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應用多二元醇飽和甘油酯做為藥物滲透之載體與增強劑的研究

Polyglycolized saturated glycerides as a carrier and enhancer for drug penetration

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主持人: 何秀娥　台北醫學院 藥學系

中文摘要

本研究利用實驗設計法定量地檢視 Gelucire 基劑其融點和 HLB 值對前列腺素 E_1 和其 alkyl ester 通過皮膚障礙層的滲透影響性。七個處方包含有 0.1mg/mg 模式藥物和不同比例的 Gelucire 44/14, 50/02 和 37/02 並以 4:1 的比例添加 lauroglycol。對於 PGE_1 而言，其最大的流通率在 35.9493 和 33.3300 nmole/cm^2 per h 之間，此時處方的 HLB 值為 6.6，融點為 41-54℃。對於 methyl PGE_1 而言，其最大的流通率為 76.6214 nmole/cm^2 per h，此時處方的 HLB 值為 5.3，融點為 46-50℃。對於 ethyl PGE_1 而言，其最大的流通率為 33.4468 nmole/cm^2 per h 之間，此時處方的 HLB 值為 5.3，融點為 46-50℃。對於 isopropyl PGE_1 而言，其最大的流通率為 15.4577，此時處方的 HLB 值為 5.3，融點為 46-50℃。對於 butyl PGE_1 而言，其最大的流通率為 13.6691 nmole/cm^2 per h 之間，此時處方的 HLB 值為 6.6，融點為 41-48℃。對於 PGE_1 和 alkyl ester 而言，在不同的 Gelucire system 其加強滲透的作用不同。對於模式選擇的結果顯示三個 Gelucire grade 對 PGE_1 的流通率其作用以三個因子沒有相互作用的 Quadratic model 最適當。而 PGE_1 alkyl estetr 最適當的是 linear model。對於 PGE_1 而言，Gelucire 44/14 和 Gelucire 50/02 相互作用有一個最大的正值，緊接著是 Gelucire 44/14 和 Gelucire 37/02。結果顯示 PGE_1 經由老鼠皮膚的的滲透速率藉由 Gelucire 44/14 和 Gleucire 50/02 的組合能大幅被加強。然而 Gelucire 50/02 和 37/02 的相互作用顯示負值。此可能是由於這二個 Gelucire grade 的 HLB 值均太低，以致於無法加速 Gelucire 處方的自身乳化作用，而阻礙了 PGE_1 的滲透。此與加強 PGE_1 和其 alkyl ester 的滲透速率必須有適當 HLB 值的 Gelucire 系統結果一致。此結果亦顯示具高融點和低 HLB 值的 Gelucire 50/02 會減少 PGE_1 alkyl ester 的滲透速率。但是，Gelucire 50/02 和 37/02 提昇 PGE_1 alkyl ester 的滲透速率相似，會隨著增加 alkyl chain 的長度而減少。此可由 Gelucire 50/02 和 37/02 的 HLB 值相同來解釋。 在本實驗中 Gelucire system 的 HLB 值影響比融點大。

關鍵詞: 前列腺素 E_1，皖基酯，滲透，Gelucire

Abstract

In this study, the influence of the melting point and HLB value of Gelucire-based formulations on the permeation of model drugs, including PGE_1 and its alkyl esters, through the skin barrier was examined quantitatively with an experimental design.

Seven formulations consisting of three grades of Gelucire (44/14, 50/02, and 37/02) at different ratio with the addition of lauroglycol at a fixed ratio of 4: 1 to a total Gelucire amount were prepared with model drugs in a concentration of 0.1 mg/mg. For PGE_1, the maximal flux at this concentration was between 35.9493 and 30.3300 nmole/cm^2 per h and occurred at the HLB value of 6.6 and melting point ranged from 41-54 ℃. For methyl ester of PGE_1, the maximal flux appeared to be 76.6214 nmole/cm^2 per h and occurred at the HLB value of 5.3 and melting point ranged from 46-50 ℃. As to ethyl ester of PGE_1, the maximal flux was around 33.4468 nmole/cm^2 per h and occurred at the HLB value of 5.3 and melting point ranged from 46-50 ℃. The maximal flux was 15.4577 nmol/cm^2 per h for isopropyl ester of PGE_1 and appeared at the HLB of 5.3 and melting point ranged from 46-50 ℃. Butyl ester of PGE_1 showed its maximal flux to be around 13.6691 nmol/cm^2 per h and occurred at the HLB value of 6.6 and melting point ranged from 41-48 ℃. The promotion of penetration for PGE_1 and its alkyl esters seem to be maximized at different Gelucire system. The results of model selection demonstrate that the quadratic model, which has no interaction term of three factors, was the most statistically appropriate model for describing the overall effect of three Gelucire grades on the flux of PGE_1. On the other hand, linear model was the most suitable for four PGE_1 alkyl esters. For PGE_1, the interactive effect of Gelucire 44/14 and Gelucire 50/02 on the flux of PGE_1 was the greatest with a positive sign, followed by Gelucire 44/14 and 37/02 with a positive sign. As a result, the penetration rate of PGE_1 through mouse skin was greatly enhanced with using a combination of Gelucire 44/14 and 50/02. However, the interactive effect of Gelucire 50/02 and 37/02 showed a negative sign. It may be that HLB value of these two Gelucire grades are too lower to accelerate the self-emulsification of Gelucire formulation hindering the penetration of PGE_1. This was consistent with the result that an optimal HLB value of Gelucire system is necessary to improve the permeation rate of PGE_1 and its alkyl esters. Results also demonstrate that a higher melting point and a lower HLB value of Gelucire 50/02 resulted in decreasing permeation rate of PGE_1 alkyl esters. But the tendency for Gelucire 50/02 and 37/02 to promote the penetration of PGE_1 alkyl esters was similar and the extent of the influence decreased with increased alkyl chain length. It is possibly explained by the fact that the HLB value of Gelucire 50/02 and 37/02 is equal. Similarly, the influence of HLB value of Gelucire system was more profound than that of the melting point examined in this study.

Keywords: Prostaglandin E1; Alkyl ester; Penetration; Gelucire

1. Introduction

Recent progress in pharmacotechniques has led to an increasingly important role for excipients because auxiliary substances not only act now as medicaments but also actively aid their transport and targeting to the correct organs. A number of medicaments have been produced that indicate the interest in these matrix forms using excipients of the Gelucire® type [1]. Gelucire® is a saturated polyglycolized glyceride consisting of mono-, di-, and

triglyceride and of mono- and di- fatty acid esters of polyethylene glycol (PEG). The nature and proportion of each component are specific to a given grade of Gelucire® and is consistent from batch to batch. These Gelucire® grades provide novel solutions to the problems of solubilization, absorption, and bioavailability of complex molecules such as enzyme inhibitor, peptides, etc [2,3]. The grade of Gelucire® is designated by two numbers separated by a slash. The first number indicates its melting point and second number stands for its HLB value [4].

The melting point and HLB value of Gelucire grades presently available range from 37 to 50 ℃ and 2 to 14, respectively. A blending with a melting point and HLB value in the middle range is obtainable by mixing different proportion of two or three grades of Gelucire. The melting point of a blending can be further reduced to be lower than body temperature by mixing with a liquidating agent of known HLB value. Lauroglycol is a liquidating agent of choice with HLB value of 4. By mixing it in a different ratio with a single grade or a blending of Gelucire, the melting point and HLB value of the drug carrier can be tailor-made to optimally deliver drug transdermally.

Among the numerous natural vasodilator prostagladins, Prostaglandin E_1 (PGE1) has found particular attention in pharmacology. PGE_1 has been applied for the treatment of peripheral arterial occulsive disease, acute mycocardial infraction, angina pectoris, acute ischaemic stroke, asthma, gastrointestinal ulcers, ulcers of skin, and organ rejection. Various routes of administration have been reported, including oral, intravenous, buccal, rectal, intraarterial, subcutaneous, sublingual, and transdermal [5,6].

Transdermal delivery of PGE_1 to achieve therapeutic effects is thus of major research interest. However, this treatment has been limited since PGE_1 is chemically labile and the diffusion through skin is not rapid enough [7]. The ester prodrug approach is one method of improving skin penetration. Recently, the use of PGE_1 ethyl ester derivatives to improve transdermal delivery has been patented and about 10-fold enhancement was reported [4]. However, the underlying mechanisms responsible for the transdermal penetration of PGE_1 and its alkyl esters has not yet been fully elucidated. To improve the penetration efficacy, a thorough study on the ester prodrugs with different alkyl chain length for PGE_1 is still promising. It would be also valuable of using Gelucires material as the basis to maximize the therapeutic efficacy of PGE_1 and its analogs.

In previous study, a systematic comparison of percutaneous delivery of PGE_1 and its four derivatives of alkyl ester in alcoholic saline solution through hairless mouse skin has been investigated [8]. In this study, the influence of the melting point and HLB value of Gelucire-based formulations on the permeation of model drugs, i.e. PGE_1 and its alkyl esters, through the skin barrier was examined quantitatively with an experimental design.

2. Experimental

2.1 Materials

PGE_1 (11α, 13*E*, 15*S*)-11,15-dihydroxy-9-

oxoprost-13-en-1-oic acid) was provided by the Department of Cell Biology, University of Medicine and Dentistry of New Jersey, USA. PGE_1 alkyl esters (methyl, ethyl, isopropyl, and butyl esters) were synthesized by the Department of Medicinal Chemistry, School of Pharmacy, Taipei Medical College, Taipei, Taiwan, R.O.C. [8]. Prostaglandins (PGE_1, PGA_1, and PGB_1) were purchased from Sigma (St. Louis, MO, USA). Gelucire® 44/14, 50/02, 37/02, and lauroglycol were obtained from GATTEFOSSE (Saint Priest, France). Acetonitrile (HPLC grade) was supplied by Merck (Darmstadt, Germany). Absolute ethanol and all other materials were of reagent grade or better.

2.2 Methods

2.2.1 Formulation design

According to the mixture design, a total of seven formulations using three grades of Gelucire (44/14, 50/02, and 37/02) was designed by Design Expert (V5.0, Stat-Ease, USA). One of them is the center point of the mixture design. These seven formulations were mixed with one liquidating agent of lauroglycol at a fixed ratio (2:1). A detailed formulation is listed in Table 1. All components of designated formulations were heated until all melt. Then the mixture was cooled to ambient temperature. The melting point of each formulation was measured. HLB value was calculated by summing the contribution of each individual component based on its weight fraction. This experimental design was employed to quantitatively describe the influence of the melting point and HLB value of Gelucire systems on the permeation of model drugs, PGE_1 and its four alkyl esters. A range of mixtures of the Gelucire systems and model drugs were prepared by accurately weighing, and then fusing. All samples after thorough mixing were then allowed to cool to room temperature and formed a semisolid medication containing each model drug in a concentration of 0.1 mg/mg.

2.2.2 Permeation studies

Hairless mice (strain ICR), aged 6-8 weeks and weighing approximately 20 g, were obtained from the National Animal Center, NSC, R.O.C. The mice were killed by spinal dislocation. Fresh skin was excised from the abdominal region, and washed with normal saline before being placed on a Franz-type diffusion cell. The Franz-type vertical diffusion cells were composed of a receptor compartment having a volume of about 5.5 mL and a donor compartment with an effective diffusional area of approximately 0.73 cm^2. In vitro permeation study was conducted as following using the hairless mouse skin as the main barrier: to attain reproducibility, a suitable quantity of the Gelucire formulations (5 mg) with known amount of model drug (0.1 mg / mg) was adsorbed onto a KBr sheet and placed on the donor side. Phosphate buffer (pH 6.8, 50 mM) was used as the receptor medium and maintained at 37 ℃,using a circulating water jacket, with stirring at a constant rate of 500 rpm. At predetermined time intervals, 200 ?L aliquots were withdrawn from the receptor compartment and replaced with an equal volume of fresh medium.

2.2.3 Quantitative analysis of the

penetrated amount of prostaglandins

The HPLC analysis method was used to quantify the penetrated amount of prostaglandins. It was based on that reported by Herman et al. [9], which relies on the assay of PGB_1 after the conversion of prostaglandins to PGB_1. In general, 0.4 mL receptor sample was mixed with 0.4 mL of 0.5 M NaOH and 0.2 mL ethanol, and then kept at ambient temperature for approximately 2 h to convert all prostaglandins to PGB_1. The pH value of the mixture was then brought to 3.0 with 1.0 M HCl (approximately 225 ?L) and extracted twice with 2 mL ethyl acetate each. The solvent volume was pooled and evaporated to dryness under nitrogen gas. The residue was dissolved in 0.4 mL of the mobile phase and 50 ?L were injected into the HPLC system. The mobile phase consisted of acetonitrile / water / acetic acid (50:50:1) at a flow rate of 1.0 mL/min. UV detection was taken at 280 nm for the determination of PGB_1 [9]. The analytical procedure was validated before the implementation by examining the accuracy and precision of inter- and intra-day assay. The accuracy and precision for assaying PGE_1, methyl, ethyl, isopropyl, and butyl esters have been reported in a previous study [8]. This was corresponded to the concentration range from 0.5 to 20 ?g/mL.

2.2.4 Data analysis of prostaglandins penetration

The *in vitro* penetration parameters were calculated from the penetration data using equation 1:

$$J_t = V/A \cdot dC/dt \qquad \text{Eq. 1}$$

where J_t is the flux at time t, V is the volume of the receiver compartment, A is the area available for penetration and dC/dt is the rate of change of the penetrant's concentration in the receiver side of the cell. Equation 1 was applied to the data and the results were presented as the mean $\pm$ S.D. of at least five replicates during the steady-state period. At steady-state, the flux (J_{ss}) through skin membrane is constant and is expressed by equation 2

$$J_{ss} = D \cdot k \cdot \Delta C_s / h \qquad \text{Eq. 2}$$

where D is the diffusion coefficient in the stratum corneum, k is partition coefficient between the stratum corneum and the vehicle, h is the thickness of the stratum corneum, and $\Delta C_s/h$ is the concentration gradient across the outermost surface of the stratum corneum. It was assumed that the sink conditions are maintained throughout the study if the total percentage of penetrated amount was less than 15%. Hence, the concentration gradient ($\Delta C_s/h$) can be considered equal to C_v/h, where C_v is the drug concentration in the vehicle. As a result, Equation 3 is obtained as in the follow. By definition, P is the permeability coefficient and equal to (Dk/h).

$$J_{ss} = D \cdot k \cdot C_v/h \quad = P \cdot C_v \qquad \text{Eq. 3}$$

3. Results and discussion

Seven formulations consisting of three grades of Gelucire (44/14, 50/02, and 37/02) at different ratio with the addition of lauroglycol at a fixed ratio of 4: 1 to a total Gelucire amount were tested their influence on the fluxes of PGE_1 and its alkyl esters using the hairless mouse skin as the barrier. Table 1 shows the melting

point of these seven formulations ranged from 36-56 ℃, and HLB value in the range of 2.6 to 10.6. Fig. 1 illustrates the penetration of PGE_1 and its alkyl esters in the same concentration (500 ug/g) from the Gelucire system through hairless mouse skin. Since sink conditions were maintained, the flux of PGE_1 and its alkyl esters at the steady state were calculated based on Eq. 1 and the corresponding permeability coefficients (P) was obtained according to Eq. 3. Results are listed in Table 2. Compared to its alkyl esters, the flux of PGE_1 penetrated through the mouse skin at steady state from most Gelucire formulations was slower than that for most of alkyl esters. For PGE_1, the maximal flux at this concentration was between 35.9493 and 30.3300 nmole/cm^2 per h and occurred at the HLB value of 6.6 and melting point ranged from 41-54 ℃. For methyl ester of PGE_1, the maximal flux appeared to be 76.6214 nmole/cm^2 per h and occurred at the HLB value of 5.3 and melting point ranged from 46-50 ℃. As to ethyl ester of PGE_1, the maximal flux was around 33.4468 nmole/cm^2 per h and occurred at the HLB value of 5.3 and melting point ranged from 46-50 ℃. The maximal flux was 15.4577 nmol/cm^2 per h for isopropyl ester of PGE_1 and appeared at the HLB of 5.3 and melting point ranged from 46-50 ℃. Butyl ester of PGE_1 showed its maximal flux to be around 13.6691 nmol/cm^2 per h and occurred at the HLB value of 6.6 and melting point ranged from 41-48 ℃. The promotion of penetration for PGE_1 and its alkyl esters seem to be maximized at different Gelucire system.

Since the melting point of most of these seven formulations are higher than 36 ℃, two mechanisms were possible for PGE_1 and its alkyl esters to be released from Gelucire®-based formulations. One is that model drugs diffuse from Gelucire matrix to the skin surface, and another is that model drugs are released from a self-emulsified Gelucire layer closed to the skin surface with the help of water evaporated from underlying layer of skin. The former would be not easier since it is a state of solid-solid partition, whereas the latter would be highly possible, especially for a Gelucire with a HLB value in the hydrophilic range. Therefore, results indicate that the influence of melting point of Gelucire system was insignificant on the fluxes of prostaglandins from Gelucire system. Nevertheless, the results demonstrate that the HLB value of these seven formulations is the main factor controlling the permeation rate of PGE1 and its alkyl ester through the hairless mouse skin.

When model drugs are already in a dissolved state, the thermodynamic activity of a fully dissolved molecule and its partition between a donor solution and the stratum corneum are considered to be important in controlling the permeation of drugs through the barrier. The Gelucire system with a optimal HLB value for maximizing the flux is different for PGE_1 and its esters with different alkyl chain length, which might determine an optimal composition needed to balance its thermodynamic activity between the vehicle and the skin. Therefore, the maximal flux for each ester with a fixed concentration would appear at different Gelucire system. Comparing with the formulation 7 having the optimal HLB value, the occurrence of the maximal flux for this fixed concentration shifted to the ester with a longer alkyl chain length. Nevertheless, the deviation from this trend

for isopropyl ester might be due to its branched nature. Moreover, PGE_1 butyl ester turned to be out of this order as a result of the lipophilic and the hindrance nature of butyl group.

Quantification of the effect of Gelucire system on the flux of PGE_1 and its alkyl esters was evaluated based on a mixture design. A suitable polynomial equation involving the individual main effects and interaction factors was selected based on the estimation of several statistical parameters such as C.V. (coefficient of variation), R^2, adjusted R^2, and PRESS etc. provided by DESIGN EXPERT. The results of model selection demonstrate that the quadratic model, which has no interaction term of three factors, was the most statistically appropriate model for describing the overall effect of three Gelucire grades on the flux of PGE_1. On the other hand, linear model was the most suitable for four PGE_1 alkyl esters. Table 3 lists the coefficients of model fit for the effect of Gelucire system on the flux of PGE_1 and its alkyl esters. The coefficients may be regarded as an indicator of the extent of the influence on the flux of PGE_1 and its alkyl esters with a unit change of each corresponding component in Gelucire system. A positive sign is regarded as an enhancement on the flux. For PGE_1, the interactive effect of Gelucire 44/14 and Gelucire 50/02 on the flux of PGE1 was the greatest with a positive sign, followed by Gelucire 44/14 and 37/02 with a positive sign. As a result, the penetration rate of PGE_1 through mouse skin was greatly enhanced with using a combination of Gelucire 44/14 and 37/02. However, the interactive effect of Gelucire 50/02 and 37/02 showed a negative sign. It may be that HLB value of these two Gelucire grades are too lower to accelerate the self-emulsification of Gelucire formulation hindering the penetration of PGE_1. This was consistent with the result that an optimal HLB value of Gelucire system is necessary to improve the permeation rate of PGE_1 and its alkyl esters.

However, the effect of Gelucire grade on the flux of four PGE_1 alkyl esters was different. For PGE_1 alkyl esters, the individual influence of Gelucire 44/14 and 37/02 was more significant compared to that of the Gelucire 50/02. As shown in Table 3, the coefficient of X_2 indicates that the extent of influence of unit change of Gelucire 50/02 on the flux of all PGE_1 alkyl esters is less profound. It implies that a higher melting point and a lower HLB value of Gelucire 50/02 resulted in decreasing permeation rate of PGE_1 alkyl esters. But the tendency for Gelucire 50/02 and 37/02 to promote the penetration of PGE_1 alkyl esters was similar and the extent of the influence decreased with increased alkyl chain length. It is possibly explained by the fact that the HLB value of Gelucire 50/02 and 37/02 is equal. Similarly, the influence of HLB value of Gelucire system was more profound than that of the melting point examined in this study.

Interestingly, the results listed in Table 3 also show the influence of each component in the Gelucire formulations on the flux was nearly maximal for PGE_1 methyl ester. Based on the previous stability study [10], the conversion of PGE_1 ethyl ester to PGA_1 and PGB_1 ethyl ester was shown to be the predominant route of degradation in the phosphate buffer and saline solution. However, as described in the previous penetration study [8] and further confirmation in this study, the only prostaglandin found in the receptor

medium was PGE_1 for the penetration studies using any alkyl esters. Since that, it was more likely that the formation of PGE_1 from PGE_1 alkyl esters during passage through the skin might occur mainly by enzymatic hydrolysis of alkyl chain. Although the promotion of partition with increasing alkyl chain length by lipophilic nature of alkyl chain from a carrier with a similar HLB value into stratum corneum, the absence of enzymatic hydrolysis of alkyl group would make the detection of any trace of PGE_1 in the receptor impossible since the partition of alkyl esters from the epidermal layer into receptor medium was less favorable. Therefore, the activity of enzymes involving in the hydrolysis could be another determinant factor to consider in the elucidation of the mechanism [11].

Their 3D plots are shown in Fig. 2. It further clearly shows that the greatest extent of improvement in the flux occurs in the middle region of the phase diagram for PGE_1. Among these Gelucire grades, the combination of Gelucire 44/14 and 50/02 can increase the flux of PGE_1. However, the improvement in the flux of PGE_1 alkyl esters is dependent on the composition of the Gelucire system. The 3D plots for methyl and isopropyl esters of PGE_1 showed the greatest extent of improvement in the flux occurs in the similar trend of the Gelucire system. The 3D plots for ethyl and butyl esters of PGE_1 show that there was a little different trend of Gelucire system in the improvement of the flux.

However, in comparison with the previous study [12] using two microemulsion systems to enhance the permeation of the same drug through the hairless mouse skin, the significant increase of the penetrated amount was observed for all seven formulations tested. It is possibly due that the concentration of PGE_1 in the Gelucire systems was formulated at a higher level than in microemulsion systems resulting in a higher concentration gradient for promoting the permeation. Another reason is that the HLB value of some Gelucire systems may be close to a value favorable for the partition of PGE_1 and its alkyl esters into the hairless mouse skin resulting in significantly increasing the permeation rate.

4. Conclusions

In conclusion, the use of Gelucire systems to enhance drug permeation seems to be workable. The optimal HLB value of Gelucire system for a model drug, PGE_1 or its alkyl esters, is a primary consideration in selecting a suitable formulation. Increasing concentration of model drug in this Gelucire system is an effective way to promote the flux of PGE_1 and its alkyl esters as a result of increasing concentration gradient.

Acknowledgements

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Table 1

The formulation components of drug carrier based on Gelucire®

Formulation	Gelucire 44/14	Gelucire 50/02	Gelucire 37/02	Lauroglycol	HLB value	Melting point (℃)
1	0.66	0.00	0.00	0.33	10.6	41-48
2	0.00	0.66	0.00	0.33	2.6	50-56
3	0.00	0.00	0.66	0.33	2.6	36-40
4	0.33	0.33	0.00	0.33	6.6	49-54
5	0.33	0.00	0.33	0.33	6.6	41-48
6	0.00	0.33	0.33	0.33	2.6	46-50
7	0.22	0.22	0.22	0.33	5.3	46-50

Table 2

The flux (nmol/cm^2 per h) and lag time (h) of PGE_1 and its alkyl esters from Gelucire carrier

Formulations	Prostagladin E_1		E_1 Methyl ester		E_1 Ethyl ester		E_1 Isopropyl ester		E_1 Butyl ester	
	Flux	Lag time	Flux	Lag time	Flux	Lag time	Flux	Lag time	Flux	Lag time
1	6.4713[a] (0.3033)	2.53	30.6469 (1.9614)	4.44	25.8797 (0.6695)	6.91	5.3281 (0.1267)	3.45	11.2639 (0.4498)	6.29
2	10.7683 (0.4032)	8.58	6.5262 (0.0618)	0.54	2.3078 (0.0896)	3.31	1.2333 (0.0108)	0.32	1.6822 (0.0395)	14.18
3	9.9912 (0.0907)	3.03	57.3633 (1.2231)	3.23	24.4755 (0.1230)	3.44	15.2175 (0.4152)	3.57	5.4223 (0.2120)	15.4641
4	35.9493 (2.7368)	8.99	12.0812 (0.1451)	1.24	-	-	5.8243 (0.0894)	3.2908	2.3758 (0.1487)	13.00
5	30.3300 (1.6207)	4.96	16.09 (0.2367)	2.60	31.4689 (0.6667)	4.20	8.5093 (0.2388)	2.60	13.6691 (0.4100)	6.69
6	8.2515 (0.6179)	2.42	-	-	-	-	-	-	-	-
7	29.32 (1.4820)	9.87	76.6214 (3.2026)	21.76	33.4468 (1.3763)	21.82	15.4577 (0.4119)	1.51	8.4820 (0.2522)	1.23

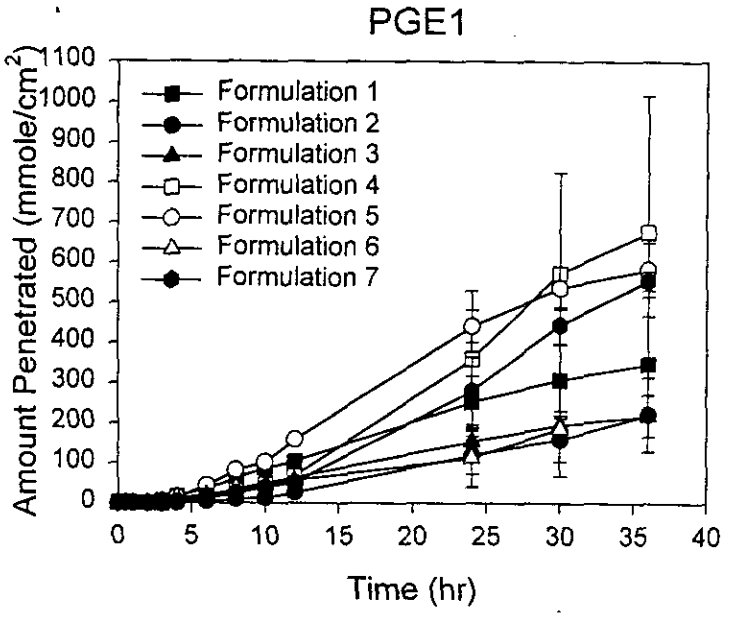
[a]Mean (S.E.); n=6

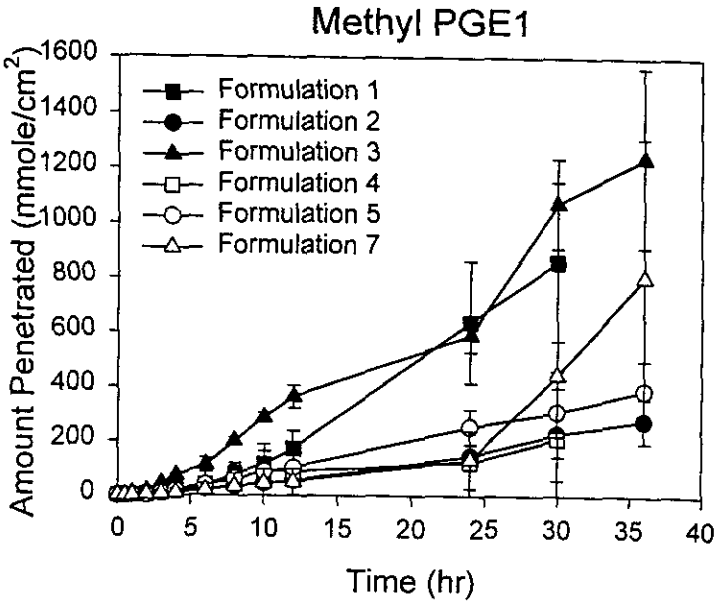
Table 3

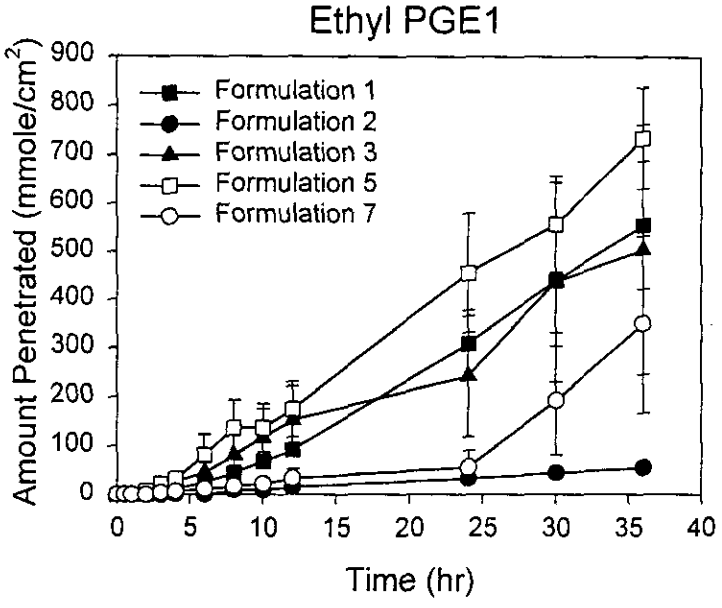
Coefficients of model fit for the effect of Gelucire on the flux of PGE1 and its alkyl ester

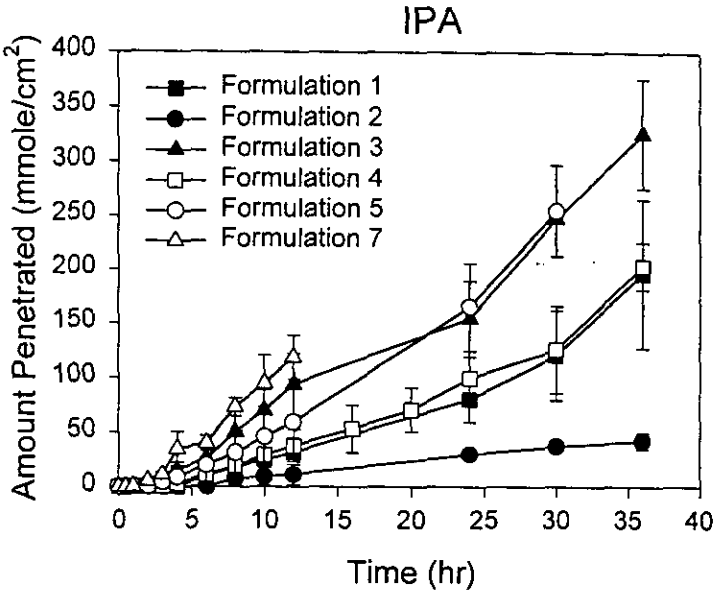
Model drug	Coefficients of model fit					
	X_1	X_2	X_3	X_1X_2	X_1X_3	X_2X_3
Prostagladin E_1	6.52	10.82	10.04	108.26	87.33	-9.58
E_1 Methyl ester	26.93	16.09	58.36	-	-	-
E_1 Ethyl ester	30.53	6.14	29.13	-	-	-
E_1 Isopropyl ester	6.50	3.79	16.06	-	-	-
E_1 Butyl ester	11.87	0.39	7.90	-	-	-

X_1:Gelucire 44/14, X_2: Gelucire 50/02, X_3: Gelucire 37/02









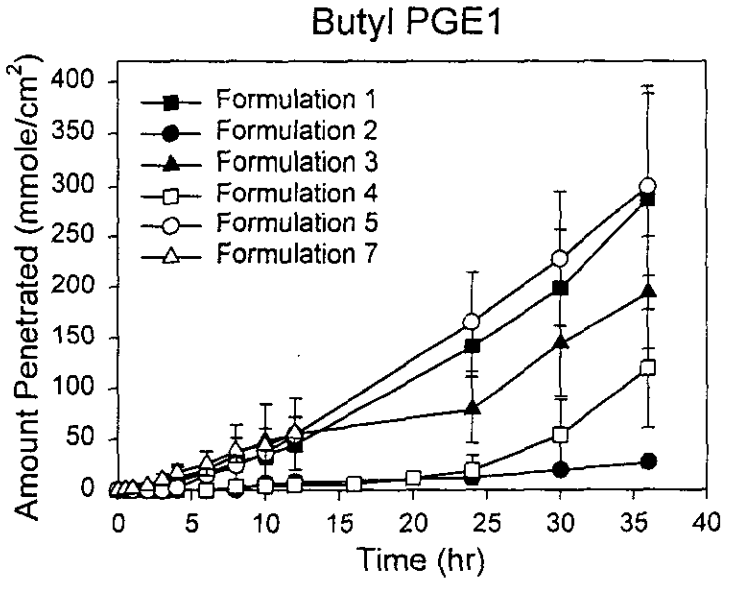


Fig.1 Penetration profiles of PGE1 and its alkyl esters through hairless mouse skin from a variety of Gelucire based formulation

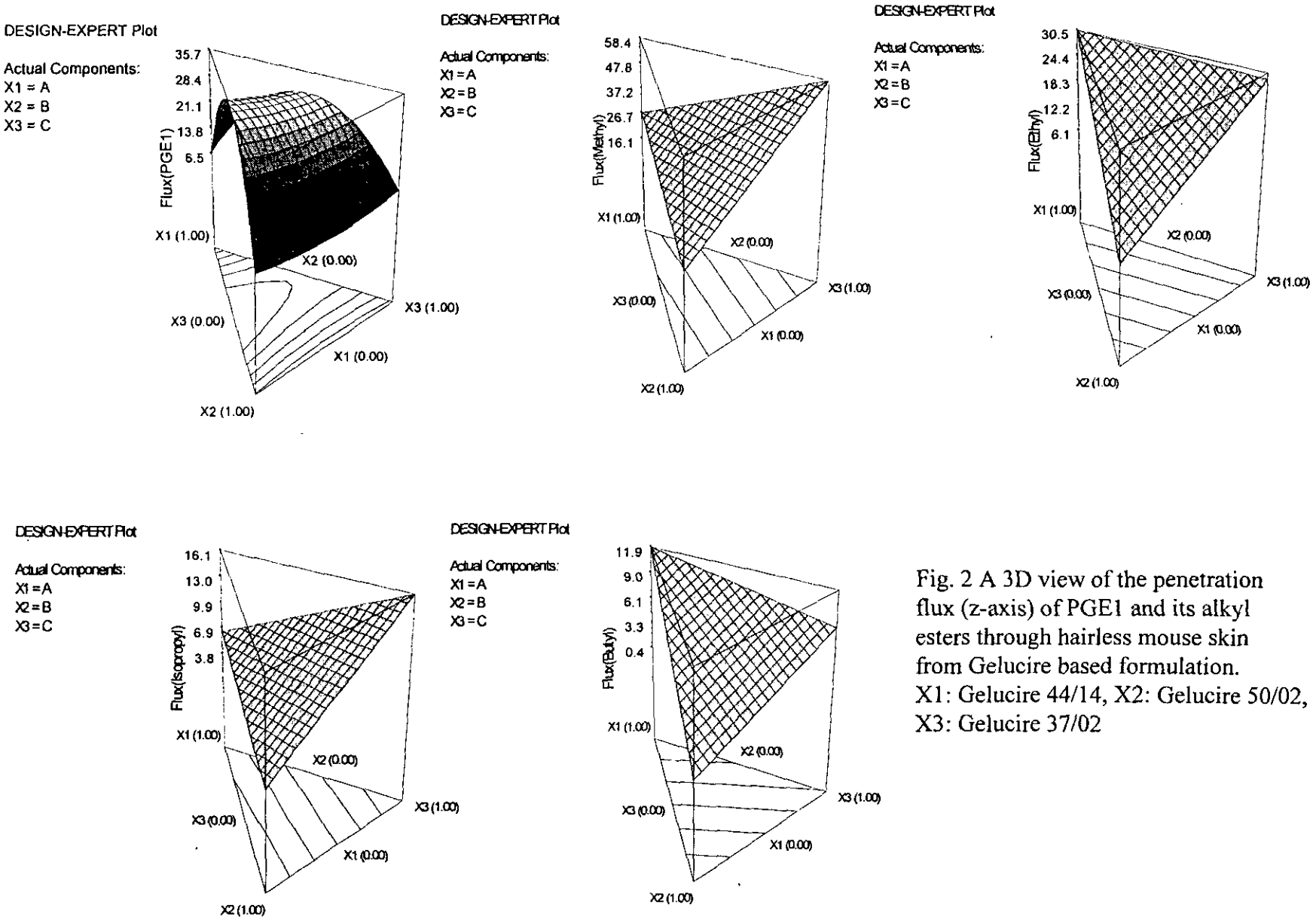


Fig. 2 Three-dimensional plot of PGE1 and alkyl esters

Fig. 2 A 3D view of the penetration flux (z-axis) of PGE1 and its alkyl esters through hairless mouse skin from Gelucire based formulation. X1: Gelucire 44/14, X2: Gelucire 50/02, X3: Gelucire 37/02