

Design and evaluation of a bioadhesive film for transdermal delivery of propranolol hydrochloride

BAZIGHA K. ABDUL RASOOL^{1*}
UDAY S. AZIZ²
OMAR SARHEED³
ALAA A. ABDUL RASOOL⁴

¹ Department of Pharmaceutics and Pharmacy Practice, Dubai Pharmacy College, Dubai, UAE

² Department of Pharmaceutics College of Pharmacy, University of Basra, Basra, Iraq

³ Department of Pharmaceutics, RAK College of Pharmaceutical Sciences Ras Al-Khaimah Medical and Health Sciences University, Ras Al-Khaimah UAE

⁴ College of Pharmacy, University of Baghdad, Baghdad, Iraq

The objective of the study was to develop a suitable transdermal delivery system for propranolol hydrochloride (PPL) *via* employing chitosan as a film former. Drug concentration uniformity, thickness, moisture uptake capacity and skin bioadhesion of the films were characterized. The effects of chitosan and PPL concentration and different penetration enhancers on the release and permeation profiles from the films were investigated. Skin irritation of the candidate film was evaluated. Chitosan film (PPL 2 mg cm⁻², chitosan 2 %, *m/m*, cineol 10 %, *m/m*) was found nonirritant and achieved 88.2 % release after 8 hours in phosphate buffer. Significant high ($p < 0.001$) permeation of PPL through rat skin was obtained using this film compared to the film without enhancer (about 8 times enhancement factor), making it a promising transdermal delivery system for PPL.

Keywords: transdermal delivery, propranolol hydrochloride, chitosan film, enhancers

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Oral administration is one of the most convenient ways that are acceptable for patients, useful and suitable for drugs that are not subjected to intestinal and/or hepatic first-pass metabolism (1). However, there are several shortcomings that should be overcome to achieve efficient drug therapy: the intestinal and/or hepatic first-pass elimination, high variance in bioavailability, difficulty in long-term and rate-regulated absorption and impossibility of arbitrary drug input and its interruption (2). Transdermal route is one of the potential alternative routes that may bypass undesirable characteristics of oral administration. Propranolol, a β -blocker, has short biological half-life and is extensively subjected to hepatic first-pass metabolism (3). Propranolol \cdot HCl (M_r 135, water solubility > 150 mg mL⁻¹) can be a potential candidate for transdermal use. Recently, development of transdermal drug delivery systems (TDDS) has been focused on the for-

* Correspondence; e-mail: bazigharasool@yahoo.com; bazigha_rasool@hotmail.com

mulation part to achieve the desirable constant rate of drug penetration into the systemic circulation. One way to design a TDDS is by employing polymers as matrices or membranes controlling the release of drugs (4). On the other hand, the impermeability of human skin is still a fundamental problem to be overcome for the therapeutic use of TDDS (5). Although many physical approaches such as ultrasound, iontophoresis and electroporation have been proposed to surmount the stratum corneum, the main barrier for transdermal drug absorption (2), chemical approaches such as the utilization of enhancers might be the easiest way to patch preparations. Among many enhancers, terpenes have been extensively investigated for their clinical use as penetration enhancers and are generally regarded as safe (GRAS) by FDA. It is suggested that terpenes increase drug diffusivity in the skin by disrupting the intercellular lipid packing in the horny layer (2). Considering the balance between efficiency and toxicity, several terpenes may be promising enhancers for clinical use (6).

In the present study, a suitable film preparation of propranolol hydrochloride (PPL) has been developed by employing chitosan polymer as a film former, and glycerine as a plasticizer. Furthermore, in order to improve the penetration of PPL, enhancers including terpenes (menthol and cineole), propylene glycol (PG), surfactants [sodium lauryl sulphate (SLS), Tween[®] 80 and benzalkonium chloride (BZK)] and oleic acid (OA) were employed. Physicochemical characterization of the films was done. *In vitro* release and permeation profiles of PPL from film preparations were examined.

EXPERIMENTAL

Materials

Chitosan (medium molecular mass), PPL, HPLC-grade acetonitrile, oleic acid, potassium dihydrogen orthophosphate, disodium hydrogen orthophosphate and phosphate buffer saline (PBS) tablets (pH 7.4) were all purchased from Sigma-Aldrich (UK). Diethyl ether, sodium hydroxide, sodium lauryl sulphate, glycerol and potassium chloride were obtained from BDH Chemicals Ltd. (UK). Silica gel was bought from Merck (Germany). Cineole, menthol and benzalkonium chloride were from Fluka AG (UK). HPLC grade glacial acetic acid was obtained from Fisons Scientific Equipment (UK). Double distilled, de-ionised water was used throughout.

Preparation of PPL-chitosan film formulation

Chitosan film was prepared by dissolving 1 g of chitosan in 100 mL of acetic acid (1 %, *m/V*) at room temperature. Glycerine was incorporated at a concentration of 10 % (*m/m*) of the total dry mass of the polymer, as plasticizer. The resultant mixture was left under stirring for 1 h until a viscous chitosan gel was formed. PPL at a predetermined loading (mg cm^{-2}) and different enhancer concentrations (% *m/m*) was dissolved and added to the gel. The viscous gel was left to stand until all air bubbles had disappeared. The final solution was spread on a clean dry glass plate in a dust-free atmosphere and dried at 50 °C for 24 h or at 37 °C for 48 h. The dry film obtained was peeled off, wrapped in aluminium foil and stored in a well closed container at room temperature until evaluation (7).

Film characterization

Film thickness. – The thickness of films was measured at three different spots using a micrometer (Mitutoyo Co., Japan) and mean values were calculated (Table I).

Determination of drug in the film. – A known mass of chitosan (1 g) film was dissolved in acetic acid (2 %, *m/V*) up to 100 mL. Sample was filtered through membrane filter 0.45 μm . The concentration of PPL was measured at 290 nm by Cintra 5, UV spectrophotometer (GBC Scientific equipment, Australia). Measurements were taken against a blank solution, which was prepared by repeating the former procedure on blank film (chitosan film without drug).

Moisture uptake. – After keeping them (4 cm^2) in desiccator with silica gel for 24 hours, the films were weighed. The films were then transferred to another desiccator containing saturated NaCl solution (relative humidity 75 %) at 25 °C. After equilibrium was achieved, the films were taken out and weighed. Moisture uptake capacity (MUC) was calculated (8) (Table I).

In vitro bioadhesive strength measurement. – The bioadhesive strength of PPL films was evaluated by employing a method described by Peh and Wong (7) using a texture analyzer (TA.XT2, Stable Micro System, UK) and adjusted automatically by the same computer software.

In vitro release study

The release of PPL was tested with a paddle type USP dissolution apparatus (Copley Scientific, UK) at 37 °C. The film was cut into a circle with an area of 3.14 cm^2 and sandwiched between double-sided sieves (as a weight). The film with the weight was placed in a glass vessel filled with 500 mL of phosphate buffer (pH 7.4). The rotating speed of the paddle was 50 rpm. The sample solutions (5 mL) were removed through a syringe filter at predetermined time intervals. The withdrawn volume was replaced by the same volume of phosphate buffer to maintain its constant volume and sink conditions (9). The concentration of PPL was determined at 290 nm.

In vitro skin permeation

Preparation of skin membranes. – The study was approved by the Research Ethics Committee of the College of Pharmacy, University of Baghdad, Iraq.

Male Wistar rats weighing approximately 150–200 g were sacrificed by ether inhalation. The abdominal skin was lightly shaved with an electrical clipper, defatted by wiping it with a cotton tip soaked in diethyl ether and kept in phosphate buffer pH 7.4 for 1 h. The skin was either used immediately or frozen (–20 °C) until ready for use.

PPL permeation study. – Rat skin obtained previously was mounted in Franz diffusion cells (Transdermal tester HDT 10, Copley Scientific, UK). The permeation area of the cell was 3.14 cm^2 . The donor compartment was left open and wrapped with cellophane to prevent film contamination from the atmosphere; the receptor chamber was filled with 17.7 mL of phosphate buffer pH 7.4, magnetically stirred at 600 rpm and ther-

mostated at 37 °C. At predetermined periods of time, samples were taken from the receptor solution and analyzed for PPL content by HPLC.

The HPLC system consisted of a model LC-6A HPLC pump (Shimadzu, Japan) and a UV detector (SPD-6A, Shimadzu) set at 289 nm. Analytical column was Inertsil ODS-3 (C18, 250 × 4.6 mm, GL Sciences, Japan). The mobile phase was CH₃CN (20 mmol L⁻¹) : NH₄Cl (0.05 %) phosphoric acid (1:1:1, V/V/V). The flow rate was set at 1 mL min⁻¹ (8). Each point on the standard curve was mean ± SD of three readings. RSD for standard curves ranged from 0.1 to 18.7 %, and R² was higher than 0.998.

Data of the skin permeation study was analyzed using two kinetic models, *viz.* the first-order rate kinetics where the rate of drug permeation is concentration-dependent and Higuchi model (10) which describes the release of drugs from an insoluble matrix where the cumulative amount of the permeated drug per unit area is proportional to the square root of time as follows:

$$Q = 2c_o \left(\frac{Dt}{\pi} \right)^{1/2}$$

where *c* is the initial drug concentration in the donor compartment, *Q* is the cumulative amount of the drug released at time, *t* and *D* is the diffusion coefficient.

Primary skin irritation

Three preparations were evaluated for their skin irritation, namely, blank film (chitosan, 2 %, *m/m*), control film (PPL, 2 mg cm⁻², chitosan, 2 %, *m/m*) and the candidate film (PPL, 2 mg cm⁻², chitosan, 2 %, *m/m* cineole, 10 %, *m/m*) in comparison with histamine (a substance of known irritancy for the purpose of calibration). The test was performed according to the reported method (11).

Statistical analysis

Results are expressed as the mean ± SD of at least three experiments. Analysis of variance (ANOVA) was used to test the statistical significance of the differences between groups.

RESULTS AND DISCUSSION

Film properties

Estimation of the drug concentration at different points of chitosan films indicated uniform distribution of PPL throughout the film of 96.1–100.7 % (Table I and II). Chitosan concentration significantly (*p* < 0.05) increased the film thickness and decreased the MUC. However, PPL loading tended to thicken the film and increased the moisture uptake significantly (*p* < 0.05), except for 3 mg cm⁻², PPL loading for which moisture uptake were capacity changed slightly (Table I).

Table I. Physicochemical properties of PPL film formulations

Chitosan (% <i>m/m</i>)	PPL (mg cm ⁻²)	Drug distribution (%) ^a	Thickness (mm) ^a	MUC (%) ^a
1	2	100.4 ± 2.5	0.30 ± 0.10	20.1 ± 1.3
2	1	97.7 ± 1.0	0.36 ± 0.05	13.4 ± 3.2
2	2	99.6 ± 3.3	0.50 ± 0.09	18.9 ± 5.4
2	3	100.5 ± 8.5	0.61 ± 0.08	19.6 ± 3.4
3	2	98.6 ± 5.5	0.60 ± 0.12	12.5 ± 4.8
4	2	98.9 ± 6.9	0.70 ± 0.06	8.80 ± 1.9

^a Mean ± SD, *n* = 3.

Enhancers showed significant increase ($p < 0.05$) in MUC compared to the control film (Table II). Cineol 10 % *m/m*, showed the highest increment in film MUC. The reason for this increment still needs to be investigated. However, propylene glycol can absorb moisture from the environment because of its humectant ability.

In vitro bioadhesion strength

Table III presents the data of adhesiveness and work of adhesion 12 obtained from the texture analyzer for different chitosan films: blank film (chitosan 2 % *m/m*), control film (PPL 2 mg cm⁻², chitosan 2 % *m/m*) and the candidate film (PPL 2 mg cm⁻², chitosan 2 % *m/m*, cineole 10 % *m/m*). There were no significant differences in either adhesiveness or work of adhesion among the tested chitosan films. However, the blank film showed the highest adhesiveness and work of adhesion. All the prepared films were applied on excised rat skin *in vitro* for 8 hours during permeation studies and it was found that they firmly attached to the skin, indicating good adhesion properties for clinical use.

Release study

PPL release was found to be affected by chitosan concentration in the film. It decreased significantly ($p < 0.05$) as the concentration of chitosan, film forming agent, increased in the film (Fig. 1a). The best drug release was obtained with 2 % (*m/m*) of chitosan which was 51.2 % at the end of the run (after 8 hours). This effect is the same as that obtained by Annuaikit *et al.* (8), who studied the *in vitro* release profile of PPL from transdermal films containing ethyl cellulose and polyvinyl pyrrolidone as film former.

The effect of PPL concentration on its release from chitosan film was studied by employing three concentrations (1, 2 and 3 mg cm⁻²) in chitosan 2 % (*m/m*) as the film former. It was found that increasing the loading of PPL in the film from 1 to 2 mg cm⁻² resulted in a significant increase ($p < 0.05$) of total drug release percentage from 33.4 % to 51.2 %, respectively (Fig. 1b). Other researchers also reported that increasing the amount of PPL dispersed in the film would increase membrane porosity, leading to a greater, release of the drug (8).

However, the results could be explained on the basis that increasing PPL concentration enhanced the film MUC (Table I) and consequently increased the PPL solubility and its release from the film.

Table II. Physicochemical properties of PPL film formulations with different enhancers

Enhancers (% <i>m/m</i>)	PPL content (%) ^a	Thickness (mm) ^a	MUC (%) ^a
Control film 2 mg cm ⁻²	99.6 ± 3.3 ^b	0.50 ± 0.09	18.9 ± 5.4
PG			
5	98.8 ± 6.1	0.53 ± 0.05	19.7 ± 2.3
10	100.3 ± 2.9	0.60 ± 0.02	23.5 ± 1.1
15	96.6 ± 9.1	0.64 ± 0.03	23.1 ± 2.9
Menthol			
5	97.9 ± 1.3	0.43 ± 0.09	20.1 ± 8.1
10	99.5 ± 2.3	0.53 ± 0.06	20.1 ± 2.5
Cineole			
5	99.6 ± 4.5	0.50 ± 0.31	25.6 ± 2.6
10	98.7 ± 4.9	0.60 ± 0.07	26.8 ± 1.9
PG 10 % + cineole			
5	100.7 ± 3.1	0.55 ± 0.02	21.1 ± 1.3
10	96.3 ± 1.2	0.53 ± 0.02	24.1 ± 1.6
PG 10 % + menthol			
5	96.5 ± 6.5	0.60 ± 0.03	20.4 ± 6.3
10	99.1 ± 7.3	0.53 ± 0.08	24.0 ± 5.4
SLS			
2.5	98.1 ± 3.2	0.60 ± 0.11	19.1 ± 4.8
5	100.1 ± 3.1	0.63 ± 0.12	19.9 ± 3.2
BZK			
1	99.5 ± 6.4	0.51 ± 0.16	20.2 ± 4.7
2.5	96.9 ± 2.4	0.53 ± 0.06	23.1 ± 7.3
5	97.5 ± 3.1	0.53 ± 0.05	24.9 ± 1.4
Tween [®] 80			
1	99.9 ± 1.6	0.51 ± 0.34	21.5 ± 2.6
2.5	100.0 ± 2.9	0.52 ± 0.13	23.1 ± 3.1
5	96.1 ± 1.1	0.52 ± 0.12	24.9 ± 2.8
Oleic acid			
1	96.7 ± 1.2	0.50 ± 0.08	20.1 ± 1.8
5	98.8 ± 0.8	0.51 ± 0.09	25.1 ± 2.1

^a Mean ± SD, *n* = 3.

^b 2 mg PPL cm⁻².

MUC moisture uptake capacity.

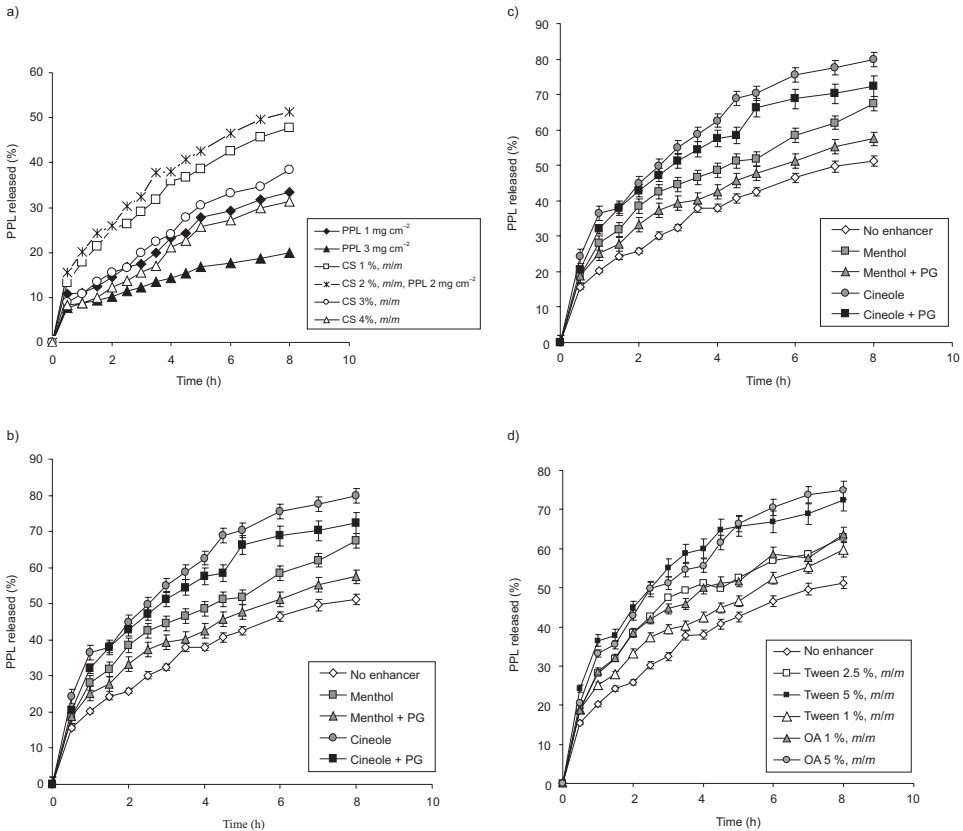


Fig. 1. Effect of: a) chitosan and PPL concentrations, b) terpenes (5%, *m/m*), c) terpenes (10%, *m/m*), d) Tween 80 and oleic acid on PPL release profile from chitosan film preparations in phosphate buffer (pH 7.4). Results are expressed as the mean with the bars showing SD values of three different experiments.

The increment of propylene glycol from 5 to 10% (*m/m*) in the chitosan film significantly enhanced ($p < 0.05$) the *in vitro* release of PPL. 65.0% and 70.4% of PPL was released during 8 h from the films containing 5 and 10% PG, respectively, compared to 51.2% released from the film without enhancer. However, a significant decrease in PPL release (31.0%) was obtained with propylene glycol 15% (*m/m*). Larger amount of water absorbed into the film by propylene glycol would contribute to the more rapid release of the drug from the film. On the other hand, the same humectants' property at higher concentrations may increase the viscosity of the film, resulting in slow drug release (13).

Moreover, addition of terpenes at a concentration of 5% (*m/m*) tended to a significant increase ($p < 0.05$) in PPL release profile while terpenes 10% (*m/m*) showed even

higher increase, as shown in Figs. 1b and c. Hence, the increase in PPL release could be correlated with the increase in MUC as enhancer concentration increased (Table II).

PPL *in vitro* release after 8 h using SLS 2.5 and 5 % (*m/m*) was 36.4 % and 42.0 %, respectively, compared to chitosan film without enhancer (51.2 %). The decrease in PPL release might be attributed to the ability of the anionic surfactant, SLS, to form complexes with the cationic drug *via* its negative charge. The presumed SLS-PPL complex may show less solubility than the free PPL and consequently less release into the dissolution medium (13). Another possibility for the retarding effect on PPL release is the increasing film viscosity with increasing SLS concentration; however, further investigations are required to explain this effect.

Benzalkonium chloride (BZK) was used to check the effect of cationic surfactants on PPL release. Concentrations of 2.5 and 5 % BZK showed an increase in the drug release (56.4 and 60.6 %, respectively), after 8 hours compared to chitosan film without enhancer (51.2 %). Wells and Parrott (14) suggested that this surfactant may lower the interfacial tension between the product and the dissolution fluid; hence, it may contribute to the increase in drug release from the prepared film.

In contrast, the concentration of the non-ionic surfactant, Tween 80, caused significant ($p < 0.05$) PPL release from chitosan films (in the order: 5 > 2.5 > 1 %), as shown in Fig. 1. This is probably due to the reduction in surface tension of the dissolution medium, which allows more rapid release of PPL from the film. Moreover, the addition of oleic acid (OA) of 1 and 5 % (*m/m*) led to a significant increase in the release of PPL ($p < 0.05$ and $p < 0.001$ respectively, Fig. 1d). The increase in release could be correlated to the increase in MUC of the film matrix as a function of OA concentration.

In vitro skin permeation

Regression analysis of the obtained results showed that the Higuchi model gave the highest value of R^2 with a significant difference ($p < 0.05$) compared to other kinetic models. Therefore, the Higuchi model was found to be a most suitable model to describe the permeation kinetics of PPL from the film preparations examined in the present study. The Higuchi rate constant was calculated and is summarized in Table IV.

Table III. Bioadhesive strength of chitosan films

Sample	Adhesiveness (g) ^a	Work of adhesion (g cm) ^a
Blank film (2 %, <i>m/m</i> chitosan)	63.6 ± 5.6	12.9 ± 9.1
Control film (2 mg cm ⁻² PPL, 2 %, <i>m/m</i> chitosan)	62.5 ± 4.3	12.6 ± 3.2
Candidate film (PPL 2 mg cm ⁻² , chitosan 2 % <i>m/m</i> , cineole 10 %, <i>m/m</i>)	60.6 ± 2.9	12.5 ± 2.3

^a Mean ± SD, $n = 5$.

Work of adhesion is defined as of the attraction between phases per unit area being in contact with each other (g cm) (15).

Table IV. Higuchi's permeation rate constant (k) \pm SD and coefficient of determination (R^2) of the PPL-chitosan film preparations

Formula	k ($\mu\text{g h}^{-1/2}$) ^a	R^2
PPL (1 mg cm ⁻²)	47.73 \pm 1.88	0.892
PPL (2 mg cm ⁻² , control)	97.56 \pm 2.65	0.911
PG (5 %)	213.25 \pm 3.80	0.979
PG (10 %)	107.75 \pm 1.56	0.912
PG (15 %)	87.04 \pm 5.98	0.839
Cineol (5 %)	226.61 \pm 3.98	0.998
Cineole (5 % + PG 10 %)	230.15 \pm 1.88	0.991
Menthol (5 %)	130.03 \pm 1.27	0.985
Menthol (5 % + PG 10 %)	164.05 \pm 8.76	0.989
Cineol (10 %)	379.92 \pm 4.23	0.996
Cineole (10 % + PG 10 %)	296.02 \pm 1.21	0.932
Menthol (10 %)	175.21 \pm 6.61	0.837
Menthol (10 % + PG 10 %)	280.33 \pm 1.32	0.902
SLS (1 %)	185.91 \pm 1.72	0.994
SLS (2.5 %)	221.49 \pm 4.32	0.972
SLS (5 %)	239.71 \pm 3.51	0.990
Tween 80 (5 %)	273.19 \pm 8.75	0.997
Tween 80 (2.5 %)	215.45 \pm 7.97	0.967
Tween 80 (1 %)	182.91 \pm 4.98	0.932
BZK (1 %)	114.75 \pm 6.94	0.981
BZK (2.5 %)	134.28 \pm 1.39	0.948
BZK (5 %)	246.21 \pm 7.56	0.938
OA (1 %)	114.02 \pm 1.93	0.897
OA (5 %)	310.33 \pm 7.95	0.990

^a Mean \pm SD, $n = 3$.

Skin permeation of PPL significantly increased ($p < 0.05$) *via* increasing the loading concentration of PPL in the prepared chitosan films (Table IV). This may be due to the fact that the loading of PPL of 2 mg cm⁻² tended to thicken the film and significantly enhance the capacity of moisture uptake.

Results showed that PG 5 % (m/m) significantly increased ($p < 0.05$) the permeation rate constant of PPL (Table IV). However, when the concentration of PG increased to 10 and 15 % (m/m) in the film, a non-significant decrease in the permeation profile was observed. For PG 5 % (m/m), the enhancement is possibly due to the increase in the solubilizing ability of the aqueous site in the stratum corneum considered to be the main probable mechanism of increasing skin permeation for PG.

Chitosan films containing terpenes 10 % generally gave significantly higher ($p < 0.05$) permeation enhancement of PPL than 5 % concentrations, which is acceptable since the effect of permeation enhancers often depends on their concentration.

Terpenes significantly increased penetration of PPL in the following order: cineole and PG > menthol and PG > menthol 10 %. However, a highly significant effect ($p < 0.001$) was obtained with cineole 10 % (m/m) alone (Table IV). The possible mechanism for cineole having the highest enhancing property among other terpenes, as suggested by Barry and Williams (15), is that cineole would interact with the lipid component of the stratum corneum more easily because its boiling point was lower than that of other terpenes and the low boiling point is an indication of weak cohesiveness or self association, which might explain why cineole showed the highest enhancing effect on skin permeation of PPL.

Although the increment in SLS concentrations did not significantly enhance *in vitro* release of PPL, a raise in SLS concentration to 5 % (m/m) resulted in a significant increase ($p < 0.05$) in PPL rat skin permeation (Table IV). It has been reported that an anionic surfactant, like SLS, can penetrate and interact strongly with the skin, producing considerable alterations in the barrier properties. For the non-ionic surfactant Tween 80, the highest permeation was observed with the film containing a concentration of 5 % (m/m) ($p < 0.05$) (Table IV). One of the possible mechanisms for the non-ionic surfactants enhancement is that surfactant may penetrate into the intercellular region of the stratum corneum, increasing fluidity and eventually solubilizing and extracting lipid components.

BZK produced the highest permeation at a concentration of 5 % ($p < 0.05$) (Table IV). High concentration of BZK caused extensive damage to the skin and consequently increased the PPL permeation profile.

On the other hand, OA 1 % seems to have greater effect on permeation of PPL and the permeation is significantly increased ($p < 0.05$) compared to OA 5 %. This may be due to slowed down drug partitioning into the stratum corneum using a large amount of OA. Previous studies have reported that OA-induced skin penetration enhancement results from a mechanism involving both stratum corneum lipid fluidization and lipid phase separation, with the latter likely to predominate.

CONCLUSIONS

To avoid extensive first-pass elimination and achieve the desirable transdermal penetration rate of PPL, we have prepared polymeric film formulations for transdermal use by employing chitosan as a film former, glycerin as a plasticizer and different types of penetration enhancers. The film containing propranolol · HCl 2 mg cm⁻², chitosan 2 % and cineole 10 % successfully improved the skin penetration of PPL. Also, the candidate film preparation was non irritant to the skin and was quite promising for safely achieving the desirable systemic absorption of PPL.

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S A Ž E T A K

Dizajniranje i vrednovanje bioadhezijskog filma za transdermalnu isporuku propranolol hidroklorida

BAZIGHA K. ABDUL RASOOL, UDAY S. AZIZ, OMAR SARHEED i ALAA A. ABDUL RASOOL

Cilj rada bio je razvoj pogodnog transdermalnog sustava na bazi kitozana za isporuku propranolol hidroklorida (PPL). Svim pripravcima ispitana je jednoličnost udjela lijeka, debljina, sposobnost vlaženja i bioadhezivnost na kožu. Ispitivan je i utjecaj kitozana, koncentracije PPL-a i sredstva za povećanje permeacije na oslobađanje i permeacijski profil, te potencijalni iritacijski učinak na kožu. Iz kitozanskog filma (PPL 2 mg cm⁻², 2 %, *m/m*, kitozana i 10 %, *m/m*, cineola), koji nije djelovao iritabilno, postignuto je 88,2 % oslobađanja nakon 8 sati u fosfatnom puferu. S ovim pripravkom postignuta je i vrlo značajna ($p < 0,001$) permeacija PPL kroz kožu štakora, oko osam puta veća u usporedbi s filmom bez sredstva za povećanje permeacije. Pripravak bi se mogao upotrijebiti za transdermalnu isporuku PPL.

Ključne riječi: transdermalna isporuka, propranolol hidroklorid, kitozanski film, sredstvo za povećanje permeacije