amount of BMV than the hydrophobic FFS, 42 versus 4 µg/cm<sup>2</sup>, respectively. The release was increased when a plasticiser was incorporated, and with higher enhancement ratios achieved with the more lipophilic plasticisers. In conclusion, the results show that FFS can sustain drug release (hence representing useful systems for prolonged dermal therapy) and emphasize the importance of the formulation on drug delivery, with the type of polymer being of greatest significance.

## Keywords

Dermal drug delivery; polymeric film-forming systems; betamethasone 17-valerate; *in vitro* release; plasticiser.

## 1 Introduction

Poor patient compliance is a well-known consequence of repetitive daily applications of conventional topical dosage forms, such as ointment, creams or gels, with less attractive cosmetic attributes. This is especially pronounced in the treatment of chronic skin diseases (1-4). While semi-solid dosage forms may exhibit sustained-release characteristics, they do not always ensure persistent contact to the skin for an extended treatment interval. Development of topical formulations permitting less frequent dosing is therefore of great interest for dermatologi-

cal therapy. Less frequent dosing may be facilitated by increasing the contact time and/or maintaining the delivery of the drug substance to the local site of action by forming a drug reservoir in or on the skin. Such an outcome will presumably rely on the composition of the formulation.

While polymeric film-forming systems (FFS) have been used for the transdermal delivery of steroidal hormones and analgesics for systemic therapeutic effect (5-11), they also represent attractive, alternative topical formulations in dermatology. The anti-fungal agent, terbinafine, has been incorporated in a FFS (Lamisil<sup>®</sup> Once<sup>\*</sup>) for the targeted treatment of dermatophytoses in the stratum corneum (SC), and exemplifies how increasing the drug residence time on the skin permits less frequent dosing (12). FFS are applied directly to the skin and form thin, transparent films *in situ* upon solvent evaporation. The drug substance is dissolved in the film-forming vehicle and thus incorporated in the film formed on the skin. The polymeric network of the formed film can function to form an external reservoir and/or limit the supply of drug substance to the skin reservoir, and thereby control the release of drug substance (6). Additionally, FFS may have superior cosmetic attributes to semi-solid formulations, as FFS are fast-drying, less greasy and almost invisible once applied on the skin (1).

Complete skin contact over the entire application period is essential. A successful formulation for prolonged delivery would therefore require high flexibility to adapt to the movements of the skin, and high substantivity and strong adhesion to the skin for a consistent delivery and absorption of the drug (11). These parameters are important to bear in mind during the formulation design process.

Several factors are likely to affect drug delivery from FFS, including: the drug's physicochemical properties (13-17), the polymer type and its concentration (5;6;18), the plasticiser type and its concentration (18-23), the incorporation of other excipients (e.g., a penetration enhancer, a lipid component, or a cyclodextrin) (5;24-27), and vehicle metamorphosis post application, such as solvent evaporation leading to increase in drug saturation and possibly supersaturation (28-32).

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\* Lamisil<sup>®</sup> Once is a registered trade name of Novartis Consumer Health SA, Nyon, Switzerland

The substantivity of a topically applied formulation on the skin, defined as its persistence and resistance to removal, e.g. by washing and wear, is crucial for prolonged drug delivery. For the formulation to sustain a therapeutic effect, a drug reservoir must be established. The type and composition of the vehicle will affect the formation of such a reservoir. For a FFS, the polymer's water solubility is likely to be crucial to the location of this reservoir. Hydrophilic film-forming polymers, to be effective, have to establish a drug reservoir in the skin, due to their low water-resistance and resulting short-term persistence on the skin. Hydrophobic films, having higher water-resistance and substantivity can form an external drug reservoir on the skin, as well one within it.

The aim of the research described here was to initiate an investigation into the potential of FFS to provide prolonged dermal drug delivery for the local, topical treatment of skin diseases. In contrast to previous work directed to transdermal drug delivery (5;6), this investigation focuses on dermal delivery. The earlier work (33) showed that differences in the mechanical properties of FFS, such as flexibility and abrasion resistance, were indistinguishable when casted on glass slides and not, therefore, predictive of the *in vivo* interface. Here, the *in vitro* drug delivery characteristics of potential FFS are used instead as criteria for further development as sustained delivery systems.

## **2 Materials and methods**

### **2.1 Materials**

Betamethasone-17-valerate (BMV, purity 100%) was purchased from Crystal Pharma SAU (Boecillo, Spain). The polymers used were Klucel™ LF (Klucel) (hydroxypropyl cellulose) provided by Azelis (Lyngby, Denmark), Kollidon® 12 PF/17 PF/25/30 (PVP) (polyvinylpyrrolidone of varying molecular weight distributions) from BASF (Germany), Aqualon EC N10/N22/N50 (ethyl cellulose) (ethyl cellulose of varying molecular weight distributions, Azelis (Lyngby, Denmark), Chitofarm® S /M /L (chitosan) (chitosan of varying molecular weight distributions) Cognis GmbH (Germany), and Eudragit® RS PO (Eudragit RS) (ammonio methacrylate copolymer type B) and Eudragit® NE 40D (Eudragit NE) (poly(ethyl acrylate-co-methyl methacrylate) 2:1) from Evonik Röhm GmbH (Darmstadt, Germany).

Dermacryl<sup>®</sup> 79 (Dermacryl) (acrylates/octylacrylamide copolymer) was purchased from Akzo Nobel Surface Chemistry AB (Stenungsund, Sweden). Triethyl citrate (TEC) and tributyl citrate (TBC) were from Merck (Darmstadt, Germany), dibutyl sebacate (DBS) from Sigma-Aldrich (Broendby, Denmark), and methyl- $\beta$ -cyclodextrin (MbCD) (Kleptose Crystmab) from Roquette (Lestrem, France). Sodium acetate trihydrate and all organic solvents were purchased from VWR – Bie Berntsen A/S (Herlev, Denmark), Merck (Darmstadt, Germany) and Sigma-Aldrich (Broendby, Denmark).

## 2.2 Preparation of polymeric FFS

The polymer was dissolved in absolute ethanol (EtOH) (mixed with water for Eudragit RS) with or without plasticiser while stirring overnight until a clear solution was obtained. FFS compositions tested for *in vitro* release are in Table 1. BMV was dissolved in the FFS with stirring at a concentration of 1.2% w/w (corresponding to 1.0% w/w betamethasone) and provided an infinite dose for the *in vitro* release tests.

The polymer concentration used depended on its type (Table 1). The concentration of plasticiser was 20% w/w relative to the dry weight of the polymer.

## 2.3 FFS Characterisation

### 2.3.1 Evaluation of FFS formulations

A range of placebo FFS compositions were evaluated visually (33) using the characteristics and ratings described below. The polymer concentration ranges tested were: chitosan (5.0 and 10.0% w/w), Dermacryl (5.0, 7.5 and 10.0% w/w) ethyl cellulose (5.00 and 10.0% w/w), Eudragit NE (5.0, 7.5 and 10.0% w/w), Eudragit RS (10.0, 15.0, 20.0% w/w), Klucel (2.5, 5.0, 7.5, 10.0% w/w) and PVP (5.0 and 10.0% w/w).

**FFS vehicle:** The *appearance* of the FFS solutions was assessed as clear or opaque, indicating complete or incomplete dissolution of the film-forming polymer, respectively. The *viscosity* was rated as low (equivalent to water), medium (equivalent to glycerol) or high (equivalent to Lamisil<sup>®</sup> Once, marketed cutaneous solution).

**Polymeric FFS film:** Porcine ears were obtained shortly after the animals were killed from the Danish Meat Trade College (Roskilde, Denmark). The ears were stored at -20°C and thawed slowly at 5°C before preparation. The ears were cleaned with water, gently trimmed with an animal hair clipper (Oster, Tennessee, USA) and used for FFS evaluation within a few hours.

The films were formed either on excised pig ear skin or in a petri dish. 10 µl/cm<sup>2</sup> FFS was applied and spread within marked areas (3.8 cm<sup>2</sup>) on the pig skin, while 1000 µl were distributed across a petri dish (58 cm<sup>2</sup>), and the solvent allowed to evaporate to form the film. The *drying time* was evaluated 5 minutes after the FFS was applied to the skin by placing a cover slide on the film; the film was considered dry if no evidence of humidity was visible on the cover slide after removal. 30 minutes after application, the *film stickiness* was evaluated by gently pressing cotton wool onto the dry film. The stickiness was rated according to the quantity of cotton wool retained: low (little or no accumulation), medium (thin layer) or high (dense accumulation).

*Film-formation* was evaluated and rated as complete/homogeneous, incomplete/heterogeneous or with precipitation of the film-forming polymer. The *cosmetic attributes* of the film were assessed in terms of *structural features* as clear, transparent or unclear, and as smooth, structured/textured or greasy. Film *flexibility* was evaluated on the basis of cracking, and skin fixation was determined by stretching the skin in 2-3 directions. The film was rated flexible (no cracking or skin fixation) or non-flexible (cracking or skin fixation).

### 2.3.2 Evaluation of plasticiser incorporation

Based on the previous experiments, one concentration of each polymer was selected for further assessment of the effect of plasticiser incorporation. Three different plasticisers of varying lipophilicity were considered and their influence on the flexibility and structural features of the formed films was assessed visually as described above.

## 2.4 BMV release from polymeric FFS *in vitro*

The experiments were conducted using modified diffusion cells (LEO Pharma A/S, Denmark) with a silicone membrane (Dow Corning<sup>®</sup> 7-4107 Silicone Elastomer Membrane, 75 $\mu$ m) (Figure 1). A 10% w/w solution of MbCD in acetate buffer pH 4.5 was used as receptor medium to maintain sink conditions (16). The cells were equilibrated for 1 hour in the heating cabinet set to maintain a temperature of 32°C at the membrane surface thereby mimicking skin conditions *in vivo*. 240  $\mu$ l FFS were then applied and distributed on the membrane and the cells placed with the membrane horizontally in the heating cabinet. The cells were occluded with Parafilm<sup>®</sup> at 95 minutes post-treatment by which time the volatile constituents of the FFS had completely evaporated. The cells were then rotated so that the membrane was in the vertical position as shown in Figure 1.

Samples of 1.5 ml were withdrawn after 1, 6, 24, 30, 48, 54 and 72 h, and were replaced with the same volume of fresh, preheated receptor medium. The cumulated amount of drug substance released, Q (corrected for sampling) was calculated as described by Jensen et al. (16).

## 2.5 HPLC analysis

The concentration of BMV in the release samples was quantified by RP-HPLC using a YMC-Pack ODS-AQ column (YMC Europe GmbH, Germany) at 35°C and acetonitrile:methanol:acetate buffer pH 4.5 as mobile phase. A flow gradient method was used varying the ratio of mobile phase A and B, acetonitrile:methanol:acetate buffer pH 4.5 (55:40:5) and (5:40:55), respectively, over 10 min, using UV detection at 240nm. A flow rate of 1.0ml/min and an injection volume of 10 $\mu$ l were applied. The retention time was about 7 min.

## 2.6 Dynamic vapour sorption measurements

Moisture sorption–desorption characteristics of cast films were studied in a dynamic vapour sorption apparatus (DVS 1, Surface Measurement Systems, London, UK). All experiments were performed at 32°C. Weight changes were determined with an ultra-microbalance ( $\pm$  0.1 mg mass resolution).



Films of 0.20 ( $\pm 0.02$ ) mm thickness were casted in a Teflon mold at room temperature. The films were dried for 10 hours at 0% relative humidity (RH). Subsequently, stepwise changes in RH (0–20–40–60–80–94–80–60–40–20–0%) were imposed and the mass variation over time ( $dm/dt$ ) was monitored to detect when equilibrium sorption/desorption had been attained.

## **2.7 Data analysis**

All data were analysed using Graph Pad Prism 5.01. Two-way ANOVA ( $p < 0.05$ ) followed by Bonferroni post-test was applied to compare means.

## **3 Results**

### **3.1 Formulation development**

As ethyl cellulose and chitosan were not completely soluble in absolute ethanol, these polymers were eliminated from further investigation. Further, it was observed that PVP films re-dissolved over the 72 h release experiment, the high hydrophilicity of this polymer resulting in substantial moisture sorption. PVP was also excluded, therefore, from further study. The visual evaluation of the remaining polymers is summarised in Table 2.

Increasing polymer concentration increased the viscosity of the solution and its drying time for Klucel and Eudragit NE, but such effects were not observed for Eudragit RS and Dermacryl at the concentrations tested. In general, the FFS compositions formed complete, homogenous and clear films and exhibit low outward stickiness. Overall, film flexibility decreased with increasing polymer concentration.

Of the FFS compositions that formed clear, fast drying and non-sticky films, 5% Klucel, 7.5% Eudragit NE, 15% Eudragit RS and 10% Dermacryl performed the best against the evaluation criteria (Table 2) and were selected for further testing. When 20% w/w plasticiser (relative to the dry polymer weight) was incorporated into the formulations of all polymers except Eudragit NE, no significant differences in structure and flexibility of the films, relative to those without plasticiser, were observed (Table 3).

In general, it was not possible to distinguish the influence of the added excipients on the formulations based on the visual evaluation of the FFS and the resulting polymeric film. The largest effect of incorporation of plasticiser was observed for the Klucel film, especially with the more lipophilic plasticisers TBC and DBS as they formed slightly hazy films. Further, while range-finding studies using hyper differential scanning calorimetry showed that the addition of plasticiser to the FFS lowered the glass transition temperature ( $T_g$ ) of the formed polymeric films (e.g., for 10% Eudragit RS and 15% Eudragit E with TEC at 5-20% and 5-10%, respectively – data not shown), these findings were not particularly predictive of film flexibility on the porcine skin model.

### 3.2 *In vitro* BMV release

The formulations that adequately satisfied the criteria pertaining to complete film formation and cosmetic acceptability (Table 1) were tested for their ability to sustain BMV release *in vitro* over a prolonged period. It was found that all of the tested FFS sustained BMV release over 72 hours (Figure 2). The release of the drug from Klucel was highest, corresponding to  $42 \mu\text{g}/\text{cm}^2$  (~3% of the loading), with clear zero-order kinetics ( $r^2 = 1.00$ ; Figure 2, upper panel) and no evidence of a lag-time (which might indicate a degree of membrane control). BMV release from the hydrophobic films was slower, but showed a classic, ‘burst’ effect (Figure 2, lower panel), again contra-indicating any suggestion of membrane control. While there were some differences in the drug release profiles observed (due, at least in part, to the different amounts of polymer used in the formulations and changes in the resulting film thicknesses), the total BMV release from the three hydrophobic films in 72 hours was quite consistent ( $4 \mu\text{g}/\text{cm}^2$  corresponding to ~0.4%), and further experiments focused only on Eudragit RS as a representative example of this type of acrylate polymer.

The constant release rate of BMV from Klucel was  $0.58 \mu\text{g cm}^{-2} \text{ h}^{-1}$  ( $r^2 = 1.00$ ). The profiles for Eudragit NE and RS closely followed a square-root of time ( $t$ ) dependence, with rates of  $0.50$  and  $0.45 \mu\text{g cm}^{-2} \text{ h}^{-1/2}$ , respectively (and both with  $r^2$  values of  $0.99$ ). BMV release from Dermacryl showed a significant “burst” effect over the first 10 hours, after which relatively slow, essentially zero-order kinetics were observed.

### 3.2.1 Influence of plasticiser on *in vitro* release

The release of BMV from Klucel and Eudragit RS polymeric films containing different plasticisers, of different lipophilicities, was subsequently assessed. For Klucel, the addition of each of the plasticisers at 20% w/w enhanced the zero-order release rate of the drug (Figure 3, upper panel;  $r^2 = 1.00$  for all cases). The rate with DBS was highest ( $1.67 \mu\text{g cm}^{-2} \text{h}^{-1}$ ), while those with TEC and TBC were similar but more modest ( $1.21$  and  $1.24 \mu\text{g cm}^{-2} \text{h}^{-1}$ , respectively). In the case of Eudragit RS, only TBC and DBS significantly increased BMV release ( $p < 0.001$ ), which uniformly followed as before, for the formulation without plasticiser, square root of time kinetics (Figure 3, lower panel). The rates of release from the plasticised Eudragit films were  $0.86$ ,  $1.20$  and  $1.70 \mu\text{g cm}^{-2} \text{h}^{-1/2}$  for TEC, TBC and DBS, respectively (again, in all cases, with  $r^2 = 0.99$ ).

For both polymers, the kinetics of BMV release increased, although not necessarily linearly (Figure 4), with the lipophilicity of the plasticiser, as measured by the compounds'  $\log\{\text{octanol/water partition coefficient}\}$  ( $\log P$ ).

### 3.3 Moisture sorption-desorption from polymeric films

Dynamic vapour sorption was used to characterise moisture sorption in Klucel and Eudragit RS films with and without 20% w/w TEC. Water uptake by Klucel was 4 times higher than that by Eudragit when the RH of the film's environment was increased from 0% to 90% at  $32^\circ\text{C}$ . This is consistent with the greater hydrophilicity of Klucel. The sorption and desorption isotherms of the Klucel film showed no detectable hysteresis, suggesting that the water was not tightly bound and was potentially available to act as a plasticiser. This behaviour was completely unchanged by the incorporation of TEC. In contrast, the Eudragit RS film had a decreased mass after desorption, perhaps indicative of some solvent entrapment during film casting. However, this negative hysteresis was abolished when TEC was incorporated, consistent with its role as an effective plasticiser.

#### 4 Discussion

This investigation has evaluated polymers of hydrophilic and hydrophobic character for their potential to be used in film-forming systems (FFS) for prolonged drug delivery applications to the skin. Visual assessment indicated that control of the polymer concentration used was essential to avoid creation of thick, brittle films. Equally the viscosity of the FFS has to be selected appropriately to achieve a smooth and complete film (34). It seems likely that lower viscosity will be most suitable when designing formulations of the FFS with the caveat, of course, that lateral spreading post-deposition be controllable.

Film flexibility is clearly of importance and a polymer  $T_g$  below that of a typical skin surface temperature ( $\sim 32^\circ\text{C}$ ) is therefore logical. The polymer, Eudragit NE, has a  $T_g$  of  $13^\circ\text{C}$  and creates flexible films (35). The  $T_g$  of Eudragit RS, on the other hand, is  $\sim 65^\circ\text{C}$  (35;36) and requires formulation with a plasticiser to render it appropriately flexible for use on the skin. Unlike the effect of polymer concentration on film formation, the incorporation of plasticisers was less easily perceived visually and the release kinetics of BMV proved to be more discriminatory.

As the principal goal of this work was to identify FFS capable of producing polymer films that would release a topical drug over a prolonged period, an *in vitro* experimental strategy was designed using an artificial membrane in an optimised diffusion cell configuration. This allowed drug release to be followed over 72 hours, a duration not recommended (for obvious reasons) for a study involving excised mammalian skin (37). The artificial membrane chosen was silicone, which has been used to investigate drug release from topical formulations and offers, at least, a barrier of lipophilic character that is more relevant to that of skin than, for example, cellulose acetate (15;38-41). It was also found that the tested polymer films made better and more uniform contact with silicone, as compared to cellulose acetate membranes (data not shown). It must be emphasised, however, that while the BMV release kinetics reported here are of value for differentiating between the different formulations tested, they are not to be considered indicative of their performance when applied to skin. In the latter case, the complex interactions of the FFS with the SC as the volatile solvent simultaneously evaporates and penetrates (and possibly enhances absorption of the drug), as well as the evolution of the polymeric film with time and the potential, transient supersaturation of BMV (and all

coupled with the greater inherent variability of such experiments), add multiple layers of complication to the interpretation of the results. A detailed skin absorption study from the FFS described here will be reported elsewhere.

The literature demonstrates that the nature of the polymer influences not only the mechanical properties and cosmetic attributes of the formed film (8-10;33;42-44) but also drug release therefrom (9;10;15;42;45). In the present study, films prepared from the relatively hydrophilic Klucel polymer released significantly more BMV over 72 hours than those formed by the more hydrophobic, polyacrylates and polymethacrylates, an observation completely consistent with previous findings (15). It has been estimated from *in vivo* experiments in humans (cf. typical bioavailability of topical corticosteroids is a few percent (46)) that conventional semi-solid formulations of BMV would deliver at least 6  $\mu\text{g}/\text{cm}^2$  of drug over 72 hours (based on once-daily dosing). Clearly, the Klucel film releases more than enough drug in this period (42  $\mu\text{g}/\text{cm}^2$ ) to satisfy this goal; in contrast, the hydrophobic films released only about one-tenth of that from Klucel, falling just below the ‘target’.

The higher release of BMV from Klucel relative to the hydrophobic films may well reflect the lower solubility of the drug in the former. When formulated at the same concentration in both types of polymer, therefore, it is clear that BMV’s “leaving tendency” from Klucel will be greater (47;48). This enhanced thermodynamic activity may be further increased by the greater water sorption into the Klucel film than that into the polymethacrylates (24% versus 6% for Eudragit RS, for example – data not shown; (49;50)). Thus, the preferential uptake of water into Klucel will make the polymer an even less sympathetic environment for BMV, the release rate of which will be increased. Water has also been proposed as a plasticiser of polymer networks (49;51;52), an effect that can reasonably be expected to facilitate drug diffusion within the film (8;53). Lastly, should any supersaturation of drug occur during the creation of the film as the volatile solvent evaporates(38;39), then it is known that different polymers are able to stabilise the resulting metastable state to different degrees (54-56). Whether this contributes to the superior release of BMV from Klucel requires further investigation and may offer a new strategy for FFS formulation optimisation.

Incorporation of plasticisers into the polymer films lowers the  $T_g$ , improves flexibility on the skin and, as mentioned above, is anticipated to increase drug diffusivity within, and hence

release from, the film. The mechanism underpinning the effect of plasticisers is believed to be via an increase in polymer chain mobility and an associated enhancement of the free volume available for drug diffusion (10;57;58). In the case of Eudragit RS, all plasticisers improved BMV release and the aim of achieving liberation of  $6 \mu\text{g}/\text{cm}^2$  was attained. Drug release appeared to increase fairly linearly with plasticiser lipophilicity (as measured by log P), perhaps through an increase in BMV's solubility in the polymer. For Klucel, the presence of plasticiser again improved drug release. The effects of TEC and TBC were comparable while the most lipophilic plasticiser (DBS) had the biggest impact on drug release.

## **5 Conclusions**

The research described here demonstrates that drug-loaded polymeric films, of acceptable substantivity, flexibility and cosmetic attributes, are capable of sustaining release of an active compound over a period of 72 hours. Liberation from a hydrophilic polymeric film was greater than that from those made from hydrophobic polymers, as expected for the lipophilic drug (BMV,  $\log P \sim 3.6$  (59)) involved. Given that the residence time of a water-soluble polymer film is unlikely to exceed 8 hours, the rapid transfer of the drug into a “reservoir” in the SC is preferred; on the other hand, greater substantivity is anticipated for hydrophobic polymer films for which the “reservoir” of drug may also be held on, as well as within, the skin. While the incorporation of plasticisers had no obvious effect on the visually-assessed mechanical properties of the polymeric films, their presence significantly enhanced drug release, such that all the systems studied were able to release the target quantity of drug over a 3-day period. The stage is now set for further work to refine the lead formulations and to evaluate their performance in terms of drug delivery into and through the skin.

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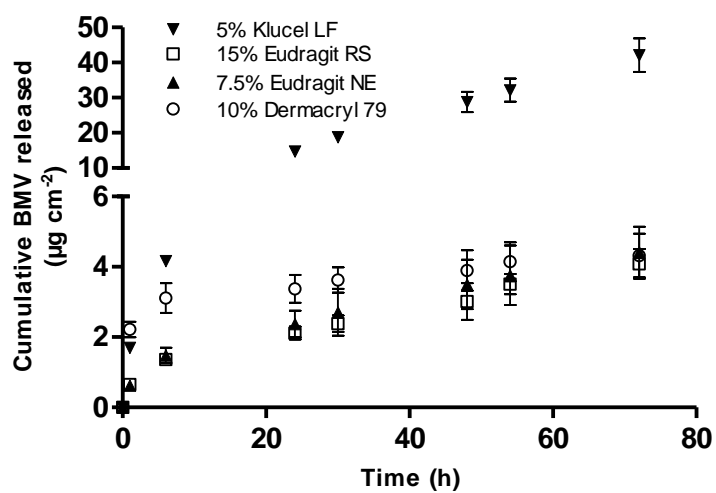
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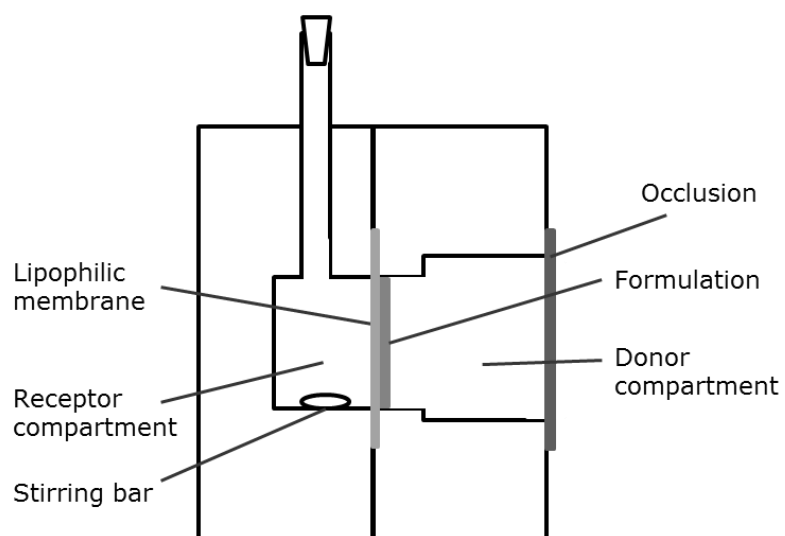
## Graphical abstract



**Table 1.** Composition of film-forming systems tested for *in vitro* release; amounts given in %w/w

Formulation constituents										
<b>Polymer</b>	Dermacryl	Eudragit	Eudragit				Klucel			
	79	NE	RS				LF			
	10.0	7.5	15.0	15.0	15.0	15.0	5.0	5.0	5.0	5.0
<b>Plasticiser</b>										
DBS				3.0				1.0		
TBC					3.0				1.0	
TEC						3.0				1.0
<b>Solvent</b>										
EtOH	90.0	81.3	80.0	77.0	77.0	77.0	95.0	94.0	94.0	94.0
Water		11.2	5.0	5.0	5.0	5.0				

DBS= dibutyl sebacate; TBC = tributyl citrate; TEC = triethyl citrate; EtOH = absolute ethanol.



**Figure 1.** Illustration of modified diffusion cell experiment. The membrane area, across which drug release was measured, was 1.9 cm<sup>2</sup>.

**Table 2.** Visual evaluation of film-forming systems with varying type and concentration of polymer.

Polymer	%	FFS		Formed film					
		Appearance	Viscosity*	Drying time	Outward stickiness	Film-formation**	Cosmetic attributes	Structural features**	Flexibility
Der-macryl	5.0	Clear	Low, runny	≤ 5 min	Low	Complete / homogeneous	Clear, slightly glossy	Smooth	Flexible
	7.5		Low, slightly runny						Non-flexible
	10.0		Low, slightly runny						Non-flexible
Eudragit NE	5.0	Clear	Low, slightly runny	7 min	Low	Complete / homogeneous	Clear, slightly glossy	Smooth / structured	Flexible
	7.5		Low	8 min		Complete / homogeneous		Structured	Flexible
	10.0		Medium	9 min		Film with little precipitation		Structured	Flexible / non-flexible
Eudragit RS	10.0	Clear	Low, runny	≤ 5 min	Low	Complete / homogeneous	Clear, slightly glossy	Smooth	Flexible / non-flexible
	15.0		Low, slightly runny		Low			Flexible / non-flexible	
	20.0		Low, slightly runny		Medium			Smooth / structured	Non-flexible
Klucel	2.5	Clear	Low, Very runny	≤ 5 min	Low	Complete / homogeneous	Clear, matt	Smooth	Flexible
	5.0		Low	8 min				Smooth	Flexible / non-flexible
	7.5		Medium	10 min				Smooth / structured	Non-flexible
	10.0		High	10 min				Structured	Non-flexible

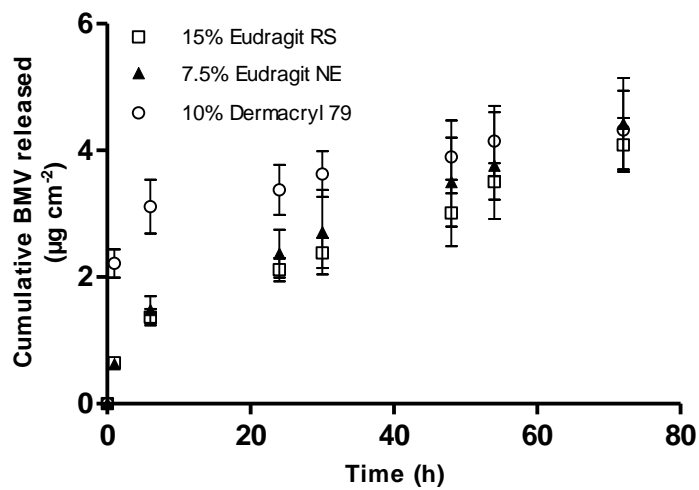
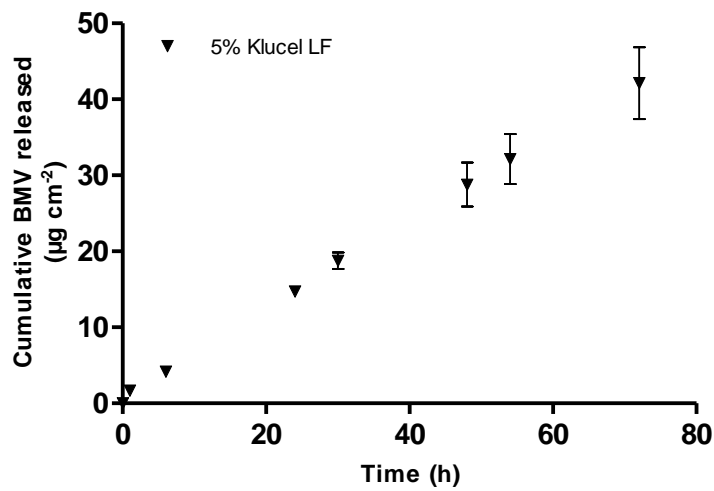
\* Viscosity was also evaluated with regards to controlling its distribution when applied to the skin. \*\* Evaluation also conducted of film formed in a petri dish for better assessment.



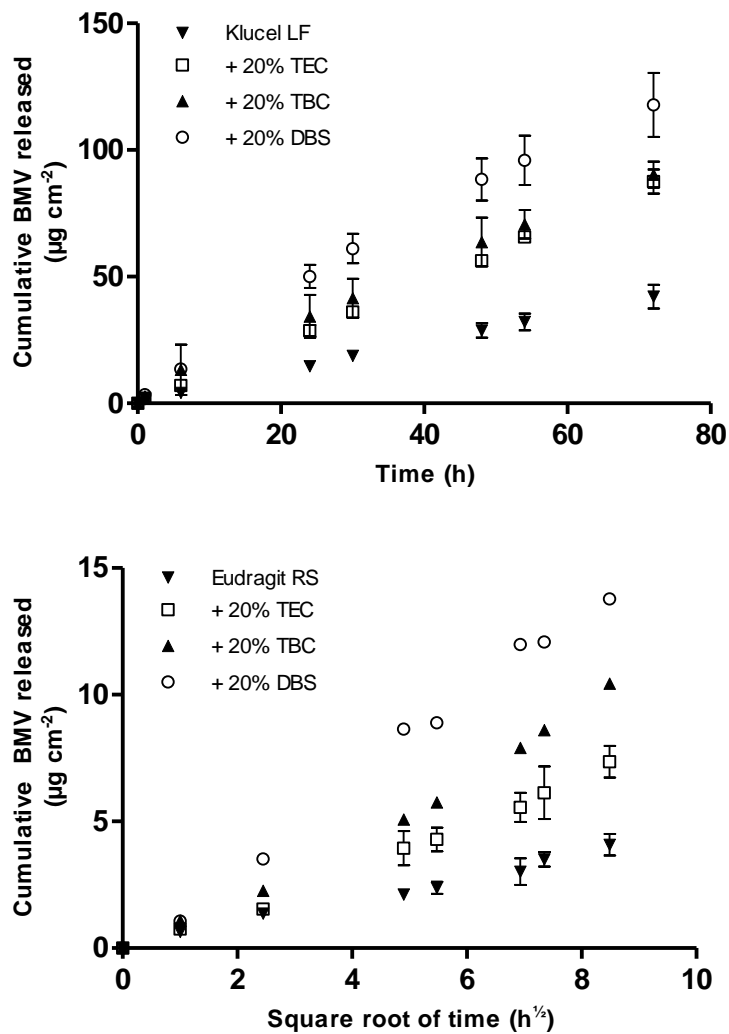
**Table 3.** Visual evaluation of film-forming systems with varying type of plasticiser.

Polymer	Plasticiser	Drying time	Outwardness	stickiness	Cosmetic attributes	Flexibility
10% Dermacryl	TEC	≤ 5 min	Low		Clear	Non-flexible
	TBC					
	DBS					
15% Eudragit RS	TEC	≤ 5 min	Low		Clear	Non-flexible
	TBC					
	DBS					
5% Klucel	TEC	6 min	Low		Clear	Flexible
	TBC				Transparent, slightly hazy	Flexible / non-flexible
	DBS				Transparent, slightly hazy	Non-flexible

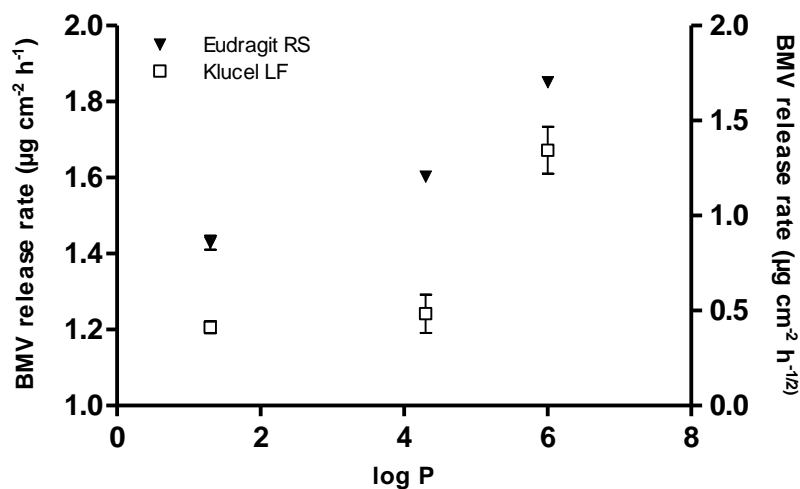
DBS= dibutyl sebacate; TBC = tributyl citrate; TEC = triethyl citrate. \* Evaluation also conducted of film formed in a petri dish for better assessment.



**Figure 2.** *In vitro* release profiles of BMV from polymeric film-forming systems (mean  $\pm$  standard deviation; n=3). Upper panel: Klucel. Lower panel: Hydrophobic polymers.



**Figure 3.** In vitro release profiles of BMV from Klucel (upper panel) and Eudragit RS (lower panel) film-forming systems with and without plasticisers (mean  $\pm$  standard deviation; n = 2 or 3).



**Figure 4.** Kinetics of BMV release rate from Klucel and Eudragit RS polymer films as a function of the lipophilicity (measured by log P) of three plasticisers (TEC, log P = 1.3; TBC, log P = 4.3; DBS, log P = 6.0) incorporated into the formulations at 20% w/w. The left-hand axis plots the zero-order release rates from the Klucel films (open squares), the right-hand axis plots the square-root of time kinetics from the Eudragit systems (filled triangles). Log P values from SciFinder, calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2014 ACD/Labs).