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Research paper

Development and characterization of film forming polymeric solutions for skin drug delivery

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Abstract

Film forming polymeric solutions as a novel approach for skin drug delivery were developed and characterized concerning their mechanical properties and water vapor permeability. They were developed by varying type and content of the film forming polymer as well as nature and content of the plasticizer. The resulting formulations were evaluated according to five criteria: drying time, cosmetical attractiveness, outward stickiness, integrity on skin (after 18 h) and viscosity. Among the 14 tested polymers 10 film formers yielded formulations with a positive evaluation in all five test criteria. Selected formulations were then investigated for tensile strength and elongation at break in vitro and for water vapor permeability in vitro (WVP) and in vivo (TEWL). Their mechanical properties determined in vitro were found to be not predictive for the flexibility and abrasion resistance observed on living skin. Similar to this, the results derived from the WVP and the TEWL methods were not in accordance with each other. Obviously, the investigated in vitro methods do not characterize the properties of the thin films on living skin satisfactorily. Nevertheless, the identified film forming solutions are a promising approach and will provide the basis for the further development of this novel dosage form.

Keywords: Film forming polymeric solution; Mechanical properties; Water vapor permeability; Transepidermal water loss

1. Introduction

The skin is a very important route for the dermal or transdermal delivery of pharmaceutically active substances. Film forming polymeric solutions are a novel approach in this area that might present an alternative to the conventional dosage forms used on the skin, such as ointments, creams, gels or patches. The polymeric solution is applied to the skin as a liquid and forms an almost invisible film in situ by solvent evaporation.

Presently, film forming polymeric solutions are well known from the field of surgery, wound care or skin protection. In surgery, film forming preparations are for example used as tissue glue for the thread-free closing of incisions [1–3] or as disinfectants for the preoperative skin preparation [4]. Film forming polymeric solutions are also utilized with or without antimicrobials active substances for the non-surgical care of minor cuts and abrasions [5,6] or in ostomy care for the protection of the skin surrounding the ostomy wound against the aggressive bodily fluids [7]. In contrast to this, only very few authors have described the use of film forming systems for the delivery of drugs to the skin. Misra et al. [8,9] reported on a liquid film forming solution for the biphasic delivery of testosterone but investigated only one formulation containing a mixture of polyvinylpyrrolidone and polyvinyl alcohol in isopropanol as film forming matrix without performing a polymer screening. Also, Misra did not investigate the mechanical or cosmetical properties of the formed film but focused mainly on the drug permeation from this system in vitro as well as in vivo. Other film forming systems

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described in the literature are not applied as liquids but as transdermal gels [10,11] or cream [12]. Similar to the works of Misra these groups investigated only one individual formulation without testing a broader range of film formers and focused also mainly on the drug delivery from the film forming system [10,11] or the clinical efficacy of the formulation [12]. Due to the fact that film forming solutions can provide many advantages over patches (higher dosing flexibility, higher patient compliance due to improved cosmetical appearance) or semisolid preparations (rub off resistance) the aim of this study was to test a wider range of materials, to select suitable excipients and to characterize the properties of the resulting formulations to provide a broader technological basis for the development of this novel dosage form.

In a first step formulation experiments were performed with 14 polymers from different chemical classes. Basically the compositions contained a film forming polymer dissolved in a volatile solvent. Further excipients such as plasticizers or crosslinkers were added if necessary. Mainly polymer content, type of plasticizer and plasticizer content were varied to find the best composition for the desired purpose. Due to the fact that no suitable evaluation method for these new application systems was available from the literature a simple score system had to be developed in order to identify suitable formulations for the intended application. The testing of the formulations was performed in vivo as pre-experiments had shown that the special properties of the skin (surface structure and movement) were very important for the differentiation between the formulation variants. The evaluation system was based on five criteria: viscosity, drying time, outward stickiness, cosmetical attractiveness and integrity after a certain wearing time (18 h). These properties were considered key features for the practical application of the novel dosage form especially from the patients' point of view: The viscosity of the film forming solution is required to be low to enable an application of the dosage form as spray, which would ensure an accurate, but at the same time flexible dosing and would be most convenient for the patient. In order to avoid long waiting times for the patient the novel dosage form is supposed to dry quickly on the skin. The formed film is required to be non-sticky to avoid adhesion to the clothes of the patient. Considering the fact that many patients complain about the high visibility of transdermal patches which is considered cosmetically unattractive the formed film is supposed to be almost invisible. In addition to this, the delivery system is required to show a certain permanence on the skin in order to be able to provide a continuous drug supply over a prolonged period of time.

Following the polymer screening selected formulations with polymers from different chemical groups were characterized concerning their water vapor permeability and mechanical properties. Based on the observation that the developed formulations had displayed similar mechanical properties, that is flexibility and abrasion resistance, during the in vivo evaluation the assumption was that they would also show similar mechanical properties in the in vitro test method. If this was the case the in vitro method could serve as a useful instrument in further polymer screening experiments for a more objective evaluation of the developed formulations. The mechanical properties (tensile strength and elogation at break) were determined according to a standard test method [13] that has been frequently used in the literature for the characterization of strength and flexibility of free polymeric films [14–18]. In addition to the mechanical properties, the water vapor permeability of the same four formulations was investigated *in vitro* according to a method from the British Pharmacopoeia [19] and *in vivo* by measuring the impairment of the transepidermal water loss to assess the occlusive properties of the formed films. Finally, characterization methods for the film forming solutions and important parameters for the development of this novel dosage form are discussed.

2. Materials and methods

2.1. Materials

All polymers (Table 1) were kindly provided by the manufacturers: Eudragit® RL PO, Eudragit® E 100, Eudragit® S 100 and Eudragit® NE 40D (Roehm Pharma Polymers, Darmstadt, Germany), Avalure® AC 118 (Noveon Inc., Cleveland, USA), SGM 36 and Dow Corning® Q7-9180 (Dow Corning S.A., Seneffe, Belgium), DynamX® and Dermacryl® 79 (National Starch and Chemical Company, Bridgewater, USA), Oppanol® B 100, Oppanol® 10SFN, Kollidon® 12 PF and Kollidon® VA 64 (BASF, Ludwigshafen, Germany), Hydagen® HCMF (Cognis, Düsseldorf, Germany), Klucel® LF (Hercules Inc., Wilmington, USA). Polyvinyl alcohol 72000, ethanol (96%), triethyl citrate, dibutyl phthalate, triacetin and succinic acid were purchased from Merck, Darmstadt, Germany.

2.2. Preparation of the polymeric solutions

Film forming solutions were prepared by adding the polymer to the solvent and stirring the solution overnight to ensure complete dissolution of the polymer. The solvent used was ethanol (96%) for all preparations except the silicone formulation. For the silicone formulation the silicon gum (SGM 36) was dissolved in a volatile silicone (hexamethyldisiloxane/octamethyltrisiloxane, Dow Corning Q7-9180). Having obtained a clear polymeric solution other optional excipients such as crosslinker or plasticizer were added. After addition of all excipients the solution was stirred for another 24 h before use. The formulations were stored in glass vials sealed tightly with a siliconized rubber plug and an aluminium cap.

2.3. Evaluation of the formulations

For a first assessment of the suitability of film forming solutions, the obtained formulations were evaluated

Table 1
Polymers used in the formulation experiments

Trade name	Polymer
Avalure® AC 118	Acrylates copolymer
Dermacryl® 79	Acrylate/octylacrylamide copolymer
DynamX®	Polyurethane-14 and AMP-acrylates copolymer
Eudragit® E 100	Poly(butyl methacrylate, (2-dimethylaminoethyl)methacrylate, methyl methacrylate) 1:2:1
Eudragit® NE 40D	Poly(ethyl acrylate, methyl methacrylate) 2:1
Eudragit® RL PO	Ammonio methacrylate copolymer
Eudragit® S 100	Poly(methacrylic acid, methyl methacrylate) 1:2
Hydagen® HCMF	Chitosan
Kollidon® 12 PF	Polyvinylpyrrolidone
Kollidon® VA 64	Polyvinylpyrrolidone–vinyl acetate copolymer
Klucel® LF	Hydroxypropylcellulose
Oppanol® B100/10SFN	Polyisobutylene
PVA 7200	Polyvinyl alcohol
SGM 36	Silicon gum

according to a rating system for five characteristics: viscosity, drying time, stickiness of the outer surface, cosmetical attractiveness and integrity on the skin after 18 h (Table 2).

The viscosity of the solution was evaluated visually and rated as low (water-like), medium (glycerol-like) or high (syrup-like).

For the assessment of the drying time the formulation was applied to the inner sides of the forearm of a volunteer, who participated in the study on informed consent basis, with the help of a steel positioning device and a pipette. The applied volume was 10 μl/cm^2 as a pre-experiment had shown that this amount was small enough to be applicable without flowing away from the application site. A dosing range from 5 to 10 μl/cm^2 is also recommended by the OECD for the conduct of skin absorption studies [20]. After 5 minutes a glass slide was placed on the film without pressure. If no remains of liquid were visible on the glass slide after removal, the film was considered dry. If remains of liquid were visible on the glass slide the experiment was repeated with a drying time of 7 minutes instead of 5 minutes.

The stickiness of the outer surface was tested by pressing cotton wool on the dry film under low pressure. Depending on the quantity of cotton fibers that were retained by the film the stickiness was rated high (dense accumulation of fibers on the film), medium (thin fiber layer on the film) or low (occasional or no adherence of fibers).

The cosmetical attractiveness of the films was assessed by visual examination of the dry films. Transparent films with a low skin fixation had a high attractiveness as they were almost invisible. Opaque films and films with a medium skin fixation were considered less attractive as they exhibited an increased visibility and a slight wrinkling of the skin. Whitish films and films causing heavy wrinkling of the skin due to strong skin fixation displayed only a low attractiveness.

To test the integrity on skin the formulation was applied to the forearm of a volunteer as described for the assessment of the drying time. The dry film was then worn overnight by the test subject. After 18 h the test area was examined visually with the help of a magnifying glass (magnification 10×) for completeness of the film, appearance of cracks or flaking.

Three rating scores were assigned to each criterion with 1 representing the most positive evaluation (meaning that the film characteristic closely matched the target) and 3 the most negative result. Formulations were considered successful when all five criteria were rated 1. These formulations showed a low viscosity, short drying time, low outward stickiness, high cosmetical attractiveness and stayed intact on the skin for a prolonged time. For these successful formulations (Table 3) the evaluation on skin was repeated on two further volunteers to support the positive findings. Formulations with one or more criteria rated 2 were considered acceptable with limitations, formulations with one or more criteria rated 3 were not acceptable.

2.4. Determination of the mechanical properties

For the determination of the mechanical properties polymeric films were produced by solvent evaporation in a teflon mould (6 cm × 10 cm). Into this mould 15 ml of the polymeric solution was cast and left to dry at room temperature for 72 h (24 h ventilated in the open air for the evaporation of ethanol, then in an exsiccator containing orange gel as desiccant). The dry films were cut into rectangular samples of 10 mm × 40 mm with the help of a scalpel. Film thickness was measured at 10 places with a digital micrometer (Mitutuyo, Kawasaki, Japan). The mechanical properties of the films were determined with a tensile tester (UPM Z010, Zwick/Roell, Ulm, Germany) based on the ASTM D882-02 [13] with a modification of

Table 2
Rating system for the evaluation of the film forming polymeric solutions

Rating score	1	2	3
Viscosity	Low	Medium	High
Drying time	<5 min	5–7 min	>7 min
Outward stickiness	Low	Medium	High
Cosmetical attractiveness	High	Medium	Low
Integrity on skin (after 18 h)	Complete film, no cracks, no flaking	Complete film with cracks or sporadic flaking	Film partly or completely missing

Table 3
Composition of the positively evaluated formulations; content of the compounds in % (w/w)

Formulation	A	B	C	D	E	F	G	H	I	J
Polymer	Avalure® AC 118	Dermacryl® 79	DynamX®	Eudragit® E 100	Eudragit® NE 40D	Eudragit® RL PO	Eudragit® S 100	Kollidon® VA 64	Klucel®LF	SGM 36
	10.0	7.0	10.0	10.0	7.0	20.0	5.0	10.0	5.0	10.0
Plasticizer										
Triethyl citrate			1.0	1.0		6.0	1.6		1.0	
Triacetin		2.1								
Dibutyl phthalate								4.0		
Solvent										
Ethanol	75.0	90.9	72.2	88.1	82.5	74.0	93.4	86.0	94.0	
Water	15.0		16.8		10.5					
Q7-9180 fluid										90.0
Other ingredients										
Succinic acid				0.9						

the sample size. The testing device was equipped with a 20 N load sensor. The films were carefully placed between the two vertical grips of the tester that were covered with a silicon gum to prevent slippage of the films during the test. The movable grip was then driven upward with a speed of 500 mm/min until the rupture of the film. From the recorded load-time profiles, tensile strength (σ) and percent elongation at break (ε) were calculated representing abrasion resistance and flexibility, respectively. The tensile strength (σ) was calculated as

$$\sigma = \frac{F_{\max}}{A} \ (\mathrm{N/m^2}) \tag{1}$$

where $F_{\max}$ (N) is the maximum force and A ($\mathrm{m^2}$) is the cross-sectional area. The values for percent elongation at break were calculated with the following equation:

$$\varepsilon = \frac{L_R}{L_0} * 100 \ (\%) \tag{2}$$

where L_R (m) is the extension of the sample in the moment of rupture and L_0 (m) is the original sample length. Each experiment was repeated five times.

2.5. Investigation of the water vapor permeability

The water vapor permeability (WVP) was investigated according to a method modified from the British Pharmacopoeia [19]. Films were produced with a solvent evaporation technique by pouring 3 ml of the preparations (50 μl/$\mathrm{cm^2}$) into a teflon mould (6 cm × 10 cm) on a polycarbonate filter (Isopore™ Membrane Filters, Millipore, Billerica, USA filter; pore size 0.2 μm, thickness 11 μm,) as supporting membrane. The films were left to dry for 72 h at room temperature (3 h ventilated in the open air to allow the evaporation of ethanol, afterwards in an exsiccator containing orange gel as desiccant). Circular samples with a diameter of 2.0 cm were cut from the dry film sheets with the help of a scalpel. For the sample preparation 10 ml glass vials with an opening of 1.2 cm diameter ($A = 1.13\ \mathrm{cm^2}$) were filled with approximately 8 g of distilled water, covered with the circular film samples and a silicone ring and sealed tightly with an aluminium vial cap. To start the experiment, the top of the vial cap was opened and the weight of the vial was determined with an analytical scale (Sartorius, type MC BA 100, Göttingen, Germany). The vials (six replicates per formulation) were then placed into an exsiccator containing either a desiccant to create a climate of low relative humidity (approximately 0%) or a saturated solution of sodium bromide (Merck, Darmstadt, Germany) creating an atmosphere of 58% relative humidity [21,22]. They were kept at a determined temperature (25 °C, 32 °C or 37 °C) for 72 h and weighted after predetermined intervals after having adjusted to room temperature for 1 h. From the weight loss of the vials W (g) the WVP was calculated as the amount of water that had permeated through the film in relation to the surface area A ($\mathrm{cm^2}$) and the time t [24 h]:

$$\mathrm{WVP} = \frac{W}{A * t} \ (\mathrm{g/cm^2} * 24\ \mathrm{h}) \tag{3}$$

The WVP ratio shows the relation of the WVP of the vials covered by the tested film to the WVP of the vials with unlimited permeability (filter only samples):

$$\mathrm{WVP\ ratio} = \frac{\mathrm{WVP\ (filter + polymeric\ film)}}{\mathrm{WVP\ (filter)}} \tag{4}$$

For each formulation the mean value and the standard deviation were calculated. Controls for this experiment were vials with the supporting filter without polymeric film (representing 100% WVP) and vials covered with aluminium discs (thickness 20 μm) to verify the tightness of the seal.

2.6. Transepidermal water loss measurement

Twelve healthy volunteers (seven males, five females) participated in the study on informed consent basis. The subjects were aged between 25 and 39 with a mean age of 29.7 years. None of the subjects had any dermatological diseases in their history. Before the experiment the subjects

were asked not to use any skin care products for at least 12 h before the test. Temperature and humidity in the laboratory were monitored throughout the experiment and showed little variation (temperature 21.3 °C ± 0.5 °C, relative humidity 54.3% ± 4.3%). For the determination of the TEWL the ventral sides of both forearms were chosen as test locations as they provide a fairly even surface with only little hair-growth, which might otherwise disturb the measurements, especially on male volunteers. On each arm two test areas (2 cm × 2 cm, minimum distance between the test fields 2 cm) were limited by applying a silicon paste (windowcolor, simplicol, Brauns-Heitmann GmbH&CoKG, Warburg, Germany) to the borders. The silicon paste was left to dry for 15 min. The area between the two test areas on each arm remained uncovered and served as a reference value for the TEWL measured on the test sites. The test subjects were allowed to acclimatize and calm down for 30 min before the start of the experiment. A volume of 200 μl of each formulation (50 μl/cm^2, corresponding to the amount applied for the in vitro experiment) was applied to one of the test fields. This amount was higher than the amount applied for the formulation screening experiments under the assumption that the differences in the TEWL impairment caused by the different films would be more pronounced with thicker films and therefore better detectable in spite of the considerable variations associated with this test method. The formulations were left to dry ventilated in the open air at room temperature for 2 h. The TEWL was measured according to published guidelines [23] with a Tewameter (Tewameter 300, Courage + Khazaka, Cologne, Germany) on the test sites and on the reference sites located close to the test sites. The TEWL ratio was calculated from the TEWL on the test sites after 2 h drying time in relation to the TEWL measured on the uncovered reference sites:

$$\text{TEWL ratio} = \frac{\text{TEWL on dry film}}{\text{TEWL without film}} \quad (5)$$

From the ratios for each individual subject the overall average ratio, standard deviation and confidence intervals ($P < 0.05$, two sided) were calculated.

3. Results

3.1. Formulation experiments

A selection of 14 polymers from different chemical groups, all described by their manufacturer or in the literature as good film formers, were tested in the formulation experiments. With these polymers over 150 formulations were manufactured containing basically one of the polymers, a plasticizer and a volatile solvent. Mainly polymer content, type of plasticizer and plasticizer content were varied for every one of the chosen polymers to determine the composition with the highest scores in the evaluation system. The evaluation of these features was performed in vivo as casting the formulations on an artificial surface such as a glass slide did not offer the possibility for a realistic assessment of the film properties. The stress exerted on the formed film by the movement of the skin is one of the key challenges for the flexibility and the adhesive properties of the film and is difficult to imitate on artificial substrates. Also the cosmetical attractiveness can be judged more realistically on skin as an increased skin fixation and wrinkling often becomes more apparent with the movement of the skin. Table 3 shows the formulations that produced the best scores in the rating system as they were rated 1 in all categories. One of the positively evaluated films applied on the skin of a human forearm is shown in Fig. 1. All formulations could either be removed by ethanol wipe or could be washed off with water and gentle rubbing.

3.2. Mechanical properties

Mechanical properties such as tensile strength and percent elongation at break are determined to characterize polymeric films for their abrasion resistance and flexibility, respectively. Deducted from these two values polymeric films can be classified as shown in Table 4. This classification, however, is not based on absolute values for the two parameters tensile strength and elongation but has to be seen as a relative comparison between different polymeric films. Hard and tough films have properties suited best for the intended application as drug delivery systems for the skin: they are flexible enough to follow the movements of the skin without breaking but at the same time they show an increased strength to prevent abrasion of the film caused for example by contact with clothing. To investigate if these features can be determined by an in vitro method three of the positively evaluated formulations (C, F and I, Table 3) with the polymers Eudragit® RL PO, DynamX®, Klucel® LF were tested for their mechanical properties. The SGM 36 formulation could not be tested as it does not form cohesive films. All these formulations had scored the highest rating in the evaluation criterion "integrity on the skin (after 18 h)" indicating that they contained sufficient strength and flexibility not to crack or to

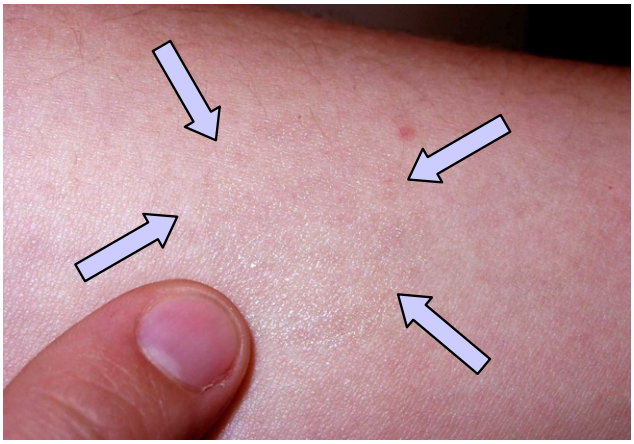

Fig. 1. Polymeric film on human forearm (Formulation F, 10 mg/cm^2).

Table 4
Classification of polymeric films according to Aulton et al. [36]

Tensile strength	Elongation at break	Film description
Low	Low	Soft and weak
Low	High	Soft and tough
High	Low	Hard and brittle
High	High	Hard and tough

be rubbed off during the wearing period. Based on this observation it was expected that all three formulations formed films with similar mechanical properties, most probably films classifiable as hard and tough. The upper half of Table 5 shows the results for tensile strength and percent elongation at break for the three tested films (C, F and I). Surprisingly, the results for the three films revealed considerable differences. While the Eudragit® RL PO film showed a high elongation with a low tensile strength (rather soft and tough), the Klucel® LF film displayed a low elongation with medium tensile strength (fairly soft and weak in comparison to the Eudragit® RL PO film). Only the third film, the DynamX® formulation, could be classified as hard due to its comparatively high tensile strength. Concerning the elongation this film was weaker than the Eudragit® RL PO film but tougher than the Klucel® LF film. The similar strength and flexibility of these three films observed on living skin was apparently not reflected in the results of the in vitro experiments.

For a better interpretation of these results the mechanical properties of three additional films were determined. The formulations F (var1), F (var2) and I (var1) were variations of the positively evaluated films F and I with changes in the plasticizer type or content. Contrary to the previously tested formulations these films had *not* displayed a sufficient strength or flexibility on the skin as they had cracked or flaked off during the integrity test (rating 2 or 3). The change in the plasticizer type or content resulted in harder and less flexible films as indicated by an increase in tensile strength and a decrease in the elongation values in comparison to the formerly tested films F and I with the same polymers (the results are shown in the lower half of Table 5). This might explain why F (var1), F (var2) and I (var1) had cracked up while the original formulations F and I had not displayed any cracks during the wearing period. Unexpectedly, however, the non-successful formulations F (var1) and F (var2) with the polymer Eudragit® RL PO displayed higher elongation values than the successful formulations I and C with other polymers. This implies that even though the elongation value is an indicator for the flexibility of a polymeric film it cannot serve to predict if a formulation will show the desired film properties in vivo when formulations with different polymers are concerned.

3.3. Water vapor permeability

The human body is constantly losing water to the environment by evaporation through the skin. This transepidermal water loss (TEWL) is a passive diffusion process and very important for skin functions such as body temperature control. Occlusion – meaning impairment of the TEWL – influences several properties of the skin such as hydration of the stratum corneum, skin temperature and blood flow and can therewith increase the percutaneous absorption of certain drug substances depending on the anatomic site and the drug vehicle [24–27]. Various skin parameters such as pH and bacterial flora are also influenced by an occlusive treatment resulting in an increased risk of infection and skin irritation [28,29]. Accordingly, the degree of occlusion is an important feature of a drug delivery system that is supposed to be worn on the skin for a prolonged period of time. Fig. 2 shows the absolute Water Vapor Permeability (WVP) of the four tested films and the WVP for the control representing unhindered water vapor permeation. According to the British Pharmacopoeia a material can be considered permeable to water vapor when the WVP exceeds $0.05\ g * cm^{-2} * 24\ h^{-1}$ [19]. Although the four films displayed different WVP values all of them showed a permeability above the limit set in the Pharmacopoeia and can therefore be considered non-occlusive.

These in vitro results, however, could not be compared directly to the results of the TEWL-measurements with the same films in vivo as the test conditions (37 °C, 0% r.h.) differed from the conditions in the in vivo experiment. The skin temperature for example is considerably lower than 37 °C. In the literature the skin surface temperature

Table 5
Mechanical properties of different polymeric films that had displayed sufficient (rating 1) or non-sufficient (rating 2–3) strength and flexibility on human skin in vivo; evaluation criterion: integrity on skin after 18 h; rating 1: complete film, no cracks, no flaking; rating 2–3: film partly or completely missing, cracks, flaking; mean value (±SD)

Formulation	Polymer	Tensile strength (N/mm^2)	Elongation at break (%)
Films with sufficient strength and flexibility in vivo (*rating* 1)			
C	DynamX®	12.2 (±1.0)	323.4 (±42.1)
F	Eudragit® RL PO	1.0 (±0.1)	798.4 (±93.9)
I	Klucel® LF	5.0 (±0.3)	131.4 (±5.8)
Films with non-sufficient strength and flexibility in vivo (*rating* 2–3)			
F (var1) (formulation F, but with less plasticizer)	Eudragit® RL PO	1.3 (±0.1)	662.0 (±83.7)
F (var2) (formulation F, but with a different plasticizer)	Eudragit® RL PO	1.3 (±0.1)	515.2 (±19.8)
I (var1) (formulation I, but without plasticizer)	Klucel® LF	10.7 (±0.8)	107.2 (±1.2)

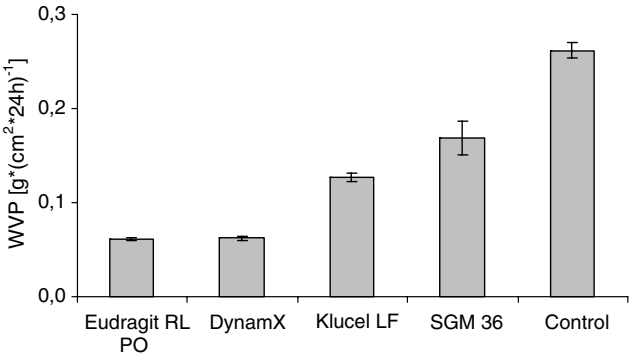

Fig. 2. WVP of polymeric films formed by the preparations F (polymer: Eudragit® RL PO), C (DynamX®), I (Klucel® LF), J (SGM 36) and of the control (without polymeric film) under the conditions of the Ph.Brit. 1993 (37 °C, 0% r.h.); $n = 6$.

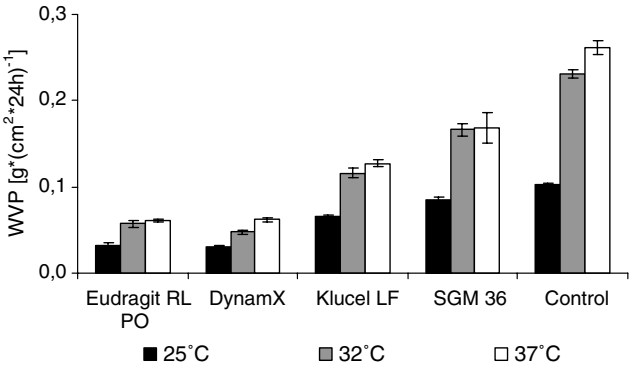

Fig. 3. Influence of the temperature on the WVP of polymeric films formed by the preparations F (polymer: Eudragit® RL PO), C (DynamX®), I (Klucel® LF), J (SGM 36) and of the control (without polymeric film); humidity: 0% r.h.; $n = 6$.

is reported to be between 28 °C and 32 °C [23], a range that our own measurements supported. As the temperature severely influences not only the TEWL measurements [30,31] but also the WVP properties of polymeric films [32] the test conditions for the in vitro test were modified, investigating the WVP at different test temperatures. Fig. 3 shows the WVP for the four tested films at 25 °C, 32 °C and 37 °C in a climate of low relative humidity (approximately 0% r.h.). The absolute WVP values increased with rising temperatures for all tested films. This was expected as higher temperatures increase evaporation and lead to a higher water vapor pressure driving more water through the films.

The second condition to be modified to match the test conditions of the TEWL measurements more closely was the humidity gradient. During the TEWL experiment the climatic conditions in the test chamber were measured and the relative humidity was found to be 54.3% ± 4.3%. Assuming a relative humidity of 100% on the other side of the tested film (that is inside the body of the test subject) the resulting water vapor gradient is much lower than the gradient used for the in vitro test (100% r.h. inside the vials

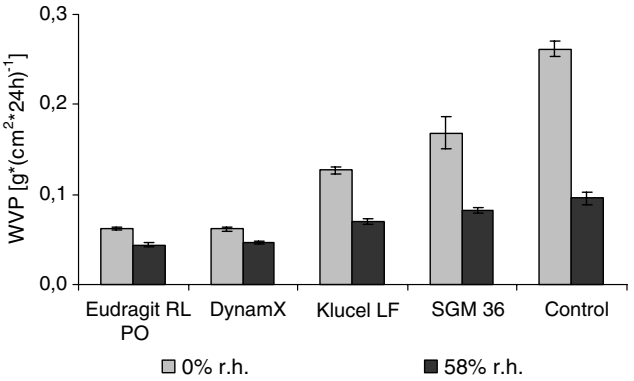

Fig. 4. Influence of the degree of humidity on the WVP of polymeric films formed by the preparations F (polymer: Eudragit® RL PO), C (DynamX®), I (Klucel® LF), J (SGM 36) and of the control (without polymeric film); temperature: 37 °C; $n = 6$.

and approximately 0% r.h. on the outside). Therefore the in vitro experiment was repeated under modified humidity conditions by using a saturated solution of sodium bromide instead of the desiccant to create a climate of approximately 58% relative humidity. Fig. 4 shows the WVP values for the four tested films and the control for both tested humidity degrees at 37 °C. As expected the WVP values dropped with a higher ambient humidity as the humidity gradient is the strongest driving factor for water vapor permeation [33].

To compare the WVP values determined in vitro with the TEWL values in vivo the results from an experiment performed at 32 °C and 58% relative humidity were chosen as these test conditions came closest to the test conditions of the TEWL experiment.

3.4. Transepidermal water loss

TEWL measurements are a well-established method for characterizing the influence of chemical substances on the barrier function of the skin. An increase in TEWL usually indicates the disturbance of this protective barrier either by physical trauma, chemical treatment or occlusion which often results in skin irritation. Therefore TEWL measurements are often conducted to characterize the occlusive properties of pharmaceutical preparations such as transdermal patches [34].

To investigate if the WVP values determined in vitro are predictive for the occlusivity of the polymeric films in vivo the impairment of the natural TEWL by the films was measured. From the literature many factors are known that can influence TEWL measurements. These factors are either instrument-related, environmental-related or individual-related [23]. Among these factors the high inter-individual variations seen in TEWL values on untreated skin play an important role [35]. Due to these high inter-individual variations comparisons between absolute TEWL values measured on different test subjects are highly problematic. Therefore we decided to compare TEWL ratios instead of

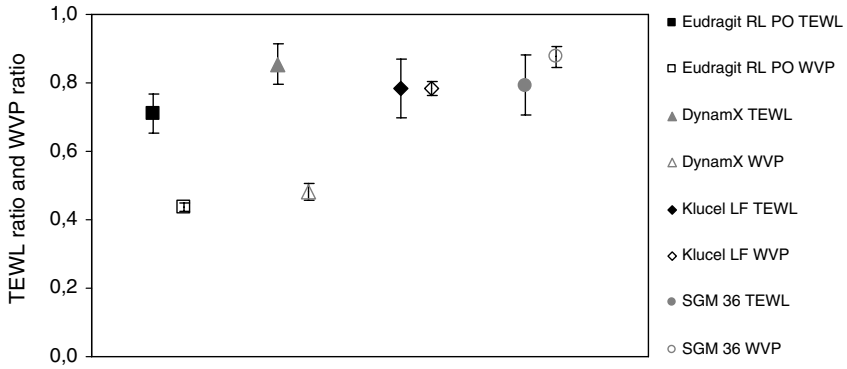

Fig. 5. Comparison of WVP ratio (open symbols) and TEWL ratio (closed symbols) of the formulations F (polymer: Eudragit® RL PO), C (DynamX®), I (Klucel® LF) and J (SGM 36); mean values with confidence intervals ($P < 0.05$); $n = 6$ (WVP), $n = 12$ (TEWL).

absolute values and to compare them with the in vitro WVP results also calculated as WVP ratios (Eq. 4). Fig. 5 shows the ratios of the in vitro (WVP) and the in vivo (TEWL) experiments. Clearly a close correlation between the results from the different methods could not be established. While both values for the Klucel® LF formulation correlated closely and the ratios for the SGM 36 formulation were fairly similar, the results for the Eudragit® RL PO and the DynamX® formulations differed widely. Nevertheless the in vivo results support the finding that all tested films are non-occlusive on the skin. This can be concluded from the high TEWL ratios (>0.7) for all films indicating that more than 70% of the water vapor given off by the skin can permeate through the films.

4. Discussion

4.1. Important parameters for the development of film forming polymeric solutions

For the formulation experiments preparations were manufactured with 14 different polymers varying polymer content as well as nature and content of the plasticizer for every one of the chosen polymers. All these parameters have an impact on the properties of the resulting film and should therefore be considered with care. The first and most important parameter for the development of a film forming polymeric solution is the choice of polymer. Suitable excipients are polymers that form clear, flexible films at moderate temperatures. This is required as the polymeric film is formed *in situ* on the skin which has a surface temperature of approximately 28 °C to 32 °C. Furthermore the polymer has to be soluble in a skin-tolerant, highly volatile solvent such as ethanol, isopropanol or ethyl acetate. Film forming polymers requiring a high percentage of water in the solvent are not suitable for the formulation of film forming solutions due to the comparatively low volatility of water that results in prolonged drying times.

Besides the type of polymer the polymer content is another crucial point in the formulation process. While the loading capacity for drug substances increases with rising polymer content in the solution due to the increasing thickness of the formed films the cosmetical attractiveness of the films deteriorates. Thicker films are less ‘‘invisible’’ and often show a stronger skin fixation than thinner films. As solutions of different polymers with the same polymer concentration do not result in films of the same thickness and the same properties the appropriate polymer content has to be determined individually for each polymer and has to be a compromise between drug loading capacity and cosmetical attractiveness. Another limiting factor for the polymer content is the increase of viscosity of the solution caused by the polymer. To permit an application of the formulation by spraying (which would be most convenient for the patient and most exact as to dosing accuracy) a low viscosity of the polymeric solution is required. Therefore the fact that different polymers may lead to different viscosities when dissolved in a given solvent has to be taken into account as well when determining the appropriate polymer content for the formulation.

Apart from polymer and solvent other excipients such as plasticizers or crosslinkers can be incorporated into the formulation. As a general observation derived from the formulation experiments with over 150 different preparations, especially the plasticizer exerts a strong influence on the properties of the formed film. In polymeric films plasticizer interacts with the polymer chains reducing the number of active centers available for rigid polymer – polymer contacts [36]. These interactions result on the one hand in a decrease in glass transition temperature and a higher flexibility of the films, on the other hand in a changed permeability for drug substances and water vapor [37]. The plasticizer content is also decisive for the adhesive properties of the film. Films with a low plasticizer concentration in the formulation did not display a sufficient adhesion to the skin. Films with a high plasticizer concentration showed sufficient adhesion but became sticky on the outer surface. Therefore determining the right amount of plasticizer is essential for a successful formulation of this dosage form. It is important to note that the adequate plasticizer concentration is individual for every plasticizer – polymer combination as the efficiency of a plasticizer is polymer dependent.

During the formulation experiments 10 of the 14 tested polymers yielded film forming polymeric solutions with the required characteristics. Experiments with the other four polymers, however, did not result in satisfactory preparations for various reasons: For Oppanol® no skin-tolerant solvent could be found contrary to the manufacturer's specifications. Hydagen® HCMF required a high water content in the solvent resulting in unacceptably long drying times. Additionally, Hydagen® HCMF showed a strong increase of viscosity already at low polymer concentrations. PVA 72000 displayed poor skin adhesion even with high plasticizer contents and developed a profound increase of viscosity during storage. Kollidon® 12 PF produced sticky films with insufficient integrity on skin after a longer wearing period.

Taking all this into account it can be stated that a careful composition of the film forming solution with a suitable polymer in an adequate concentration and an individually adjusted plasticizer content is essential to achieve a formulation with the required properties concerning viscosity, drying time, outward stickiness, cosmetical attractiveness and integrity on skin after a longer wearing period. Minor variations might be acceptable but major changes in the composition should be avoided as they would have an unfavorable impact on the properties of the film forming system and lead to a deterioration of the mechanical or cosmetical performance of the system on the skin.

4.2. Characterization methods for film forming polymeric solutions

The finding of suitable methods for the characterization and evaluation of film forming polymeric solutions posed a considerable problem during the development process. No screening process for film forming polymeric solutions and therefore no evaluation method of the macroscopic properties of this dosage form was available from the literature. Beneficial macroscopic properties such as a short drying time or a good cosmetical appearance, however, are prerequisites for the acceptance of a new dosage form by the patients. Therefore the development of a simple evaluation method covering several important macroscopic properties of the formulation (viscosity, drying time, outward stickiness, cosmetical attractiveness, integrity on skin after a longer wearing time) was necessary. The evaluation was performed on living skin as this allowed the assessment of the performance of the formed film under actual wearing conditions. Casting the formulations on artificial substrates such as glass slides did not provide the opportunity to distinguish between different formulations (almost all formulations yielded smooth, transparent films) and was therefore no adequate testing method. Although the developed evaluation method was fairly simple and to a certain extent subjective it surprisingly turned out to be an efficient method for the differentiation between the various formulations. Especially the criterion "integrity on skin (after 18 h)" provided valuable information during the screening process to eliminate those formulations that formed attractive films on the skin but that were not suitable for the practical application due to their lack of persistence on the skin.

The results of the screening process indicated that the flexibility of the film is a very important parameter for the successful formulation of this dosage form as considerable mechanical stress is exerted on the formed film by the movement of the skin. However, the attempt to replace the visual inspection concerning the appearance of cracks by an established in vitro method for the determination of the film flexibility was not successful. Although the tested formulations had displayed a similar flexibility on skin in vivo the in vitro results differed widely. In Table 5 it is shown that the non-successful formulations F (var1) and F (var2) yielded higher elongation values than the successful formulations I and C with other polymers. Even though the elongation value is a measure for the flexibility of a polymeric film it does apparently not indicate if a formulation will also show the required flexibility in vivo when formulations with different polymers are regarded. This is surprising as the formed films are supposed to display the same properties, that is to remain intact and free of cracks during the wearing time, *independent* of the polymer that is used for the formulation. Apparently it is not possible to define a polymer-independent limit value for the elongation at break that has to be reached by a formulation in order to yield a film of sufficient flexibility on the skin. Therefore the in vitro determination of the mechanical properties cannot serve as a suitable method for a further polymer screening for this novel dosage form and cannot replace the described visual assessment of the formed films in vivo at this point.

Similar to the observations for the mechanical properties the in vitro and in vivo values for the water vapor permeability were not in good accordance either as demonstrated in Fig. 5. Based on these results we speculate that the film and its properties are considerably influenced by the contact with the skin. It is possible that a part of the plasticizer is absorbed by the skin [38]. This would lead to a plasticizer depletion in the film, resulting in harder and more brittle film. On the other hand it is also possible that the films absorb water that is evaporating from the skin [39] and that the water serves as additional plasticizer in the film [40,41], resulting in softer and more flexible films. While these complex diffusion processes between skin and film might not lead to a noticeable change in commonly used transdermal patches they might alter the properties of the film forming system to a considerable extent due to the extreme thinness of the formed films (approximately 5–25 μm). Such changes in the film properties, however, that are related to the contact of the film with the skin cannot be mirrored sufficiently under the artificial conditions of an in vitro experiment. We presume that this might be one possible explanation for the different results seen in vitro and in vivo. However, due to the fact that a suitable in vitro method could not be established for an objective evaluation of developed polymeric film forming solutions

an in vivo evaluation similar to the one we used in our investigations seems to be inevitable at this point if further polymers or further formulations are to be screened.

5. Conclusion

Film forming solutions were successfully formulated with polymers from different chemical groups such as acrylates (Eudragit® RL PO, Eudragit® S 100, Eudragit® NE 40D, Eudragit® E 100, Dermacryl®79, Avalure® AC 118), polyurethane-acrylates (Dynamx®), cellulose derivatives (Klucel® LF), polyvinylpyrrolidones (Kollidon® VA 64) and silicones (SGM 36). These formulations contained one of the polymers, a volatile solvent and other optional excipients such as plasticizers and were fixed compositions concerning the concentrations of all excipients involved. The developed rating system, even though based on simple test methods, provided a good basis for the evaluation of the developed formulations concerning the five key criteria viscosity, drying time, outward stickiness, cosmetical attractiveness or integrity on the skin (after a defined wearing time). The in vitro testing methods for the determination of the water vapor permeability and the mechanical properties of the films did not adequately describe the film properties observed in vivo. Further research will be necessary to develop adequate in vitro testing methods for this new dosage form. At this point, however, an evaluation on living skin seems inevitable if further polymers or formulation variations are to be tested. Independent of this, the positively evaluated preparations resulting from the formulation experiments provide the basis for the development of film forming polymeric solutions as a novel dosage form for the skin. This development will be pursued further with the incorporation of drug substances into the formulations and the investigation of drug release from the polymeric films to evaluate the actual potential of these formulations as dermal or transdermal drug delivery systems.

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References

[1] M. Donkerwolcke, F. Burny, D. Muster, Tissues and bone adhesives – historical aspects, Biomaterials 19 (1998) 1461–1466.
[2] L.T. Hall, J.E. Bailes, Using Dermabond for wound closure in lumbar and cervical neurosurgical procedures, Neurosurgery 56 (2005) 147–150.
[3] D.C. Ritterband, S.W. Meskin, D.E. Shapiro, J. Kusmierczyk, J.A. Seedor, R.S. Koplin, Laboratory model of tissue adhesive (2-octyl cyanoacrylate) in sealing clear corneal cataract wounds, Am. J. Ophthalmol. 140 (2005) 1039–1043.
[4] D.K. Jeng, A new, water-resistant, film-forming, 30-second, one-step application iodophor preoperative skin preparation, Am. J. Infect. Control 29 (2001) 370–376.
[5] S.M. Foroutan, H.A. Ettehadi, H.R. Torabi, Formulation and in vitro evaluation of silver sulfadiazine spray, Iran. J. Pharm. Res. 1 (2002) 47–49.
[6] W.H. Eaglstein, T.P. Sullivan, P.A. Giordano, B.M. Miskin, A liquid adhesive bandage for the treatment of minor cuts and abrasions, Dermatol. Surg. 28 (2002) 263–267.
[7] K. Campbell, M.G. Woodbury, H. Whittle, T. Labate, A. Hoskin, A clinical evaluation of 3M No Sting Barrier Film, Ostomy Wound Manage. 46 (2000) 24–30.
[8] A. Misra, R.S. Raghuvanshi, S. Ganga, M. Diwan, G.P. Talwar, O. Singh, Formulation of a transdermal system for biphasic delivery of testosterone, J. Control. Release 39 (1996) 1–7.
[9] A. Misra, R. Pal, S.S. Majumdar, G.P. Talwar, O. Singh, Biphasic testosterone delivery profile observed with two different transdermal formulations, Pharm. Res. 14 (1997) 1264–1268.
[10] N.M. An, D.D. Kim, Y.H. Shin, C.H. Lee, Development of a novel soft hydrogel for the transdermal delivery of testosterone, Drug Dev. Ind. Pharm. 29 (2003) 99–105.
[11] P. Maffei, A. Sforzini, S. Lombardi Borgia, C. Ronchi, N. Festo, G.C. Ceschel, Design and evaluation of a new transdermal formulation containing Estradiol, Pharm. Ind. 65 (2003) 1279–1282.
[12] H.A. Bryan, T.S. Alster, The S-Caine Peel: a novel topical anestetic for cutaneous laser surgery, Dermatol. Surg. 28 (2002) 999–1003.
[13] American Society for Testing and Materials, D 882-02 Standard Test Method for Tensile Properties of Thin Plastic Sheeting, ASTM International, 100 Barr Harbor Drive, P.O. Box C700, West Conshohocken, USA, 2002.
[14] A. Rindlav-Westling, M. Stading, A.M. Hermansson, P. Gatenholm, Structure, mechanical and barrier properties of amylose and amylopectin films, Carbohydr. Polym. 36 (1998) 217–224.
[15] M.A. Repka, J.W. McGinity, Physical–mechanical, moisture absorption and bioadhesive properties of hydroxypropylcellulose hot-melt extruded films, Biomaterials 21 (2000) 1509–1517.
[16] J. Liu, R.O. Williams, Properties of heat-humidity cured cellulose acetate phthalate free films, Eur. J. Pharm. Sci. 17 (2002) 31–41.
[17] P. Rama Rao, P.V. Diwan, Permeability studies of cellulose acetate free films for transdermal use: influence of plasticizers, Pharm. Acta Helv. 72 (1997) 47–51.
[18] C. Padula, G. Colombo, S. Nicoli, P.L. Catellani, G. Massimo, P. Santi, Bioadhesive film for the transdermal delivery of lidocaine: in vitro and in vivo behavior, J. Control. Release 88 (2003) 277–285.
[19] Water-vapour Permeability, in: British Pharmacopoeia, 1993, Appendix XXJ.
[20] OECD. Guidance document for the conduct of skin absorption studies, OECD series on testing and assessment, No. 28, 2004.
[21] M. Tarvainen, R. Sutinen, S. Peltonen, P. Tiihonen, P. Paronen, Starch Acetate – a novel film-forming polymer for pharmaceutical coatings, J. Pharm. Sci. 91 (2002) 282–289.
[22] M. Patel, J.M. Patel, A.P. Lemberger, Water vapor permeation of selected cellulose ester films, J. Pharm. Sci. 53 (1964) 286–290.
[23] J. Pinnagoda, R.A. Tupker, J. Serup, Guidelines for transepidermal water loss (TEWL) measurement, Contact Dermatitis 22 (1990) 164–178.
[24] P. Treffel, P. Muret, P. Muret-D'Aniello, S. Coumes-Marquet, P. Agache, Effect of occlusion on in vitro percutaneous absorption of two compounds with different physicochemical properties, Skin Pharmacol. 5 (1992) 108–113.
[25] G.L. Qiao, S.K. Chang, J.E. Riviere, Effects of anatomical site and occlusion on the percutaneous absorption and residue pattern of 2, 6-(ring-14C)Parathion in vivo in pigs, Toxicol. Appl. Pharmacol. 122 (1993) 131–138.
[26] D.A. Bucks, J.R. McMaster, H.I. Maibach, R.H. Guy, Bioavailability of topically administered steroids: a "mass balance" technique, J. Investig. Dermatol. 91 (1988) 29–33.

[27] S.A. Hotchkiss, J.M. Miller, J. Caldwell, Percutaneous absorption of benzyl acetate through rat skin in vitro. 2. Effect of vehicle and occlusion, Food Chem. Toxicol. 30 (1992) 145–153.
[28] H. Zhai, H. Maibach, Effects on skin occlusion on percutaneous absorption: an overview, Skin Pharmacol. Appl. Skin Physiol. 14 (2001) 1–10.
[29] H. Matsumura, K. Oka, K. Umekage, H. Akita, J. Kawai, Y. Kitazawa, S. Suda, K. Tsubota, Y. Ninomiya, H. Hirai, et al., Effect of occlusion on human skin, Contact Dermatitis 33 (1995) 231–235.
[30] K. Grice, H. Sattar, M. Sharratt, H. Baker, Skin temperature and transepidermal water loss, J. Investig. Dermatol. 57 (1971) 108–110.
[31] K. Grice, H. Sattar, H. Baker, The effect of ambient humidity on transepidermal water loss, J. Investig. Dermatol. 58 (1972) 343–346.
[32] J. Swarbrick, A.H. Amann, R.E. Lindstrom, Factors affecting water vapor transmission through free polymer films, J. Pharm. Sci. 61 (1972) 1645–1647.
[33] O.L. Sprockel, W. Prapaitrakul, P. Shivanand, Permeability of cellulose polymers: water vapour transmission rates, J. Pharm. Pharmacol. 42 (1990) 152–157.
[34] A. Casiraghi, P. Minghetti, F. Cilurzo, L. Montanari, A. Naik, Occlusive properties of monolayer patches: in vitro and in vivo evaluation, Pharm. Res. 19 (2002) 423–426.
[35] J. Pinnagoda, R.A. Tupker, J.A. Smit, P.J. Coenraads, J.P. Nater, The intra- and inter-individual variability and reliability of transepidermal water loss measurements, Contact Dermatitis 21 (1989) 255–259.
[36] M.E. Aulton, M.H. Abdul-Razzak, The mechanical properties of hydroxypropylmethylcellulose films derived from aqueous systems, part I: the influence of plasticizers, Drug Dev. Ind. Pharm. 7 (1981) 649–668.
[37] S.Y. Lin, C.J. Lee, Y.Y. Lin, Drug-polymer interactions affecting the mechanical properties, adhesion strength and release kinetics of piroxicam-loaded Eudragit E films plasticized with different plasticizers, J. Control. Release 33 (1995) 375–381.
[38] A. Mint, S.A.M. Hotchkiss, J. Caldwell, Percutaneous absorption of diethyl phthalate through rat and human skin, Toxicol. In Vitro 8 (1994) 251–256.
[39] H.E. Boddé, E.A.C. Van Aalten, H.E. Junginger, Hydrogel patches for transdermal drug delivery; in-vivo water exchange and skin compatibility, J. Pharm. Pharmacol. 41 (1989) 152–155.
[40] J.C. Gutierrez-Rocca, J.W. McGinity, Influence of aging on the physical–mechanical properties of acrylic resin films cast from aqueous dispersions and organic solutions, Drug Dev. Ind. Pharm. 19 (1993) 315–332.
[41] L. Stubberud, H.G. Arwidsson, V. Hjortsberg, C. Graffner, Water–solid interactions. III. Effect of glass transitions temperature, Tg, and processing on tensile strength of compacts of lactose and lactose/polyvinyl pyrrolidone, Pharm. Dev. Technol. 1 (1996) 195–204.