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Fabrication and evaluation of polymeric films for transdermal delivery of pinacidil

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The objective of the present work was to fabricate Eudragit RL 100-polyvinyl acetate films and evaluate their potential for transdermal drug delivery in a quest to develop a suitable transdermal therapeutic system for pinacidil. The polymeric films (composed of Eudragit RL 100 and polyvinyl acetate in 2 : 8, 4 : 6, 6 : 4, 8 : 2 ratios in films P-1, P-2, P-3, P-4 respectively, together with 5% w/w of pinacidil and 5% w/w of dibutylphthalate in all the films) were cast on a glass substrate and evaluated for physicochemical parameters viz. thickness, weight, folding endurance (a measure of fragility), percent elongation at break (a measure of flexibility), drug content uniformity, water absorption capacity, moisture vapour transmission, drug-polymer interaction, in vitro drug release and skin permeation profiles. The films were also evaluated for appearance, smoothness and transparency. The film finally selected was assessed for its skin irritation potential, and its stability on storage under accelerated temperature and humidity conditions. The values of thickness, weight, folding endurance, percent elongation at break, percentage water absorbed, moisture vapour transmission, cumulative amount of drug released and permeated for different films were in the following order: P-1 < P-2 < P-3 < P-4. The results suggest that Eudragit RL 100, a freely permeable polymer, has a major influence on the physicochemical profile of the films. The higher the quantity of Eudragit RL 100 in the film, the better its strength and flexibility as well as its higher drug release and skin permeation potential. The final optimized film (with a composition of Eudragit RL 100: polyvinyl acetate: pinacidil monohydrate: dibutylphthalate in 8.0 : 2.0 : 0.5 : 0.5 ratio) was found to be the best in terms of drug release (cumulative amount of drug released in 48 h was 96.09%) and skin permeation (permeability coefficient, 0.0164 cm/h). There was no apparent drug-polymer interaction in the films. The optimized film was seemingly free of potentially hazardous skin irritation. The film was found to be stable and intact at ambient temperature and humidity conditions. The films hold promise for the development of a matrix type transdermal therapeutic system for pinacidil.

1. Introduction

The benefits of transdermal drug administration have been well documented, in particular avoidance of hepatic first pass metabolism, enhancement of bioavailability, reduction in frequency of drug administration, minimization of side effects, ease of application and improvement in patient compliance (Chein 1987; Toon et al. 1989; Carbo et al. 1990; Ghosh et al. 1995 and Dias et al. 1999).

The polymeric films used for such systems need to be evaluated to ascertain the effect of various physicochemical parameters and formulation variables on the drug release and skin permeation pattern of the prospective transdermal therapeutic system.

A number of matrix-forming polymers have been used by many workers in the development of transdermal therapeutic systems (Bhalla et al. 1988; Baichwal et al. 1988; Krishna et al. 1994; Singh et al. 1996; Ramarao et al. 1998; Minghetti et al. 1999; Verma et al. 2000; Iordanskii et al. 2000; Kotiyan et al. 2001; Raffie et al. 2001; Valenta et al. 2001; Aqil et al. 2002; Tipre et al. 2002, 2003; Samanta et al. 2003; Devi et al. 2003; Shin et al. 2002; Jain et al. 2003). However, there are no reports on the use of Eudragit RL 100 (ERL 100) and polyvinyl acetate (PVAc) as the matrix-forming polymer combination. The objective of the present work was to formulate and evaluate matrix-forming polymeric films of ERL 100 and PVAc for their physicochemical characteristics as well as for their *in vitro* drug release and skin permeation potential. Pinacidil was used as the model drug and dibutylphthalate (DBP) as the plasticizer. The films were evaluated for various parameters such as thickness, weight, folding endurance, percent elongation at break, drug content uniformity, drug polymer interaction, *in vitro* drug release, skin permeation, preliminary skin irritation potential and film stability.

Table 1: Physicochemical characteristics of polymeric films

Parameters	Film			
	P-1	P-2	P-3	P-4
Thickness (mm)	*0.403 (± 00.52)	0.412 (± 00.54)	0.425 (± 00.47)	0.436 (± 00.58)
Weight (mg)	802 (± 6.24)	815 (± 5.38)	822 (± 4.67)	832 (± 6.98)
Folding endurance	207 (± 2)	218 (± 5)	229 (± 6)	248 (± 4)
% elongation at break	65 (± 1.28)	69 (± 1.88)	75 (± 0.86)	83 (± 1.04)
% water absorbed	0.82 (± 0.04)	1.06 (± 0.03)	1.17 (± 0.08)	1.26 (± 0.06)
Moisture vapour transmission ($g/cm^2/h \times 10^5$)	4.01 (± 0.16)	4.15 (± 0.21)	4.53 (± 0.19)	4.82 (± 0.28)
Drug content (mg/cm^2)	7.34 (± 0.07)	7.37 (± 0.11)	7.39 (± 0.38)	7.40 (± 0.27)
Cumulative amount of drug released (%)	49.70 (± 5.33)	68.08 (± 4.97)	78.68 (± 6.41)	96.09 (± 5.72)
Cumulative amount of drug permeated (%)	32.75 (± 3.26)	44.72 (± 2.72)	58.10 (± 3.68)	76.32 (± 4.22)
Flux ($mg/cm^2/h \times 10^2$)	08.89 (± 0.65)	09.36 (± 0.38)	10.48 (± 0.72)	11.89 (± 0.53)
Permeability coefficient ($cm/h \times 10^2$)	0.82 (± 0.05)	1.06 (± 0.07)	1.38 (± 0.06)	1.64 (± 0.09)
Lag time (hours)	4.0	3.0	2.5	2.0

*Results are the mean of triplicate observations. SE values are given in parentheses

2. Investigations, results and discussion

There was an increase in thickness and weight as the content of ERL 100 was increased with a corresponding decrease in PVAc across the films from P-1 to P-4 (Table 1). The folding endurance value could be defined as 'the number of times a film can be folded at the same place without breaking'. This test is an index of the brittleness of the film, the lower the folding endurance value, the more brittle the film is. It is an important test to assess the integrity of the film. The increase in folding endurance value of the films P-1, P-2, P-3, P-4 in that order (Table 1) suggested an increase in film strength with film thickness and weight as expected. An assessment of the tensile strength of the films was made by 'percent elongation at break' value which could be described as 'the percentage in change in length when the film specimen breaks'. Again, an increase in the tensile strength of the films was found with a maximum for P-4 (Table 1). The films were found to be more elegant, smooth and transparent with the addition of a plasticizer. The moisture vapour transmission and water absorption capacity of the films were again in the order: P-1 < P-2 < P-3 < P-4, suggesting an increase in film porosity with a rise in the content of ERL 100 (Table 1). It was thus predicted, that film P-4 would provide the maximum drug release and drug permeation through skin. The results corroborated our assumptions. The cumulative amount of drug released from formulations P-1, P-2, P-3 and P-4 was found to be 49.70%, 68.08% 78.68% and 96.09% respectively (Table 1). The corresponding amount of drug permeated from the formulations was 32.75%, 44.72%, 58.10% and 76.32% respectively (Table 1). Hence, it is clear from the data that the rate of drug release and permeation increased as the amount of ERL 100 (a freely permeable polymer) was increased (Figs. 1 and 2). Initially rapid release (burst effect) was observed up to 4–6 h. The release rate was, however, found to be constant for most of the duration of the test, falling only towards the end as the concentration

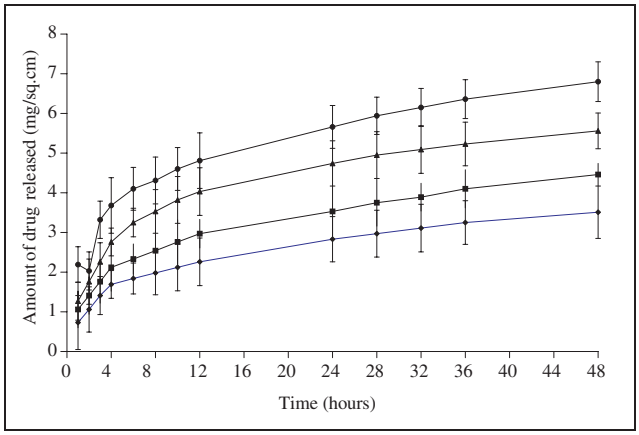

Fig. 1: *In vitro* release profiles of pinacidil from polymeric films P-1, P-2, P-3 and P-4 carrying ERL 100 and PVAc in 2 : 8, 4 : 6, 6 : 4 and 8 : 2 ratio, respectively (n = 3). —◆— P-1; —■— P-2; —▲— P-3; —●— P-4

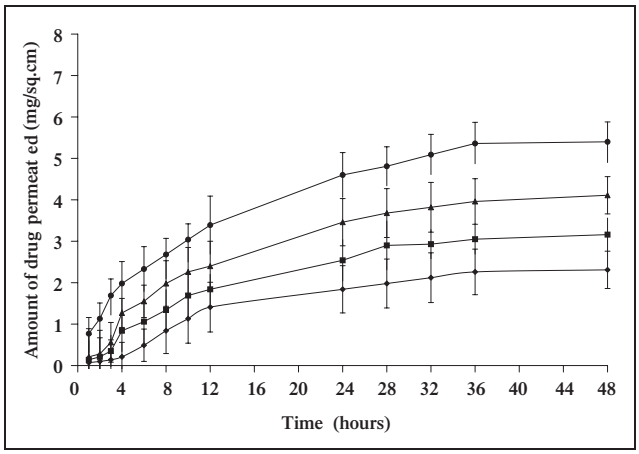

Fig. 2: *In vitro* skin permeation profiles of pinacidil from polymeric films P-1, P-2, P-3 and P-4 carrying ERL 100 and PVAc in 2 : 8, 4 : 6, 6 : 4 and 8 : 2 ratio, respectively (n = 3). —◆— P-1; —■— P-2; —▲— P-3; —●— P-4

Table 2: Skin irritation scores of polymeric films

Rabbit #	Placebo film		Medicated film (P-4)		Formalin control	
	Erythema	Oedema	Erythema	Oedema	Erythema	Oedema
1	0	0	0	0	4	6
2	0	0	1	0	6	8
3	0	0	2	0	6	7
4	0	0	0	0	5	6
Mean combined score	0.0 (None)		(0.375) Mild		(6.0) Severe	

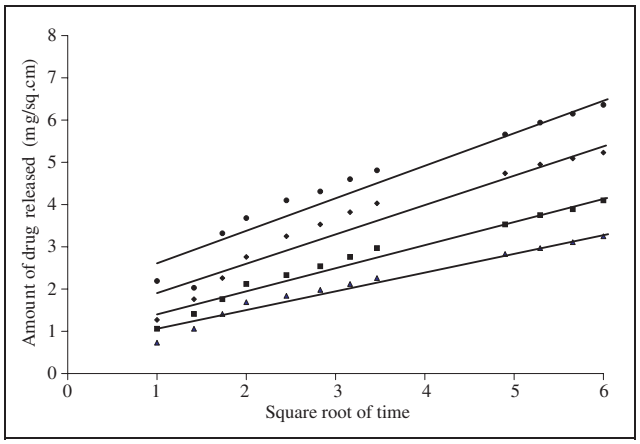

Fig. 3: Plot of cumulative amount of drug released vs. square root of time for polymeric films P-1, P-2, P-3 and P-4; ▲ P-1; ■ P-2; ◆ P-3; ● P-4

Table 3: TLC analysis of polymeric films and pure drug sample of pinacidil

S.No.	Sample	R_f value
1.	Pure drug	0.73 (± 0.007)
2.	Film P-1	0.75 (± 0.015)
3.	Film P-2	0.74 (± 0.003)
4.	Film P-3	0.73 (± 0.005)
5.	Film P-4	0.72 (± 0.009)

of the drug in the films declined. This is in good agreement with the controlled release behaviour of the polymeric films, which was expected in the final TTS as well. A linear relationship between the amount of drug released and the square root of time suggested a Higuchian matrix diffusion type pattern of drug diffusion from the films (Fig. 3). The flux and the permeability coefficient of the films increased with a corresponding decrease in the lag time as the amount of ERL 100 was increased (Table 1). Uniformity of drug content was observed on determination of the drug in the films (Table 1).

The polymeric film (P-4) seemed to be free from any marked skin irritation as suggested by the irritation scores (Table 2).

TLC studies revealed that there was negligible difference in the R_f values of films and the pure drug (Table 3) which suggested that there was no drug-polymer interaction in the film and the polymer would not interfere with the estimation of drug in films.

Thickness, weight, folding endurance, elongation at break, drug content and water absorption capacity of the films declined with an increase in their storage temperature (Table 4). The amount of drug released and permeated also declined slightly for the films stored at higher temperatures. The values of all the above parameters were found to increase when the films were stored at higher humidities (Table 4). This could be attributed to the amount of moisture gained or lost during storage of the films under varying temperature and humidity conditions.

3. Experimental

3.1. Materials

Eudragit RL 100 (ERL 100) was purchased from Röhm Pharma, Germany. Polyvinyl acetate (PVAc) was donated by Ranbaxy Research Laboratories, India. Pinacidil monohydrate (PM) was provided by courtesy of Leo Pharmaceuticals, Denmark. Dibutyl phthalate (DBP) was supplied by Merck, Schuchardt, Germany. Isopropyl alcohol (IPA) and dichloromethane (DCM) were purchased from E. Merck, India. All the solvents used were of analytical grade.

Table 4: Comparison of physicochemical characteristics of fresh and 12 weeks stored samples of polymeric film (P-4) at different temperatures and humidities

Parameter	Initial value (fresh sample)	Temperature (°C)			Relative humidity (%)		
		40 ± 0.5	50 ± 0.5	60 ± 0.5	50 ± 2	75 ± 2	96 ± 2
Thickness (mm)	*0.436 (± 0.0058)	0.424 (± 0.0046)	0.411 (± 0.0056)	0.396 (± 0.0038)	0.439 (± 0.0044)	0.447 (± 0.0053)	0.468 (± 0.0062)
Weight (mg)	832 (± 6.98)	819 (± 5.26)	804 (± 5.91)	788 (± 6.02)	846 (± 5.12)	852 (± 3.76)	866 (± 4.77)
Folding endurance	248 (± 4)	240 (± 6)	232 (± 5)	226 (± 4)	253 (± 2)	258 (± 1)	264 (± 3)
% elongation at break	83 (± 1.04)	80 (± 1.58)	76 (± 1.23)	72 (± 1.42)	87 (± 1.12)	89 (± 1.60)	95 (± 1.56)
% water absorbed	1.26 (± 0.06)	1.14 (± 0.07)	1.02 (± 0.09)	0.92 (± 0.06)	1.32 (± 0.09)	1.39 (± 0.005)	1.45 (± 0.03)
Drug content (mg/cm^2)	7.41 (± 0.48)	7.39 (± 0.36)	7.36 (± 0.52)	7.17 (± 0.41)	7.38 (± 0.35)	7.40 (± 0.61)	7.39 (± 0.44)
%of drug released	96.09 (± 5.72)	95.28 (± 2.27)	94.84 (± 2.92)	94.23 (± 2.78)	96.28 (± 2.52)	96.36 (± 1.88)	96.51 (± 2.06)
%of drug permeated	76.32 (± 4.22)	75.72 (± 2.46)	75.30 (± 1.27)	74.92 (± 1.63)	76.63 (± 2.14)	77.42 (± 2.18)	80.32 (± 2.44)

* Results are the mean of triplicate observations. SE values are given in parentheses

3.2. Fabrication of films

The polymeric solution was prepared by dissolving ERL 100 and PVAc (in ratios of 2 : 8, 4 : 6, 6 : 4 and 8 : 2 for films P-1, P-2, P-3 and P-4) together with 5% w/w of PM and 5% w/w of DBP in a mixture of DCM and IPA (80 : 20 v/v). The solution was poured into glass plates with raised edges (Bhalla et al., 1988) and allowed to evaporate under ambient conditions (temperature 32 ± 2 °C, RH 45 ± 5%) for 24 hours. The dried films were removed from the glass plates, packed in aluminium foil and stored in airtight containers.

3.3. Evaluation of films

The films were evaluated for the following physicochemical parameters.

3.3.1. Thickness

The thickness of a uniform area ($2 \times 4\ cm^2$) of the films was measured using a film thickness measuring instrument (Links, India).

3.3.2. Weight

The weight of the films ($2 \times 4\ cm^2$) was determined using a digital electronic balance (Sartorius, India).

3.3.3. Folding endurance

For determining folding endurance, a film ($2 \times 4\ cm^2$) was folded in the centre between finger and thumb and then opened. This was called as 'one folding'. The procedure was repeated until the film showed breakage or cracks in the centre. The total number of folding operations was termed the 'folding endurance value'.

3.3.4. Tensile strength

The tensile strength of the film was determined by the percent elongation at break value. Rectangular $2 \times 4\ cm^2$ strips of film were cut using a sharp blade and a scale and marked 1 cm from the edges lengthwise. The film was held between the jaws of an apparatus (tensile tester) fabricated for the purpose giving a free film of $2 \times 2\ cm^2$ dimensions. One jaw was kept stationary and another was pulled slowly with the help of the moving screw mechanism of the apparatus until the film just broke. Percent elongation at break was calculated using eq. (1):

$$\text{Percent elongation at break} = \frac{(I_B - I_A)}{I_A} \times 100 \quad (1)$$

Where I_A = Initial length of film (cm)
and I_B = Length of film (cm) at break

3.3.5. Other film characteristics

Other film characteristics such as appearance, smoothness and transparency were also observed.

3.3.6. Water absorption capacity

Films of uniform dimensions ($2 \times 4\ cm^2$) were placed in a humidity chamber (84% RH). The water absorption capacity of the films was calculated on the basis of the difference in initial and final weights of the films.

3.3.7. Moisture vapour transmission

Moisture vapour transmission was determined according to a reported method (Krishna et al. 1994).

3.3.8. Drug content uniformity

The specified area ($2 \times 4\ cm^2$) of the films was cut into pieces, dissolved in 10 ml of IPA and kept in a shaking incubator at 37 ± 1 °C for 24 h. A blank determination was also performed by treating a placebo film in the same manner. Aliquots (1 ml) of the film solution were filtered and centrifuged and absorbances were determined at 280 nm (Hitachi spectrophotometer, Japan).

3.3.9. Drug polymer interaction studies

The interaction studies were performed by TLC analysis of the pure drug and the medicated films. The method reported in the literature supplied by the drug manufacturer was slightly modified by using iodine vapours as visualizing agent. Silica gel plates were used as the stationary phase with chloroform-methanol-25% ammonia solution (18 : 19 : 1 v/v/v) as the mobile phase.

3.3.10. In vitro drug release studies

A modified paddle over disc assembly (USP 23, Apparatus 5) was used for assessment of the release of the drug from the patches. The medicated film was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml isotonic phosphate buffer (IPB) of pH 7.4 which was composed of 0.16% (w/v) of sodium dihydrogen phosphate, 0.76% (w/v) of disodium hydrogen phosphate and 0.44% (w/v) of sodium chloride. The apparatus was equilibrated to 32 ± 0.5 °C and operated at 50 rpm. The samples (5 ml aliquots) were withdrawn at appropriate time intervals up to 48 h and analyzed at 257 nm (Beckman DU-64 spectrophotometer, USA).

3.3.11. In vitro skin permeation studies

A modified Franz diffusion cell (Franz 1975) with a diffusional area of 7.065 cm^2 was used. The skin was removed from the abdominal portion of an albino rat after killing the animal. The hairs were removed by treating the skin with a depilatory. After removing the subcutaneous fat, the stratum corneum side of the skin was kept in intimate contact with the release surface of the TTS (kept in the donor cell). The receiver phase was 50 ml IPA : IPB of pH 7.4 (30 : 70% v/v) stirred at 500 rpm on a magnetic stirrer. The contents of the receiver cell were kept at 32 ± 0.5 °C with prewarmed water flowing through a jacket lined with the receiver cell. The skin was allowed to stabilize (until zero UV absorbance was observed) before mounting the film in the donor cell. The amount of drug permeated was determined by UV analysis at 257 nm (Beckman DU-64 spectrophotometer, USA) of 100 µL aliquots of the receiver fluid removed at appropriate time intervals up to 48 h. The volume was replenished with an equal quantity of pre-warmed receiver solution. The flux (skin permeation rate of the drug) was determined directly as the slope of the curve between the steady state values of the amount of drug permeated (mg cm^{-2}) vs. time in hours (Bonina et al. 1993) and the permeability coefficient was calculated by dividing the flux by the initial drug load (mg cm^{-2}).

3.3.12. Preliminary skin irritation studies

Medicated film (P-4) and a placebo film were placed on the back of the depilated back skin of each albino rabbit (2 kg, n = 4) at designated sites using an adhesive (Johnson and Johnson, India). A 0.8% aqueous solution of formalin was also applied as a standard irritant. Animals were observed for development of flare and wheal for 7 days. The following scoring pattern was followed: 0 = NIL, 0–2 = mild, 2–4 = Moderate, 4–6 = severe, 6 and above = very severe.

3.3.13. Accelerated stability studies

The films were stored at different temperatures (40 ± 0.5 °C, 50 ± 0.5 °C, 60 ± 0.5 °C) for three months. To investigate the effect of elevated humidity, the films were stored in three different humidity chambers (50 ± 2%, 75 ± 2% and 96 ± 2% RH). The films were then reevaluated for physicochemical characteristics viz., thickness, weight, folding endurance, tensile strength, drug content uniformity and water absorption capacity.

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