














Development of a transcutaneous form of desloratadine

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Abstract

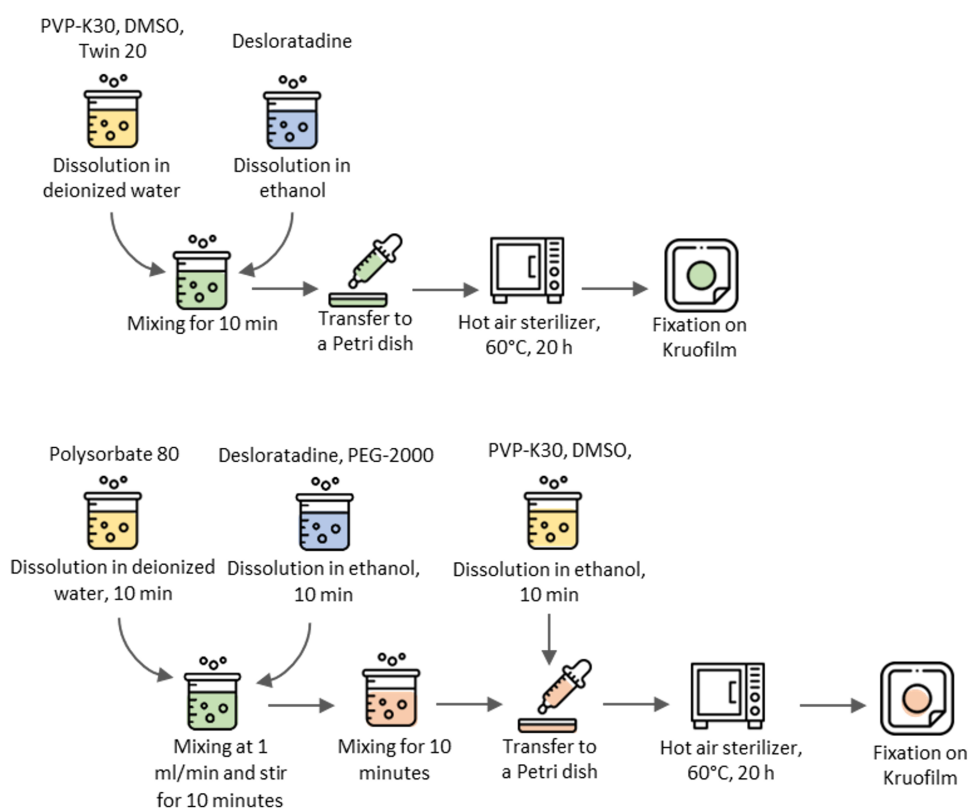
Introduction: For people with allergies, it is not always possible to prevent allergens admission to the body. For this reason, it is essential to create a long-acting drug that can prevent an allergic reaction. The very promising option is a transdermal therapeutic system (TTS), with H1 blockers. **The aim of the study:** To create a technology for the production of desloratadine-based TTS, suitable for routine use with prolonged drug releasing.

Material and Methods: Polyvinylpyrrolidone K30 (PVP) was used as the main matrix polymer for TTS, and the Kruofilm polymer membrane was used as the adhesive layer. The formation of the polymer membrane was carried out by drying a water-alcohol solution of the components at a temperature of 60°C. Characterization of the obtained dosage forms was made by spectrophotometry. The resulting micelles size was measured by dynamic light scattering.

Results and Discussion: Round shaped TTS (patches) with water-dissolved DL and its micellar form were obtained. The size of micelles with DL was 22.8±5.2 nm. The spectrophotometric method for determining DL has been developed. The containing of DL in the patches ranged from 5 to 25 mg per patch, depending on the manufacturing technology.

Conclusion: We have developed TTSs containing DL by a solution and a micellar form. A top adhesive layer has been selected that has moisture resistance, strength and reliable fixation of the matrix with the active substance on the skin. A method for the spectrophotometric determination of DL in solutions and patches was developed and validated.

Graphical abstract



Keywords

allergy, desloratadine, transdermal therapeutic system, patch, micelles

Introduction

Allergic diseases are extremely widespread and can manifest with various symptoms: from seasonal rhinitis and urticaria to a bronchial asthma, severe skin diseases and life-threatening anaphylactic reactions (Dribin et al. 2023; Warrant et al. 2023).

The most important thing in allergy sufferers health management is to prevent exacerbation by avoiding contact with the allergen. Drugs are used in cases when contact with the allergen is unavoidable. Most often these are seasonal types of allergies (pollinosis). During such periods, antiallergic drugs are used continuously. The most common medications for treating and preventing allergic reactions are antihistamines (Parisi et al. 2020). Currently, three generations of antihistamines are used in clinical practice. The first generation can cause serious side effects: drowsiness, dizziness, loss of coordination, decreased ability to concentrate, increased or decreased appetite, nausea, vomiting, diarrhea, dry mouth, hypotension, tachycardia, arrhythmia (Fein et al. 2019). Second generation is almost free of side effects from the central nervous system, but, at the same time,

cardiotoxicity is higher, therefore those medications prohibited for a long-term use (Ołasińska-Wiśniewska et al. 2019). Third generation drugs have active metabolites of second generation, which nearly do not have side effects. Second and third generation drugs can keep their action within 24 hours. One of the popular medications of the 3rd generation of histamine blockers is DL (Li et al. 2022). Desloratadine (DL) is the primary active metabolite of loratadine with high affinity for H₁ receptors. It suppresses the release of histamine and pro-inflammatory cytokines, so can prevent the initiation of characteristic symptoms of allergic diseases (bronchospasm, erythema, itching of the skin and mucous membranes, sneezing, lacrimation, nasal congestion, and angioedema) (Devillier et al. 2008).

Most cases of prevention or therapy of allergic manifestations requires long-acting drugs. In this regard, systems that ensure prolonged delivery of the drug into the body get of great importance. One example is transdermal therapeutic systems (TTS). Their main advantages are the absence of the need to regularly take tablets orally and the possibility of long-term maintenance of therapeutic concentrations of the active substance in the blood (Machekposhti et al. 2017; Nefodov et al. 2022).

Currently, transdermal therapeutic systems are actively developing and there are several generations of TTS.

First generation of transdermal delivery systems are adhesive membranes with an integrated active ingredient. They are used primarily to deliver small doses of low molecular weight of lipophilic drugs (Prausnitz et al. 2008).

Second-generation delivery systems use chemical permeation enhancers, non-cavitating ultrasound, and iontophoresis (Kováčik et al. 2020). There are already several commercial clinical products on the market based on transdermal systems (Prausnitz et al. 2008). Third generation transdermal delivery systems are based on different ways for skin permeability rising (using microneedles, nanoparticles, thermal ablation, microdermabrasion, electroporation, and cavitation ultrasound etc.). Microneedles and thermal ablation are currently being tested in clinical trials to deliver macromolecules and vaccines such as insulin, parathyroid hormone, and influenza vaccine (Zhang et al. 2023). Improvements of the second and third TTSs can significantly increase the scope in medicine (Joshi et al. 2023).

The manufacturing technology of TTS has two main directions: membrane and matrix.

Membrane TTSs act like a reservoir with a liquid or gel-like drug substance, separated from the skin by a semi-permeable membrane that regulates the rate of its resorption (intake) (Romualdi et al. 2008).

Matrix system that has been chosen for current research has a simple structure compared to a membrane system: the outer covering layer is a flexible polymer film impermeable to the active substance, to which is attached a polymer adhesion matrix containing the active and auxiliary substances (Lee et al. 2015).

The purpose of the study was to create a technology for the production of DL-based TTS, suitable for routine use with prolonged drug releasing.

Materials and Methods

Reagents

Desloratadine, chemical grade (Sigma-Aldrich, USA), polyvinylpyrrolidone K-30, chemical grade (Ashland, USA), polysorbate 80, chemical grade (Sigma-Aldrich, USA), polysorbate 20 (Sigma-Aldrich, USA), ethyl alcohol, 96% (Vekton, Russia), methanol, 96% (Vekton, Russia), DMSO, 99.5% (Servicebio, China), and polyethylene glycol – 2000 (PEG-2000) (JSC Nizhnekamskneftekhim, Russia).

Manufacturing of transdermal dosage form

A biocompatible water-soluble polymer, PVP, was chosen as a matrix containing active substance. PVP is widely used in the pharmaceutical industry and has unique physicochemical properties: chemically inert, colorless, heat-resistant and pH-stable. Gel form of PVP has a high ability to adsorb low-molecular compounds. This polymer has been repeatedly used to create a similar delivery system for a number of drugs (Gupta et al. 2003; Dinesh et al. 2008; Valeveti et al. 2023).

As an outer covering and protective layer, we used Kruofilm membrane (Meditek Znamya Truda, Russia). It is a hypoallergenic transparent adhesive film based on a

particularly thin polymer, air- and vapor-permeable. Kruofilm is water-resistant and does not leave marks on the skin after removal.

Two versions of DL-based TTS have been made: the first one is based on DL molecular solution and the second one is based on DL micelles.

1. TTS based on a molecular solution of DL

In the first case, we obtained a polymer matrix with deposit of desloratadine solution. The initial solution of membrane-forming components was prepared in the ratios given in Table 1.

Table 1. Weights of membrane-forming components for obtaining TTS using method 1

Component	Weight, g
1. DL	0.005; 0.010; 0.015; 0.020; 0.025
2. PVP	1.0
3. Ethyl alcohol	2.5
4. Polysorbate 20	0.05
5. DMSO	0.05
6. Deionized water	45.375-45.395

2. TTS based on micelles with DL

The second version of TTS contains micelles with DL. The general composition of the TTS is presented in Table 2.

Table 2. Weights of weighed membrane-forming and micelle-forming components

Component	Weight, g
1. DL	0.005; 0.010; 0.015; 0.020; 0.025
2. PVP	1.0
3. PEG-2000	0.25
4. Polysorbate 80, chemical grade	0.25
5. Ethyl alcohol, 96%	32.5
6. DMSO	0.05
7. Deionized water	75

The production of TTS with micellar form of DL included 2 stages: the production of micelles with DL and the actual production of the membrane matrix.

The preparation of micelles with DL began by dissolving the required amount of DL (from 5 to 25 mg depending on the series) in 22.5 g of ethyl alcohol. PEG-2000 (0.25 g) was added to the resulting solution and continued stirring for 10 minutes at room temperature. Then 0.25 g of polysorbate-80 was added to 75 mL of deionized water with constant stirring. After 20 minutes, the previously obtained alcohol solution was slowly (at a rate of 1 mL/min) added to this mixture and stirred for 10 minutes. As a result, micelles with DL and PVP were formed in the dispersed medium.

Free fraction of DL from micelles suspension was removed by ultrafiltration. To do this, 50 mL of the resulting micelles were placed in an ultrafiltration chamber (Amicon-8200, USA) with a cellulose membrane MF-1210-76 with a pore size of 12-14 kDa (MFPI, USA) and filtered under a nitrogen pressure of 3 MPa while constantly stirring at room temperature.

To calculate the mass of DL in the micelles, the concentration of DL in the ultrafiltrate was determined. The mass of the incorporated DL was calculated by the formula: $X=(X_0 - C*V)*k$, where X is the mass of DL included in the micelles, X_0 is the theoretical mass of DL in 50 mL of the initial solution of micelles, C is the concentration of DL in the ultrafiltrate, V is the volume of the resulting ultrafiltrate, k is the volume ratio of the prepared micelle solution to the volume of the solution subjected to ultrafiltration (1,96). A total of 5 micelle samples were obtained. The size of the resulting micelles was measured by dynamic light scattering (NanoFlex+Stabino, Germany, Microtrac Flex 11.0.0.2. software) (Kulikov et al. 2023).

The membrane matrix was prepared as follows. In a separate glass, 1g of PVP and 0.05g of DMSO were dissolved in 10g of ethyl alcohol. This solution was mixed with the previously obtained micelle solution and evaporated to 50 mL in a dry-heat oven at a temperature of 60°C with constant stirring. At the next stage, the resulting solution was poured into a Petri dish and dried for 20 hours at a temperature of 60°C. The resulting composition was transferred to Kruofilm film similarly to the first version of TTS.

Quantitative determination

Quantitative determination of DL was carried out by spectrophotometric method at a wavelength $\lambda = 242$ nm (spectrophotometer UV-2600, Shimadzu, Japan). Methanol was used as a reference solution. To get calibration standard solutions, solutions of DL in methanol with concentrations of 0.5, 1, 2, 3, 4, 5 $\mu\text{g}/\text{mL}$ were used. For this purpose, 5 mg of DL was dissolved in 100 mL of methanol to obtain a stock solution with a concentration of 50 $\mu\text{g}/\text{mL}$. Next, 1, 2, 4, 6, 8, and 10 mL of this solution were taken and brought to 100 mL with methanol, obtaining calibration solutions of a given concentration.

Validation of the method for quantitative determination of DL in TTS

Validation of DL solutions in methanol was carried out according to the following characteristics: linearity, accuracy, and precision.

Statistic analysis

Data are presented as means \pm SEM or their 95% confidence intervals (CI 95%) obtained using nonlinear regression.

Results and Discussion

Characteristics of micelles used for the preparation of TTS based on the micellar form of DL

Table 3 shows the characteristics of the obtained micelles.

Table 3. Characteristics of the resulting micelles

Index	Sample №				
	1	2	3	4	5
Initial mass of DL taken for the production of micelles	5	10	15	20	25
Size up to CA, nm Mean \pm SD	20.4 \pm 2.2	23.7 \pm 2.4	22.3 \pm 2.5	21.6 \pm 1.9	22.8 \pm 3.1
Size after CA, nm Mean \pm SD	20.3 \pm 2.0	23.9 \pm 2.7	22.1 \pm 2.4	21.3 \pm 2.3	23.2 \pm 2.8
Relative amount of DL included in micelles (for you this is the inclusion efficiency)	30.2 \pm 2.1	27.6 \pm 1.8	28.6 \pm 2.2	28.4 \pm 2.4	29.5 \pm 1.9
Weight of DL per 1g of PEG-2000	0.02	0.04	0.06	0.08	0.1

As is seen, the size of the micelles and the relative amount of incorporated DL did not depend on the concentration of DL in the initial solution. The size was 20.3-23.9 nm; the suspension was homogeneous (the relative standard deviation of the size did not exceed 1.25%; there were no additional peaks in the size distribution curves).

The amount of DL per unit mass of the micelle matrix increased proportionally with an increase concentration of DL in the initial and amounted to 0.02 in series No. 1 and 0.1 in Series No. 5. Important point is that dimensional characteristics of the micelles did not change after ultracentrifugation (Fig. 1).

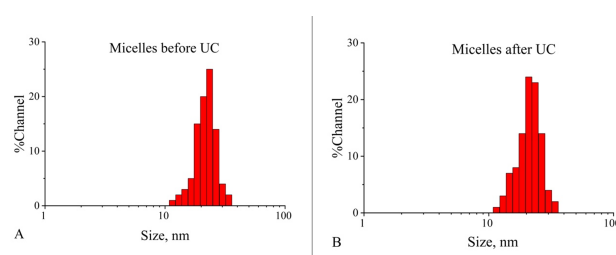


Figure 1. Size distribution of micelles with DL (sample No. 5, 25 mg/g DL). *Note:* A – up to UC; B – after UC.

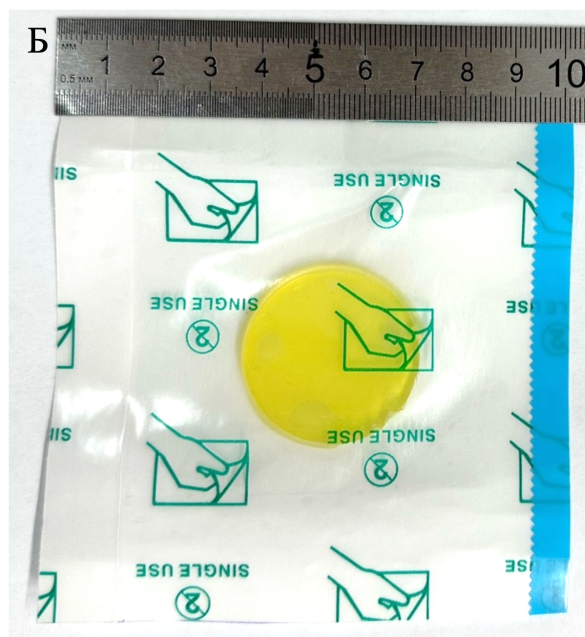
This indicates the possibility of using the developed technique for obtaining micelles for serial production. For the production of TTS, micelles of series 5 were selected as containing the largest amount of active substance.

Characteristics of TTS based on the micellar form of DL

Round patches with a diameter of 3.5 cm and a thickness of 2.5 mm were obtained (Fig. 4). They were dense elastic gel-like transparent membranes with an active drug releasing layer on one side and covered with the Kruofilm membrane on the other. Five samples of each type of patches with dissolved and micellar forms of DL were produced. The DL content in the samples was 5-25 mg (a detailed description of the determination of DL in the TTS is given below). Photographs of patch samples are shown in Fig. 2.



TTS molecular solution of DL (type I)



TTS with micelles of DL (type II)

Figure 2. TTS with solution (A) and micellar form of DL (B).

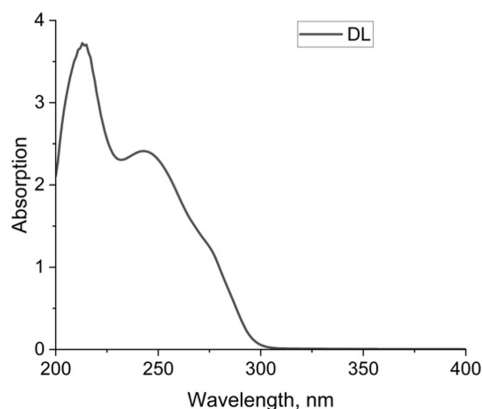
Development and validation of DL determination method

To assess the possibility of clinical use of the obtained TTSs, it is necessary to evaluate the content of the active substance in them. At the first stage, the method was developed for determining the concentration of DL in a methanol solution, and then, on its basis, in the TTS itself.

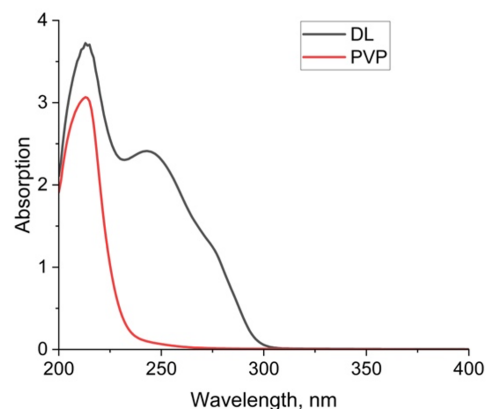
Figure 3 shows the absorption spectra of a solution of

DL and PEG in methanol.

We can see that the DL absorption spectrum has an absorption maximum at 242 nm. This wavelength was chosen for spectrophotometric determination of DL concentration. Figure 4 shows the calibration graph for methanol solutions of DL, and Table 4 shows the deviations of the experimental data from the straight line when assessing the linearity of the quantitative determination technique.



A



B

Figure 3. Absorption spectra: A – DL in methanol; B – comparative spectrum of PVP and DL in methanol.

The calibration graph had the linear form: $y = 0.0366x - 0.0007$ in the range from 0.5 $\mu\text{g/mL}$ to 5 $\mu\text{g/mL}$. The correlation coefficient is 0.9963. Deviations of the found concentrations of DL from the theoretically calculated ones were 1.91–10.4%, which meets the accuracy requirements (Kulikov et al. 2023).

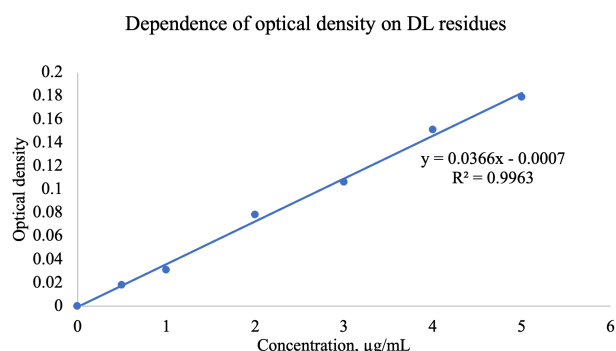


Figure 4. Calibration graph of the dependence of optical density on the concentration of DL in a methanol solution at $\lambda = 242$ nm.

Table 4. Deviations of experimental data from the straight line when assessing the linearity of the quantitative determination technique

True value, $\mu\text{g/mL}$	Obtained values, $\mu\text{g/mL}$	Deviation of points from the calibration line, %
0.5	0.512	2.45
1	1.06	6.27
2	2.21	10.4
3	3.10	3.54
4	4.33	8.31
5	5.095	1.91

To confirm the precision of the method, 6 solutions with concentrations from 0.5 to 5 $\mu\text{g/mL}$ DL in methanol were prepared. The results of precision for the quantitative determination of DL in methanol are given in Table 5.

The patches contain PVP, the absorption spectrum of which partially overlaps the spectrum of DL. Therefore, direct determination of DL after patches dissolving in any organic solvent is impossible. To solve this problem, a

Table 5. The precision for the quantitative determination of DL in methanol

Parameters	Theoretical solution concentration, $\mu\text{g/ml}$ (taken as 100%)					
	0.5	1	2	3	4	5
Found values for DL content, %	92.00-106.00	96.00-109.00	97.50-103.50	98.33-102.33	97.75-101.25	97.80-100.80
Average content of DL, %	98.7	102.7	101.1	100.5	99.8	99.0
RSD, %	2.80	5.01	5.88	4.85	5.95	6.24

method for isolating the active substance from micelles and TTS, based on ultrafiltration, has been developed. To determine DL in TTS, one sample of the patch was dissolved in 80 mL of methanol, after which the volume of the solution was adjusted to 100 mL. Then 10 mL of the resulting mixture was ultracentrifuged three times using a Cobetter centrifugal concentrator with a 10 kDa filter. The DL concentration in ultrafiltrate was determined by the spectrophotometric method described above. Figure 4 shows the values of the expected and found concentrations of the substance in samples of both types (with dissolved and micellar forms of DL). We can see that the found and expected concentrations of DL in the patches are practically the same for all series; the relative deviation of the found concentration from the theoretical one did not exceed 5.88%.

Figure 5 demonstrates the dependency of DL content in the patch, depending on the manufacturing technology.

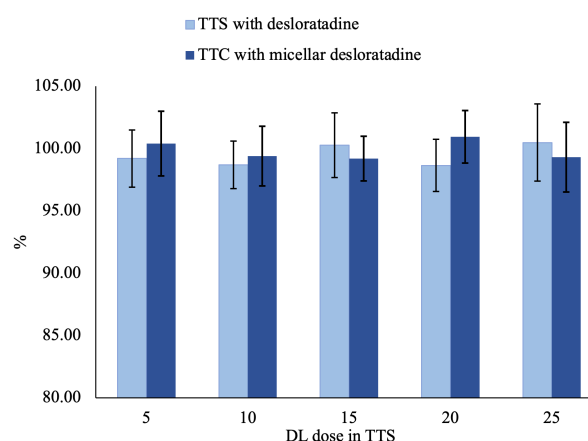


Figure 5. Percentage of found amount of the DL from expected one in the manufactured TTS samples.

This indicates the acceptability of the method for determining DL in TTS for characterizing finished dosage forms during their mass production. Table 6 shows the absolute values of the DL content in the manufactured samples.

Conclusion

Thus, we showed the possibility of creating TTSs containing DL by solution and micellar forms.

Table 6. DL content in manufactured TTS samples

Type of TTS	Amount of DL in the sample				
	1	2	3	4	5
Based on DL solution, µg	4.96±0.11	9.87±0.19	15.04±0.39	19.73±0.41	25.12±0.78
Based on the micellar form of DL, µg	5.02±0.12	9.94±0.19	14.88±0.39	20.19±0.42	24.83±0.77

It is assumed that the presence of DL nanoparticles ensures greater penetration of the active component through the skin and an increased duration of action of the patch. A top adhesive layer has been selected that has moisture resistance, strength and reliable fixation of the matrix with the active substance on the skin. A method for the spectrophotometric determination of DL in solutions and patches was also developed and validated, which allows for rapid and accurate characterization of dosage forms under development and study of the pharmacokinetics of solids.

Conflict of interest

The authors have declared that no competing interests exist.

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Data availability

All of the data that support the findings of this study are available in the main text.

References

- Cheow Chee LEE (2015) Transdermal Drug Delivery Patch: A technology outline. <https://doi.org/10.13140/RG.2.1.2929.6162>
- Devillier P, Roche N, Faisy C (2008) Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. *Clinical Pharmacokinetics* 47(4): 217–230. <https://doi.org/10.2165/00003088-200847040-00001> [PubMed]
- Dinesh B, Patil U, Desai B, Raghu K, Sadashivaiah R (2008) Design and *in vitro* evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers. *Asian Journal of Pharmaceutics* 2: 43. <https://doi.org/10.4103/0973-8398.41565>
- Dribin TE, Motosue MS, Campbell RL (2022) Overview of allergy and anaphylaxis. *Emergency Medicine Clinics of North America* 40(1): 1–17. <https://doi.org/10.1016/j.emc.2021.08.007> [PubMed] [PMC]
- Fein MN, Fischer DA, O'Keefe AW, Sussman GL (2019) CSACI position statement: newer generation H1-antihistamines are safer than first-generation H1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. *Allergy, Asthma & Clinical Immunology* 15: 61. <https://doi.org/10.1186/s13223-019-0375-9> [PubMed] [PMC]
- Gupta R, Mukherjee B (2003) Development and *in vitro* evaluation of diltiazem hydrochloride transdermal patches based on povidone-ethylcellulose matrices. *Drug Development and Industrial Pharmacy* 29(1): 1–7. <https://doi.org/10.1081/DDC-120016678> [PubMed]
- Joshi N, Azizi Macheuposhti S, Narayan RJ (2023) Evolution of transdermal drug delivery devices and novel microneedle technologies: A historical perspective and review. *JID Innovations* 3(6): 100225. <https://doi.org/10.1016/j.xjidi.2023.100225> [PubMed] [PMC]
- Kováčik A, Kopečná M, Vávrová K (2020) Permeation enhancers in transdermal drug delivery: benefits and limitations. *Expert Opinion on Drug Delivery* 17(2): 145–155. <https://doi.org/10.1080/17425247.2020.1713087> [PubMed]
- Kulikov OA, Yunina DV, Ageev VP, Shlyapkina VI, Avdyushkina IS, Akmaeva IA, Zaborovsky AV, Tararina LA, Tsaregorodtsev SV, Pyataev NA (2023) Evaluation of cellular toxicity and preclinical safety of using an inhalable liposomal form of dexamethasone. *Pharmaceutical Chemistry Journal* 56(2): 1573–1576. <https://doi.org/10.1007/s11094-023-02829-w> [PubMed] [PMC]
- Li L, Liu R, Peng C, Chen X, Li J (2022) Pharmacogenomics for the efficacy and side effects of antihistamines. *Experimental Dermatology* 31(7): 993–1004. <https://doi.org/10.1111/exd.14602> [PubMed]
- Macheuposhti SA, Soltani M, Najafzadeh P, Ebrahimi SA, Chen P (2017) Biocompatible polymer microneedle for topical/dermal delivery of tranexamic acid. *Journal of Controlled Release* 261: 87–92. <https://doi.org/10.1016/j.jconrel.2017.06.016> [PubMed]
- Nefodov OO, Belenichev IF, Fedchenko MP, Popazova OO, Ryzhenko VP, Morozova OV (2022) Evaluation of methods of modeling and formation of experimental allergic encephalomyelitis. *Research Results in Pharmacology* 8(2): 37–48. <https://doi.org/10.3897/rpharmacology.8.77361>
- Ołasińska-Wiśniewska A, Ołasiński J, Grajek S (2014) Cardiovascular safety of antihistamines. *Advances in Dermatology and Allergology* 31(3): 182–186. <https://doi.org/10.5114/pdia.2014.43191> [PubMed] [PMC]
- Parisi GF, Licari A, Papale M, Manti S, Salpietro C, Marseglia GL, Leonardi S (2020) Antihistamines: ABC for the pediatricians. *Pediatric Allergy and Immunology* 24: 34–36. <https://doi.org/10.1111/pai.13152> [PubMed]
- Prausnitz MR, Langer R (2008) Transdermal drug delivery. *Nature Biotechnology* 26: 1261–1268. <https://doi.org/10.1038/nbt.1504> [PubMed] [PMC]
- Romualdi P, Santi P, Candeletti S (2017) Alghedon fentanyl transdermal system. *Minerva Medica* 108(2): 169–175. <https://doi.org/10.23736/S0026-4806.16.04930-2>
- Valeveti SK, Pashikanti S (2023) Design, development, and evaluation of transdermal patches containing memantine hydrochloride. *International Journal of Applied Pharmaceutics* 15(5): 181–197. <https://doi.org/10.22159/ijap.2023v15i5.48481>
- Warren C, Nimmagadda SR, Gupta R, Levin M (2023) The epidemiology of food allergy in adults. *Annals of Allergy, Asthma & Immunology* 130(3): 276–287. <https://doi.org/10.1016/j.anai.2022.11.026> [PubMed]
- Zhang J, Li H, Albakr L, Zhang Y, Lu A, Chen W, Shao T, Zhu L, Yuan H, Yang G, Wheate NJ, Kang L, Wu C (2023) Microneedle-enabled therapeutics delivery and biosensing in clinical trials. *Journal of Controlled Release* 360: 687–704. <https://doi.org/10.1016/j.jconrel.2023.07.023> [PubMed]

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