DOI: 10.15825/1995-1191-2025-1-188-197

TRANSCUTANEOUS PERMEATION ENHANCER COMPLEX FOR POLYMER-BASED TRANSDERMAL PATCHES

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Selecting a permeation enhancer complex (PEC) for inclusion in a matrix-type transdermal patch (TP) is a primary task in creating a new dosage form with percutaneous administration. **Objective:** to develop a biologically safe PEC capable of regulating percutaneous diffusion of low-molecular-weight drugs from the polyacrylate matrix of a TP and without causing adverse skin reactions. **Materials and methods.** The PEC contained apricot kernel oil, dioctyl sodium sulfosuccinate, dihydroquercetin and alpha-tocopherol acetate – substances that have a good impact on the functional properties of polymer-based TPs. Low-molecular alcohol-soluble drugs (chlorpropamide, caffeine and sodium benzoate and lidocaine hydrochloride) used to treat diseases of various etiologies were used as active ingredients. *In vitro* studies of percutaneous drug delivery were carried out on male Chinchilla rabbits in Franz glass diffusion cells using a drug diffusion analyzer. Using spectrophotometry and high-performance liquid chromatography, concentrations of drugs in aqueous solutions and in the blood plasma of the laboratory animals were measured. The irritant effect of the lidocaine-loaded transdermal polymeric matrix was tested on sexually mature young male New Zealand White rabbits. **Results.** When PEC was introduced into the polymer matrix film, percutaneous diffusion of the drugs increased significantly from 2.1 ± 0.4 to 9.2 ± 1.4 mg over 24 hours of experiment for the chlorpropamide-loaded TP and from 9.2 ± 1.2 to 35.2 ± 7.5 mg for the caffeine-loaded TP. Additionally, there was a 1.7- and 2.9-fold decrease and a 2.3- and 2.7-fold increase in the time to reach a constant drug concentration in blood for the chlorpropamide- and caffeine-containing TPs, respectively. Using the lidocaine- and chlorpropamide-loaded TPs, it was shown that the presence of PEC in the polymer matrix film causes no skin irritation and that the shelf life of the transdermal form increases from 1 to 3 years. **Conclusion.** Introduction of the proposed PEC into the polymeric matrixes of TPs enhanced percutaneous diffusion of the drugs, reduced skin irritation from the TP components, and increased the shelf life of the finished dosage forms.

Keywords: transdermal patches, polymer matrix film, transcutaneous permeation enhancers, chlorpropamide, caffeine and sodium benzoate, lidocaine hydrochloride.

INTRODUCTION

Transdermal patches (TPs) are an external dosage form designed for the controlled delivery of active substances into the systemic circulation by passive diffusion through intact skin [1]. They are widely used in modern medicine, particularly for managing chronic conditions. Their ease of application and the straightforward manufacturing process of polymeric matrix systems – especially the drug-in-adhesive subtype – make them a preferred choice for both manufacturers and consumers [2].

The composition of a TP is carefully designed to maintain a therapeutic drug concentration in the bloodstream throughout its duration of action [3–5]. Most commercially available TPs utilize polymeric adhesive matrices, which not only ensure skin contact but also serve as a reservoir for the active drug and excipients. The polymer matrix must be biocompatible, avoiding local irritation or allergic reactions. The most suitable adhesives include polysiloxane polymers, polyisobutylene, and acrylic polymers [3]. Among acrylic adhesives, DURO-TAK and GELVA, manufactured by Henkel (Germany) [6], are the most widely used.

In addition to form-forming components, permeation enhancers are incorporated into the TP matrix to facilitate drug penetration through the skin. These enhancers include various chemical compounds such as alcohols, monoterpenes, sulfoxides, phospholipids, fatty acids and their esters, surfactants [7–9]. All excipients used in a TP must be carefully selected to minimize the risk of toxicity, irritation, allergic reactions, or interactions with the active drug.

When developing TP formulations, multiple excipients are often combined to enhance and complement each other's effects. This approach helps maintain the stability and functionality of the active drug over extended storage periods while also reducing potential skin irritation caused by the TP components [8].

This study aimed to develop a biologically safe permeation enhancer complex (PEC) that effectively regu-

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lates percutaneous diffusion of low-molecular-weight drugs from the polyacrylate matrix of a TP while minimizing the risk of adverse skin reactions.

MATERIALS AND METHODS

Materials

The following drug substances were used as active substances in the TP: hypoglycemic agent chlorpropamide (MM 276.74) (Dipharma Francis, Spain), psychostimulant caffeine and sodium benzoate (MM 338.29) (Shandong Xinhua Pharmaceutical Co. Ltd., China), and local anesthetic lidocaine hydrochloride (MM 234.34) (Peptek, Russia).

For the manufacture of laboratory samples of TPs, we used the acrylic adhesive Duro-Tak 87-4287 (Henkel Chemical Company, Germany). This adhesive forms a strong bond with the skin, facilitates drug release, and can be easily removed after application. Its low shear resistance eliminates the need for plasticizers, and it has a viscosity of 8000 mPa·s [10].

To enhance the functional properties of the polymeric TP, a complex of excipients was incorporated into the polymer matrix, including apricot kernel oil (Desert Whale Jojoba Company Ltd., USA), alpha-tocopherol acetate (BASF SE, Germany), dihydroquercetin (Research and Production Company 'FLAVIT'), and dioctyl sodium sulfosuccinate (Sigma, USA).

Table 1 shows the ranges of variation of the content of permeation enhancers in the polymer matrix film of TP.

Drug substances intended for incorporation into the polymer matrix film were pre-dissolved in 95% ethyl alcohol (RFK, Russia) to ensure uniform distribution. Laboratory samples of TPs loaded with chlorpropamide, caffeine, and lidocaine were fabricated using high-quality film materials: Cotran 9715 film (3M, USA) as the substrate and Scotchpack 1022 PET film (3M, USA) as the protective layer. For primary packaging, sachets from Proflex (Russia) were utilized.

Table 1

Composition of the polymer matrix film of transdermal patches

S/N	Matrix components	Mass, %
1	Alpha-tocopherol acetate	0.02–0.1
2	Dihydroquercetin	0.04–0.14
3	Dioctyl sodium sulfosuccinate	0.06–0.14
4	Apricot kernel oil	4.0–9.6
5	Acrylic adhesive	≤100%

Equipment

Quantification of drug concentrations in aqueous solutions and blood plasma of laboratory animals was performed using spectrophotometric analysis (UV-2600 spectrophotometer, Shimadzu, Japan) and high-performance liquid chromatography (HPLC) on an Agilent 1260 Infinity chromatograph (Agilent Technologies, USA). The HPLC system was equipped with a G1311A pump, a G1314B diode array detector, a column thermostat, and ChemStation software (Agilent, USA).

Drug diffusion studies were conducted using a HDT 1000 diffusion analyzer (Copley Scientific Ltd., UK). Additional laboratory equipment included an Elmasonic S 60 H ultrasonic bath (Elma, Germany), GH-200 analytical scales (AND, Japan), a Rotina 38R centrifuge (Hettich, Germany), and a Simplicity water purification system (Millipore, Germany).

Research algorithm

The paper presents and experimentally validates an algorithm for developing safe and effective polymeric TPs incorporating a complex of low-molecular-weight drug permeation enhancers (Fig.). The proposed algo-

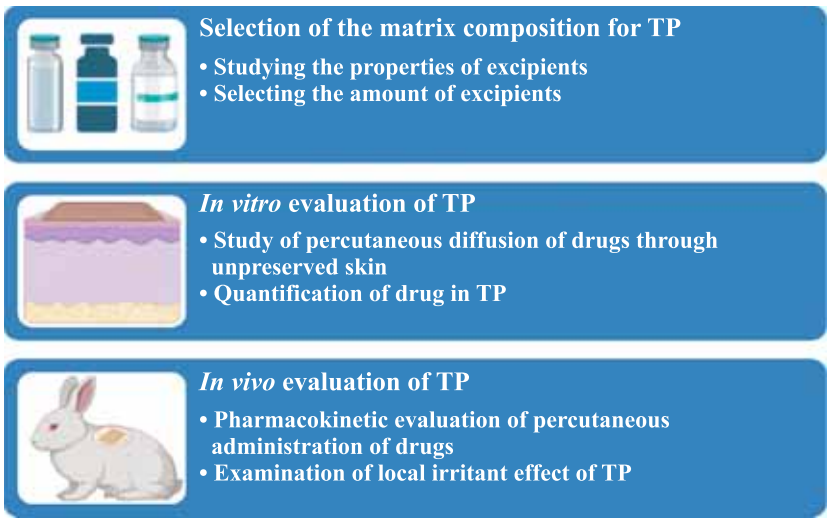

Fig. Algorithm for creating transdermal patches with a permeation enhancer complex. TP, transdermal patch

rithm consists of three key stages: theoretical analysis, *in vitro* studies, and *in vivo* evaluations. A comprehensive laboratory study was conducted for each drug substance.

Laboratory animals

The studies were conducted on male Chinchilla rabbits (3.5–4.0 kg) and New Zealand White rabbits (2.0–3.7 kg), obtained from the laboratory animal nursery of KrolInfo LLC. The producer provided a veterinary certificate confirming the animals' health status. All experimental animals were specifically bred for research purposes and had not previously participated in any studies.

All procedures were designed to minimize discomfort and adhered to ethical guidelines, including the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (ETS 123, Strasbourg, 1986). The study was also conducted in compliance with Russian regulations: GOST 33215-2014 (Guidelines for the Maintenance and Care of Laboratory Animals, Rules for Equipping Premises and Organizing Procedures) and GOST 33216-2014 (Guidelines for Housing and Care of Laboratory Animals, Rules for the Maintenance and Care of Laboratory Rodents and Rabbits).

In vitro studies of transdermal drug delivery

The diffusion of drugs through unpreserved rabbit skin from a TP with a polymer matrix containing a PEC and a control TP without enhancers was studied using glass Franz diffusion cells and a drug diffusion analyzer. The receiving chamber of the diffusion cells was filled with degassed 0.9% sodium chloride solution, which was prepared using an ultrasonic bath. After 24 hours of incubation at 32 °C, samples were collected from the receiving chamber and analyzed.

Quantification of chlorpropamide in aqueous solutions was performed using HPLC under the following conditions: column NF28948 (150 mm length, 4.6 mm inner diameter 5 μm grain size), mobile phase acetonitrile : water : trifluoroacetic acid 250 : 750 : 1, isocratic elution mode, mobile phase flow rate 0.8 mL/min, column thermostat temperature 25 °C, sample volume 5 μL, detection wavelength 240 nm, retention time 2.3 min.

The optical density of aqueous caffeine solutions was determined using spectrophotometric analysis at a wavelength of 273 ± 2 nm, corresponding to the maximum absorption of the substance.

Quantification of lidocaine in aqueous solutions was performed using HPLC under the following conditions: Column: Hypersil BDS-C18 (length 150 mm, inner diameter 4.6 mm, grain size 5 μm), mobile phase: acetonitrile : (water + 0.05 M KH_2PO_4 + trifluoroacetic acid) 30 : 70, isocratic elution mode, mobile phase flow rate 1 mL/min, column thermostat temperature 25 °C, sample volume 20 μL, detection wavelength: 254 nm, retention time 3.8 min.

Determination of drug concentration in blood plasma of laboratory animals in transdermal administration *in vivo*

The concentration of drugs released from the TP into blood plasma was evaluated in male Chinchilla rabbits. The animals were divided into two groups of three each. The first group received a PEC-containing TP applied to a shaved area on the back near the neck for 24 hours, while the second group received a PEC-free TP under the same conditions.

Blood samples were collected from the marginal ear vein into tubes containing 3.8% sodium citrate solution (RENAM, Russia) before TP application and at specific time points: 1, 2, 4, 6, 12, 15, 18, 20, and 24 hours after application. Blood plasma was obtained by centrifugation at 1500 rpm for 10 minutes. Before chromatographic analysis, the samples were filtered through a polytetrafluoroethylene membrane with a 0.45 μm pore size (Supelco, USA).

Drug concentrations in rabbit blood plasma were determined using HPLC.

Quantitative analysis of chlorpropamide in plasma was performed under the following conditions: a Diabond C16T column (Elsico, Russia) was used, with a mobile phase consisting of acetonitrile (Merck, Germany) and a 0.03% aqueous phosphoric acid solution (Merck, Germany) in a gradient elution mode. The mobile phase flow rate was set at 1 mL/min, with the column thermostat maintained at 25 °C. The injection volume was 5 μL, and detection was carried out at a wavelength of 240 nm. The retention time for chlorpropamide was 2.3 minutes.

Quantification of caffeine and sodium benzoate (CSB) in rabbit blood plasma during TP application was performed using HPLC under the following conditions: a Hypersil ODS C18 column (Elsico, Russia) was used with a mobile phase consisting of acetonitrile (Merck, Germany) and a 0.03% aqueous phosphoric acid solution (Merck, Germany) in a gradient elution mode. The mobile phase flow rate was set at 1 mL/min, and the column thermostat was maintained at 25 °C. The injection volume was 5 μL, with detection carried out at a wavelength of 254 nm.

Assessment of local irritant effect when using a transdermal patch

The local irritant effect of a lidocaine-loaded TP was assessed in accordance with GOST ISO 1099-10-2011 Medical Devices – Evaluation of the Biological Action of Medical Devices, Part 10: Studies of Irritant and Sensitizing Effects.

Rabbits were divided into two groups of three animals each. A lidocaine-loaded TP (2.5 × 4.0 cm^2) with a po-

lymer matrix was applied to a shaved skin area on both sides of the back and secured with a bandage. The first group received a PEC-containing TP, while the second received a PEC-free TP. After 24 hours, the patches were removed, and skin condition was evaluated at 1, 24, 48, and 72 hours post-exposure.

Quantification of drug content in laboratory samples of transdermal patches

To determine the chlorpropamide content in the dosage form, TP samples (without protective and covering layers) were placed in a conical flask containing 200 mL of 0.01 N hydrochloric acid solution. The flask was maintained in a boiling water bath for 1 hour. The resulting solution was then filtered through a paper filter into a 2000 mL volumetric flask. This extraction process was repeated four additional times under the same conditions.

Chlorpropamide concentration was quantified using spectrophotometric analysis by measuring the optical density of the solution at a wavelength of 231 ± 2 nm. A 0.01 N hydrochloric acid solution served as the reference.

The content of chlorpropamide in TP in grams (X) was calculated according to the formula:

$$X = \frac{D_x \cdot m \cdot 2000 \cdot 5}{D_0 \cdot 100 \cdot 50} = \frac{2D_x \cdot m}{D_0},$$

where D_x is the optical density of the test solution; D_0 is optical density of chlorpropamide standard sample solution; m is the weight (in grams) of chlorpropamide taken for preparation of the standard sample solution.

The experiment was repeated six times, and the average result calculated.

Statistical data processing

Significance of differences was determined using Student's t-test (standard software package Microsoft Excel 2010). Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Characteristics of substances included in the permeation enhancer complex

The developed polymer matrix for the TP consisted of an acrylic adhesive combined with a PEC containing apricot kernel oil, dioctyl sodium sulfosuccinate, dihydroquercetin, and alpha-tocopherol acetate [11]. The PEC composition was carefully selected based on an analysis of the individual properties of each excipient incorporated into the matrix.

Alpha-tocopherol acetate and dihydroquercetin, key components of the PEC, are well known for their potent antioxidant properties [12, 13]. These substances possess unique characteristics that mitigate potential adverse effects of the polymer composition on the skin during TP application. Alpha-tocopherol acetate (vitamin E), for instance, enhances the skin's water-binding capacity when applied topically. It optimizes nutrient delivery to the dermis and epidermis, facilitates detoxification, promotes tissue healing and regeneration, and improves microcirculation in the skin [14].

Dihydroquercetin exhibits a range of beneficial effects, including angioprotective, regenerative, detoxifying, anti-edematous, antibiotic, radioprotective, and immunomodulatory properties [13].

In the PEC formulation, alpha-tocopherol acetate and apricot kernel oil interact synergistically to preserve each other's functional properties while providing protection against oxidation. Vegetable oils play a crucial role in replenishing lost epidermal lipids, restoring the skin's barrier function, and stimulating lipid metabolism [15]. Due to its high oleic acid content, apricot kernel oil is readily absorbed into the skin, facilitating the penetration of other active ingredients and enhancing their bioavailability [16].

Dioctyl sodium sulfosuccinate (DSS) is a synthetic surfactant with both lipophilic and hydrophilic properties, making it structurally similar to phospholipids. This anionic surfactant readily forms micelles in aqueous and organic media, adapting its spatial orientation based on solvent polarity [17]. The ability of micelles to transport drugs through the stratum corneum is attributed to their hydrophobic outer surface, which facilitates penetration. As micelles diffuse through the hydrophilic dermis, sodium docusate molecules gradually reorient their hydrophilic groups toward the surrounding environment, enabling the controlled release of drugs, which then diffuse into the bloodstream through capillary walls [17]. Previous studies have demonstrated that DSS significantly enhances the percutaneous diffusion of bromocaine in emulsion-based TPs [18]. Subsequent research has explored its use in microemulsions for transdermal delivery of essential amino acids [19, 20]. In this study, DSS was incorporated into the PEC to improve drug diffusion from the polymer matrix.

Study of transdermal diffusion of drugs through unpreserved skin *in vitro* from polymer matrices of different compositions

In preliminary studies, the optimal composition of the PEC for chlorpropamide-loaded, caffeine-loaded, and lidocaine-loaded TPs was determined to achieve the desired transdermal diffusion rate for a dosage form with an area of 10 cm^2.

Tables 2 and 3 present the *in vitro* results of the 24-hour transdermal diffusion study of chlorpropamide and caffeine from TPs. PEC components are indicated with an asterisk (*).

Tables 2 and 3 demonstrate a significant enhancement ($p < 0.05$) in transdermal drug diffusion from a TP in-

corporating a PEC-containing polymer matrix. Diffusion of chlorpropamide increased from 2.1 ± 0.4 mg to 9.2 ± 1.4 mg, while caffeine diffusion rose from 9.2 ± 1.2 mg to 35.2 ± 7.5 mg over 24 hours.

A similar improvement in drug diffusion through unpreserved rabbit skin *in vitro* was observed for lidocaine-loaded TPs with a PEC-containing polymer matrix, as shown in Table 4.

It is important to note that when developing a TP for a specific drug, the ratio of PEC components must be carefully optimized based on the drug's properties and the target therapeutic concentration in the blood.

Effect of the permeation enhancer complex on drug concentration in blood during transdermal administration to laboratory animals

Table 5 presents the *in vivo* results of PEC's effect on drug concentration in rabbit blood during for chlorpropamide-loaded TP (15 mg drug, 10 cm^2). PEC components are indicated with *.

Table 6 summarizes the time required to achieve a steady-state blood concentration of caffeine and sodium benzoate (CSB), as well as the duration for which this concentration was maintained, during application of both PEC-containing and PEC-free TPs (50 mg drug, 10 cm^2). PEC components are indicated with *.

As shown in Tables 5 and 6, incorporating PEC into the polymeric TP reduces the time required to reach a steady-state drug concentration in the blood – by 1.7 times for chlorpropamide-loaded TP and 2.9 times for caffeine-loaded TP – while also increasing the achieved concentration – by 2.3 times for chlorpropamide TP and 2.7 times for caffeine TP.

Calculations indicate that to achieve the target drug concentration in rabbit blood, a PEC-free chlorpropamide-loaded TP would require a contact area of 23 cm^2 – 2.3 times larger than the PEC-containing formulation. Similarly, a PEC-free caffeine-loaded TP would require

Table 2

Effect of the permeation enhancer complex on percutaneous diffusion of chlorpropamide from the transdermal patch (15 mg, 10 cm^2)

S/N	Polymer matrix composition	Quantity in the matrix, mass %	Quantity in the TP, g	Mass of the drug that passed through the skin, mg, n = 20	Release of drug from TP, %
1	Acrylic adhesive	95.88	0.155	9.2 ± 1.4	61.3
	Apricot kernel oil*	4.0			
	Alpha-tocopherol acetate*	0.02			
	Dioctyl sodium sulfosuccinate*	0.06			
	Dihydroquercetin*	0.04			
	Ethanol		0.100		
	Chlorpropamide		0.015		
2	Acrylic adhesive	100	0.155	2.1 ± 0.4	14.0
	Ethanol		0.100		
	Chlorpropamide		0.015		

Note: TP, transdermal patch.

Table 3

Effect of the permeation enhancer complex on percutaneous diffusion of caffeine from the transdermal patch (50 mg, 10 cm^2)

S/N	Polymer matrix composition	Quantity in the matrix, mass %	Quantity in the TP, g	Mass of the drug that passed through the skin, mg, n = 15	Release of drug from TP, %
1	Acrylic adhesive	90.02	0.12	35.2 ± 7.5	70.4
	Apricot kernel oil*	9.6			
	Alpha-tocopherol acetate*	0.10			
	Dioctyl sodium sulfosuccinate*	0.14			
	Dihydroquercetin*	0.14			
	Ethanol		0.10		
	Caffeine		0.05		
2	Acrylic adhesive	100	0.12	9.2 ± 1.2	18.4
	Ethanol		0.10		
	Caffeine		0.05		

Note: TP, transdermal patch.

a 27 cm^2 contact area, which is 2.7 times larger than its PEC-containing counterpart. These findings highlight the effectiveness of PEC in significantly reducing the required TP contact area.

Pharmacokinetic studies of the lidocaine-containing TP revealed that drug concentrations in the blood of laboratory animals were near the HPLC detection limit, consistent with the characteristics of topical formulations.

Table 4

Effect of the permeation enhancer complex on percutaneous diffusion of lidocaine from the transdermal patch (50 mg, 10 cm^2)

S/N	Polymer matrix composition	Quantity in the matrix, mass %	Quantity in the TP, g	Mass of the drug that passed through the skin, mg, n = 15	Release of drug from TP, %
1	Acrylic adhesive	94.76	0.12	21.8 ± 3.0	43.6
	Apricot kernel oil*	5.0			
	Alpha-tocopherol acetate*	0.1			
	Dioctyl sodium sulfosuccinate*	0.06			
	Dihydroquercetin*	0.08			
	Ethanol		0.10		
	Lidocaine		0.05		
2	Acrylic adhesive	100	0.12	9.1 ± 0.2	18.2
	Ethanol		0.10		
	Lidocaine		0.05		

Note: TP, transdermal patch.

Table 5

Results of the study of chlorpropamide content in the blood of laboratory animals *in vivo*

S/N	Polymer matrix composition	Quantity in the matrix, mass %	Quantity in the TP, g	Time (h) to reach a constant concentration, n = 3	Constant concentration (μg/mL) in blood, n = 3
1	Acrylic adhesive	95.88	0.155	4.4 ± 0.5	1.73 ± 0.16
	Apricot kernel oil*	4.0			
	Alpha-tocopherol acetate*	0.02			
	Dioctyl sodium sulfosuccinate*	0.06			
	Dihydroquercetin*	0.04			
	Ethanol		0.100		
	Chlorpropamide		0.015		
2	Acrylic adhesive	100	0.155	7.3 ± 0.3	0.75 ± 0.11
	Ethanol		0.100		
	Chlorpropamide		0.015		

Note: TP, transdermal patch.

Table 6

Results of the study of caffeine and sodium benzoate content in the blood of laboratory animals *in vivo*

S/N	Polymer matrix composition	Quantity in the matrix, mass %	Quantity in the TP, g	Time (h) to reach a constant concentration, n = 3	Constant concentration (μg/mL) in blood, n = 3
1	Acrylic adhesive	90.02	0.12	2.2 ± 0.4	2.63 ± 0.15
	Apricot kernel oil*	9.6			
	Alpha-tocopherol acetate*	0.10			
	Dioctyl sodium sulfosuccinate*	0.14			
	Dihydroquercetin*	0.14			
	Ethanol		0.10		
	Caffeine and sodium benzoate		0.05		
2	Acrylic adhesive	100	0.12	6.3 ± 0.9	0.96 ± 0.10
	Ethanol		0.10		
	Caffeine and sodium benzoate		0.05		

Note: TP, transdermal patch.

Table 7

Extent of skin reaction in rabbits to the lidocaine-containing transdermal patch

TP composition	Rabbit no.	Time after detachment of TP							
		1 hr		24 hr		48 hr		72 hr	
Polymer matrix with PEC: – Apricot kernel oil, 5.0% – Alpha-tocopherol acetate, 0.1% – Dioctyl sodium sulfosuccinate, 0.06% – Dihydroquercetin, 0.08%	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
Polymer matrix without PEC	1	1	1	0	0	0	0	0	0
	2	1	1	1	1	0	0	0	0
	3	1	1	1	1	0	0	0	0

Note: 0, no irritation; 1, faint erythema; TP, transdermal patch; PEC, permeation enhancer complex.

Table 8

Quantity of chlorpropamide in the transdermal patch at different storage periods

TP composition	Quantity of chlorpropamide in the TP, g			
	Immediately after production, g (n = 6)	After 1 year, g (n = 6)	After 2 years, g (n = 6)	After 3 years, g (n = 6)
Polymer matrix with PEC: – Apricot kernel oil, 5.0% – Alpha-tocopherol acetate, 0.1% – Dioctyl sodium sulfosuccinate, 0.06% – Dihydroquercetin, 0.08%	0.0151 ± 0.0006	0.0148 ± 0.0009	0.0148 ± 0.0006	0.0146 ± 0.0003
Polymer matrix without PEC	0.0150 ± 0.0010	0.0148 ± 0.0006	0.0142 ± 0.0003	0.0120 ± 0.0008

Note: TP, transdermal patch; PEC, permeation enhancer complex.

Effect of introducing the permeation enhancer complex in the matrix on the possibility of local irritant effect of a transdermal patch

An assessment of the possibility of skin irritation from polymeric TPs was conducted using laboratory samples of lidocaine-loaded TP (50 mg, 10 cm^2) as a topical agent. The extent of skin reaction in rabbits following TP application is summarized in Table 7.

Table 6 indicates that in all three rabbits from the second group, mild erythema was observed at both application sites one hour after removing the lidocaine-loaded TP with a PEC-free polymer matrix. This erythema persisted for 24 hours in two rabbits but resolved completely within the next 24 hours. In contrast, no signs of irritation were observed at the application site in the group of animals that received the lidocaine-loaded TP with a PEC-containing polymer matrix throughout the study period. Similar findings of reduced local irritation were noted in the studies of caffeine-loaded and chlorpropamide-loaded TP.

Effect of the permeation enhancer complex in the polymer matrix on the shelf life of transdermal patches

To demonstrate the effect of PEC in the polymer matrix composition on the shelf life of the TP, Table 8 presents the results of a three-year study on the quantitative content of chlorpropamide in the TP.

According to the 15th edition of the State Pharmacopoeia of the Russian Federation, deviation in the active substance content of a TP should not exceed 15% [1]. Therefore, chlorpropamide content in a single TP must not be lower than 0.0150 ± 0.00225 g. The study results indicate that the shelf life of a chlorpropamide-loaded TP with a PEC-containing polymer matrix extends up to three years, whereas a similar TP without PEC has a shelf life of only one year.

Similar studies have demonstrated that incorporating PEC into caffeine-loaded and lidocaine-loaded TPs also enhances their shelf life.

CONCLUSION

The findings of this study demonstrate that incorporating the proposed PEC – comprising of apricot kernel oil, dioctyl sodium sulfosuccinate, dihydroquercetin, and alpha-tocopherol acetate – into polyacrylate TP matrices significantly enhances the functional properties of these dosage forms. Specifically, the PEC:

– Increases transdermal drug diffusion, enabling a substantial reduction in the required contact area of the dosage form.
– Shortens the time needed to reach a stable equilibrium drug concentration in the bloodstream compared to PEC-free formulations.

– Reduces the risk of skin irritation at the application site.
– Extends the shelf life of the dosage form.

The authors declare no conflict of interest.

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The article was submitted to the journal on 27.08.2024