FABAD J. Pharm. Sci., 50, 3, 671-688, 2025
Doi: 10.55262/fabadeczacilik.1727150
RESEARCH ARTICLE

Development of Mirtazapine Loaded Transdermal Drug Delivery System

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SUMMARY

Mirtazapine, alpha-2 receptor antagonist is an atypical antidepressant drug used in the treatment of major depression in adults; commercially available in oral tablet, disintegrating tablet and oral solution forms. Transdermal drug delivery systems can deliver the active drug substance subcutaneously into the systemic circulation, which provides a higher bioavailability by avoiding hepatic first-pass metabolism in the oral route and maintains a constant plasma level. The oral bioavailability of Mirtazapine is limited to 50%. The objective of this study is to design and formulate Mirtazapine into a transdermal drug delivery system, conduct the in-vitro drug product performance tests and introduce a suitable transdermal film formulation. In this study, transdermal film formulations of Mirtazapine were designed and generated. Films have a matrix type structure in which HPMC, HEC and PVP K30 are used as polymers and PEG 400 as a plasticizer. The prepared films have been proven to be stable by physical tests and FT-IR analysis. It has been experimentally obtained that in the best formulation, Mirtazapine can be released for more than 24 hours, and 14.41% of the drug in the dosage form permeates cumulatively through the artificial membrane within 24 hours. With the addition of oleic acid to the formulation, an 11.53% increase in permeation through the artificial membrane was achieved ($p < 0.05$). This study implies that Mirtazapine can be stably formulated into a transdermal film, providing sustained release and permeating through transdermal diffusion membrane, which presents a promising point of reference for research pursuits and commercial medicine development.

Keywords: *Mirtazapine, transdermal film, transdermal patch, antidepressant, oleic acid..*

Mirtazapin İçeren Transdermal Taşıyıcı Sistemin Geliştirilmesi

ÖZ

Mirtazapin, yetişkinlerde majör depresyon tedavisinde kullanılan, alfa-2 reseptör antagonisti atipik bir antidepresan ilaçtır. İlacın, oral tablet, dağılan tablet ve oral solüsyon formları ticari olarak mevcuttur. Transdermal ilaç salım sistemleri, ilaç etkin maddesini deri altından sistemik dolaşıma verebilen; böylece oral yoldan ilaç alımındaki hepatik ilk geçiş etkisinden kaçınarak daha iyi bir biyoyararlanım ve plazma seviyesi sürekliliği sağlayan, dozaj formlarıdır. Mirtazapinin oral biyoyararlanımı %50 ile sınırlıdır. Bu çalışmanın amacı, Mirtazapin içeren transdermal ilaç salım sisteminin tasarlanması ve formüle edilmesi, in-vitro performans testlerinin gerçekleştirilmesi ve uygun bir transdermal film formülasyonunun ortaya konmasıdır. Bu çalışmada, Mirtazapin'in transdermal film formülasyonları tasarlanmış ve ortaya konmuştur. Polimer olarak HPMC, HEC ve PVP K30, plastifiyan olarak PEG 400'ün kullanıldığı filmler matriks yapıdadır. Hazırlanan filmlerin, yapılan fiziksel testler ve FT-IR analizi ile stabil olduğu kanıtlanmıştır. Ortaya konan en iyi formülasyondan, 24 saatten daha fazla süre boyunca Mirtazapin salınabildiği ve dozaj formundaki ilacın % 14,41'nin 24 saat içinde yapay membrandan kümülatif olarak geçtiği deneysel olarak elde edilmiştir. Formülasyona oleik asit ilavesi ile, yapay membrandan permeasyonda %11,53 artış elde edilmiştir ($p < 0,05$). Bu çalışma, Mirtazapin'in sürekli salım sağlayabilen ve stabil transdermal filmlerinin formüle edilebileceğini, transdermal difüzyon membranından geçebileceğini ortaya koymakta; ileri araştırmalar ve ticari ilaç ürünleri geliştirilmesi için gelecek vaadeden bir referans oluşturmaktadır.

Anahtar Kelimeler: *Mirtazapin, transdermal film, transdermal yama, antidepresan, oleik asit.*

Recieved: 2.07.2025
Revised: 21.09.2025
Accepted: 13.10.2025

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INTRODUCTION

Mirtazapine is an alpha-2 receptor antagonist atypical antidepressant drug, which is named as 1,2,3,4,10,14b-hexahydro-2-methylpyrazino (2,1-a) prido (2,3-c) benzazepine. It is generally prescribed for the treatment of major depressive disorder in adults. Panic disorder, insomnia, post-traumatic stress disorder and social anxiety are the other indications Mirtazapine is prescribed for (Croom et al., 2009; Watanabe et al., 2011). The drug is also often off-label prescribed for the geriatric patients to treat the sleep disorders (Eronen et al., 2024; Nguyen et al., 2025). Currently, Mirtazapine is commercially available in tablet, disintegrating tablet and oral solution dosage forms (RX Media Pharma, 2023).

Transdermal drug delivery systems are advanced dosage forms that enable drug delivery across the skin barrier into the systemic circulation. Although it is a non-invasive application method, since permeation through the skin barrier is limited by various factors, this has made the transdermal delivery systems one of the focal points in drug research studies and commercial product development in recent years (Buzia et al., 2023; Jeong et al., 2021; Tiwary & Sapra, 2007; Ramadon et al., 2022). Nowadays, painkillers, hormonal therapy drugs and some drugs used in the treatment of central nervous system and cardiovascular system diseases are prosperously administered via transdermal dosage forms (Bird & Ravindra, 2020).

Drug administration via the transdermal delivery systems has several advantages over the oral route. Through the passage of the drug from the skin barrier into the systemic circulation, high systemic bioavailability is obtained, avoiding hepatic first-pass metabolism. More consistent plasma levels can be attained since the transdermal systems maintain plasma concentrations in the therapeutic window for prolonged periods, possibly allowing reduction in dosing frequency, eliminating dose fluctuations of oral medication (Carat, 2025; Escobar-Chavez et al., 2012). Transdermal systems avoid unpredictable absorption issues caused by food intake and other gastrointestinal (GI) factors, providing more reliable results (Laurn & Arean, 2024). Transdermal drug delivery systems typically provide controlled and sustained drug release, which results in an extended duration of therapeutic effect, half-life, compared to oral administration. Since the transdermal systems assure gradual and continuous drug input into the systemic circulation rather than a rapid bolus, improved half-life is attained. Subsequently, plasma concentrations decline more slowly, maintaining therapeutic levels for a longer period (Berner & John, 1994; Guy & Hadgraft, 1985). The ability to identify the applied medicine, stop the administration of medication and the side effects at any time is another substantial advantage of the transdermal systems, which offers safety in case of emergencies (Pastore et al., 2015; Patel et al., 2012; Tanwar & Sachdeva, 2016). Transdermal drug delivery systems ensure an alternative drug delivery route for the patients, especially elderly patients, with swallowing difficulties or cognitive challenges and those who receive multiple medications (Harnett et al., 2023). Besides improving patient compliance, transdermal technology generates possibilities for product line extensions for pharmaceutical companies, which provides strategic benefits in competitive therapeutic categories.

There are mainly four types of transdermal patches: matrix-type, membrane, drug-in-adhesive and micro-reservoir systems (Wong et al., 2023). Matrix-type transdermal system comprises a drug layer with a semi-solid matrix that holds a dispersed drug solution or drug suspension with a polymeric part directly in contact with the skin. The adhesive layer surrounds the drug layer and keeps the system adhered to the skin during dosing. In matrix-type systems, drug release is controlled by loading dose, solubility of drug in the polymer and the diffusion behavior of the drug in the polymer matrix (Ping, 2011; Siepmann & Peppas, 2011). A membrane-controlled transdermal sys-

tem contains a drug reservoir and a rate-controlling polymeric membrane. The drug molecules are released only through this membrane, which consists of semipermeable materials that provide the regulated passage of the drug (Bathe & Kapoor, 2015; Zhan et al., 2015). Drug-in-adhesive systems consist of an adhesive layer containing the drug. Following the application, the adhesive layer adheres onto the skin and the drug is gradually released during the dosing period (Pastore et al., 2015; Wolff, 2000). The micro-reservoir system comprises a matrix dispersion system and a reservoir. The drug is suspended in an aqueous solution of water-soluble liquid polymer, then this mixture is evenly dispersed in lipophilic polymer, producing a large number of microscopic drug reservoirs (Hanbali et al., 2019; Waghulde et al., 2013).

Despite the potential benefits of transdermal drug delivery, currently there is no commercial product available for transdermal Mirtazapine treatment in the field of human medicine. Moreover, the scientific literature on Mirtazapine delivery via transdermal systems is highly limited. There are a few studies covering a transdermal Mirtazapine system, and those studies are all published very recently, which indicates a growing interest in the topic. In one of these studies, therapeutic deep eutectic solvents, which are utilized to improve the solubility of drugs, were combined with Mirtazapine and medium-chained fatty acids to create a transdermal drug delivery system. The study performed *in vivo* studies as well and concluded that the relative bioavailability of Mirtazapine was improved 6.4-fold by including medium-chain fatty acids and provided 24-hour sustained release characteristics (He et al., 2025). In a very recent study, drug-in-adhesive formulations were generated by incorporating a pressure-sensitive adhesive system along with oleic acid as a permeation enhancer. The performed *ex vivo* and *in vivo* studies showed sustained drug release, enhanced skin permeation, and improved pharmacokinetics outperforming the oral route (Satpute et al., 2025). Another study developed a drug-in-adhesive transdermal patch using a pressure-sensitive adhesive and a chemical penetration enhancer. *In vivo* experiments were performed to investigate the pharmacokinetics of the optimized formulation, and the results demonstrated that a long-acting patch was developed (Liu et al., 2025).

Although there is no commercial product and very limited literature regarding the transdermal Mirtazapine system for human medicine, a noteworthy veterinary product, FDA-approved Mirtazapine transdermal ointment is commercially available (Mirataz®) in the United States (mirataz.com/pi). The product was designed and produced to benefit the off-label indication of Mirtazapine, appetite stimulation. It is currently recommended for application in cats only. Few prior related studies to this product were conducted and published. In these studies, Mirtazapine transdermal ointment formulation was fabricated and applied to owned healthy young cats in veterinary clinical conditions. The drug was applied to the skin of the inner ear pinna. The evaluation was made as per the analyzed serum Mirtazapine levels and the increase in appetite behaviors in cats. Single and repeated transdermal doses of Mirtazapine transdermal ointment attained measurable plasma concentration in cats (Benson et al., 2017; Buhles et al., 2018; Poole et al., 2019).

There are certain drug properties that should be considered while developing a transdermal drug delivery system. Drugs with lower molecular weight (<500 g/mol) can be absorbed through the skin via passive diffusion (Brown et al., 2006). The partition coefficient (Log P) is one of the key determinants of permeability, and should be between 1.0 and 4.0 (Chandrashekar & Shobha Rani, 2008). It is commonly accepted that an optimal drug candidate for transdermal delivery should possess a low melting point (< 200°C) (Velasco-Aguirre & Sintov, 2019). Mirtazapine has a molecular weight of 265.35 g/mol, a melting of 114-116°C (British Pharmacopoeia 2023), and a log P value of 2.9 (Ezealisiji et al., 2015). For this study, Mirtazapine was selected as the ideal drug

candidate to formulate into a transdermal film due to its appropriate molecular properties for transdermal drug delivery. Among the different types of transdermal patches, the matrix type patch was selected essentially due to the simple design and relative ease of fabrication. The conventional manufacturing process is also cost-effective.

This study centers on the design, formulation, and optimization of a novel matrix-type transdermal drug delivery system. By incorporating oleic acid as a penetration enhancer, the study optimizes the drug content and flux.

MATERIALS AND METHODS

Materials

Mirtazapine hemihydrate was purchased from Zhejiang Liaoyuan Pharmaceuticals Co, Ltd. (China). Hydroxypropyl methylcellulose (HPMC) (Benecel TM K4M) and hydroxyethyl cellulose (HEC) (Natrosol TM 250 HHX) were obtained from Ashland Global (USA) as gift samples. Polyvinylpyrrolidone (PVP K30) was received as a gift sample from BOAI NKY Pharmaceuticals (China). Polyethylene glycol 400 (PEG 400) and oleic acid were procured from BASF (Germany). All other solvents and chemicals were used during this study were analytical grade and purchased from Merck (Germany).

Preparation method for transdermal film formulations

The preparation method was developed based on the solvent-casting method (Cherukuri et al., 2017; Yener et al., 2010). The following process steps were consecutively applied for this purpose. HPMC, HEC and distilled water were weighed into a beaker. The beaker was airtightly covered with parafilm and left at room temperature for 24 hours to create the aqueous gel. The resulting gel was mixed with a magnetic stirrer at 90 rpm for 30 minutes at 35 °C (Beaker A). The temperature was lowered to 25°C just after this step, and the process was proceeded.

The 5% (w/v) PVP K30 solution that provides matrix formation, was prepared in a separate beaker, mixed with a magnetic stirrer at 180 rpm for 1 hour (Beaker B). The PVP K30 solution in Beaker B was added dropwise to the gel mixture in Beaker A. It was mixed in a magnetic stirrer at 150 rpm for 1 hour.

The 4.5% (w/v) Mirtazapine/ ethanol solution was prepared in another beaker (Beaker C). Mirtazapine-ethanol solution in Beaker C was added dropwise to the contents of Beaker (A+B) and mixed at 200 rpm for 1 hour. The weighted amount of PEG 400 was added dropwise to this mixture and mixed with a magnetic stirrer at 250 rpm for 30 minutes. The resulting gel was kept in an ultrasonic water bath for 1 hour. 20 grams of the final gel mixture were placed in a petri dish. To remove the last air bubbles in the gel, the petri dishes were left at room temperature for 1 hour. It was dried at 38°C for 18 hours.

The basis of formulations, quantification, and the ratio of the selected polymers were created after a detailed review of the previous studies (Cherukuri et al., 2017; Kriplani et al., 2020; Parhi et al., 2022; Saidin et al., 2018; Singh & Bali, 2016; Vlad et al., 2025; Yener et al., 2010). Several films were fabricated with this method, simple physical characterization was carried out (was checked for homogeneous appearance, ease of peeling from the petri dish, being durable and flexible), and 20 formulations were determined to be suitable for carrying out the study. The formulations are given in Table 1. The transdermal films containing Mirtazapine were prepared with the method explained. After determining the formulation that had the highest penetration rate, that formulation was prepared with incorporated oleic acid at a formulation in 4% concentration, to investigate the penetration enhancement effect of oleic acid on the formulated film.

Table 1. Formulation of Mirtazapine transdermal films

Formulation ID	Quantity							
	HPMC		HEC		PVP K30		PEG 400	
	(mg)	(%)*	(mg)	(%)*	(mg)	(%)*	(mg)	(%)*
F1	250	0.8	250	0.8	250	0.8	210	0.7
F2	250	0.8	150	0.5	250	0.8	210	0.7
F3	200	0.6	250	0.8	250	0.8	210	0.7
F4	350	1.1	150	0.5	250	0.8	210	0.7
F5	300	1.0	350	1.1	250	0.8	210	0.7
F6	350	1.1	100	0.3	250	0.8	210	0.7
F7	350	1.1	200	0.6	250	0.8	210	0.7
F8	350	1.1	250	0.8	250	0.8	210	0.7
F9	400	1.3	150	0.5	250	0.8	210	0.7
F10	400	1.3	200	0.6	250	0.8	210	0.7
F11	300	1.0	100	0.3	250	0.8	210	0.7
F12	200	0.6	200	0.6	250	0.8	210	0.7
F13	400	1.3	100	0.3	250	0.8	210	0.7
F14	450	1.4	200	0.6	250	0.8	210	0.7
F15	450	1.4	100	0.3	250	0.8	210	0.7
F16	450	1.4	150	0.5	250	0.8	210	0.7
F17	500	1.6	250	0.8	250	0.8	210	0.7
F18	250	0.8	200	0.6	250	0.8	210	0.7
F19	300	1.8	250	0.8	250	0.8	210	0.7
F20	400	1.3	300	1.0	250	0.8	210	0.7

* % amount of the component in the total weight (25 grams) of the gel prepared to form transdermal films.

Physicochemical evaluation of the transdermal films

Weight variation

1 cm^2 sections were cut out from 10 different points of each prepared film. The sections were weighed one at a time on a precision scale, and the measurements were noted. The mean and SD values of the obtained measurements were calculated (Nandi & Mondal, 2022; Prabhu et al., 2011).

Thickness

1 cm^2 sections were cut out from 10 different points of each film. The thickness of the sections was measured with a digital caliper. The mean and SD values of the measurements obtained were calculated and recorded (Hanbali et al., 2019; Parmar et al., 2023).

Content uniformity test

1 cm^2 sections were cut out from 6 different points of each transdermal film containing Mirtazapine. Each section was placed in a 25 mL volumetric flask, and 10 mL of ethanol was added. It was kept in an ultrasonic water bath to dissolve for 24 hours. The obtained solution was filtered through a membrane filter with a 0.45 µm pore size. The filtrate was then quantitatively analyzed with HPLC to determine the drug content. The mean and SD values of the measurements obtained were calculated and noted (Shivalingam et al., 2021).

Folding endurance test

2 x 2 cm were cut out from each prepared film. The section was folded repeatedly from a precise point until the crack formation was observed on the film surface. The folding endurance value is determined as the number of times the film can be folded at the same place without creating any crack line on the film surface. The test was performed with three films from each formulation (Idrees et al., 2014).

Stability studies

Mirtazapine transdermal films were tested for their physicochemical stability. The films were placed in stability chambers in closed glass petri dishes. They were kept in stability chambers under conditions of 25 ± 2°C, 40 ± 2°C and 75 ± 5% relative humidity. Quantification was performed on samples taken at 1, 3, and 6th months. FTIR examination was also performed on the samples taken in the 6th month.

***In vitro* drug product performance tests**

***In vitro* dissolution test**

Dissolution studies were carried out to obtain dissolution profiles of the six film formulations selected as per their physicochemical properties. The Disk Assembly method was used from the "Dissolution Test for Transdermal Patches" section in the Guide on the Quality of Transdermal Patches in the European Pharmacopoeia (EMA/CHMP/QWP/608924/2014, 2014). For this purpose, a 2x2 cm section was cut out from the film and fixed between the watch glass and a 125 µm mesh stainless steel net. In the study, pH 7.4 phosphate buffer solution (PBS) was used as the dissolution medium. 900 mL of pH 7.4 PBS was taken into the vessel of the dissolution device. The temperature was set at 32±0.5°C. The stirring speed was set at 50 rpm. A sample of 1 mL was taken from the solvent medium at 15 minutes, 30 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours. Following each sample collection, 1 mL of pH 7.4 PBS was immediately added to the vessel. The collected samples were filtered through 0.45 µm pore size PTFE syringe filters. The test was repeated 6 times for each film formulation.

***In vitro* permeation test**

To test the permeation of Mirtazapine from the prepared films through the synthetic skin membrane, a method was created by following the recommendations in the relevant guide of the European Medicines Agency (EMA) (EMA/CHMP/QWP/608924/2014, 2014). The experiment was performed using the Franz diffusion cell system. The Franz cell system used has a heated water jacket. The receptor compartment volume is 12 mL, and the orifice area is 1.77 cm^2. In studies conducted with Franz diffusion cells, the synthetic skin membrane Strat M®, which can simulate human skin, was used. pH 7.4 phosphate buffer was chosen as the dissolution medium, and the study was carried out at 32±0.5°C (Neupane et al., 2020). Before starting the experimental timing, it was ensured that the temperature of both the pH 7.4 phosphate buffer in the receptor chamber and the Strat M® membrane on top of it was allowed to reach 32°C. Experimental timing was initiated by placing the test film section on the membrane. Samples were taken at 15 and 30 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours. Following sample collection, the receptor from the dissolution medium was added to the receptor chamber. Air bubbles that formed in the receptor chamber during sample collection were removed. The samples taken were filtered through a PTFE syringe tip filter with a 0.45 µm pore opening and analyzed by the HPLC quantification method. The experiment was repeated 6 times for each formulation.

Data treatment and statistics

Statistical evaluations of the data were made by using one-way analysis of variance (ANOVA) test in order to determine their differences. The level of significance was set to $\alpha = 0.05$.

RESULTS AND DISCUSSION

In this study, transdermal film formulations of Mirtazapine were successfully prepared using the solvent-casting method. The physicochemical properties of the Mirtazapine transdermal films were investigated, and test results are shown in Table 2.

It was observed that incorporating a higher concentration of HEC into the formulations made the transdermal films remarkably more elastic and durable. This correlates with the existing literature (Birsan et al., 2018; Tudoroiu, 2025).

The weight of different films per cm^2 varied between 9.10 mg ± 0.352 and 14.14 mg ± 0.401. The thickness of different formulations ranged from 0.101 mm ± 0.018 to 0.193 mm ± 0.038. These SD values as-

sured that the preparation method was capable of developing patches with the least intra-batch variability.

Mirtazapine quantity in different formulations varied from 0.47 mg/cm^2 ± 0.044 to 0.56 mg/cm^2 ± 0.058. Minimum SD values in the film drug content variation ensured the uniformity of the prepared films using the solvent casting method.

For all of the formulations, the folding endurance value was greater than 100, which proved that the prepared transdermal film formulations were flexible enough to withstand mechanical force and would be able to keep their physical integrity following the film application onto the skin.

Table 2. The physicochemical properties of Mirtazapine transdermal films

Film ID	Thickness (mm)	SD ±	Film weight (mg/cm^2)	SD ±	Mirtazapine quantity (mg/cm^2)	SD ±	Folding endurance
F1	0.122	0.028	11.48	0.941	0.50	0.031	> 100
F2	0.114	0.019	9.75	0.579	0.51	0.032	> 100
F3	0.126	0.015	9.10	0.352	0.50	0.037	> 100
F4	0.0116	0.020	11.48	1.099	0.53	0.062	> 100
F5	0.193	0.038	13.45	0.793	0.52	0.057	> 100
F6	0.115	0.016	10.47	0.662	0.53	0.045	> 100
F7	0.143	0.029	13.28	0.554	0.53	0.042	> 100
F8	0.123	0.018	10.5	0.714	0.59	0.023	> 100
F9	0.127	0.013	10.85	0.632	0.52	0.068	> 100
F10	0.132	0.024	13.84	0.471	0.54	0.068	> 100
F11	0.101	0.018	11.91	0.395	0.50	0.026	> 100
F12	0.123	0.017	10.91	0.457	0.53	0.050	> 100
F13	0.105	0.018	10.62	0.703	0.56	0.058	> 100
F14	0.146	0.022	14.14	0.401	0.51	0.058	> 100
F15	0.113	0.018	9.84	0.674	0.53	0.059	> 100
F16	0.128	0.026	11.84	0.740	0.48	0.054	> 100
F17	0.187	0.031	12.74	0.696	0.51	0.024	> 100
F18	0.111	0.017	10.48	0.620	0.48	0.054	> 100
F19	0.111	0.009	9.70	0.635	0.47	0.044	> 100
F20	0.159	0.025	12.93	0.827	0.52	0.032	> 100

The stability studies proved that there is no significant change in drug content and the physical characteristics of the prepared film formulations. The results were given in Table 3.

An FT-IR spectrophotometer was used, and IR spectra were obtained by direct analysis with the ATR unit. The device and software are activated in transmission mode. Measurements were made in the wavelength range of 4000-400 cm-1 with a spectral resolution of 4 cm-1. The FT-IR spectra were obtained on day zero and day 180 of the stability studies. Both the overlapping Mirtazapine spectra are given in Figure 1.

Peaks observed in the FT-IR spectrum of Mirtazapine λ (cm-1): 2981-2964: Aliphatic C-H stretch band, 1585-1566: C=N- stretch band, 1442-1494: Aromatic C=C stretch band, 3016-3057: Aromatic C-H stretch band, 763-786: 1.2 disubstituted benzene out-of-plane deformation band.

Table 3. Stability study of Mirtazapine transdermal films

	25 ± 2°C and 75 ± 5% RH				40 ± 2°C and 75 ± 5% RH			
	% Drug content				% Drug content			
Formulation ID	**initial**	**30 days**	**90 days**	**180 days**	**initial**	**30 days**	**90 days**	**180 days**
F1	99.97	99.46	99.37	98.94	99.97	99.38	99.28	98.75
F2	100.06	99.93	99.87	99.80	100.06	99.74	99.70	99.60
F3	100.07	99.99	99.95	99.92	100.07	99.80	99.61	99.19
F4	99.99	99.97	99.91	99.84	99.99	99.70	99.52	99.17
F5	99.73	99.61	99.54	98.92	99.73	99.25	98.89	98.24
F6	99.75	99.68	99.60	98.87	99.75	99.44	99.19	98.22
F7	99.49	99.33	99.21	98.75	99.49	99.12	98.78	98.23
F8	99.62	99.59	99.56	99.47	99.62	99.36	99.11	98.92
F9	99.86	99.78	99.73	99.63	99.86	99.46	99.16	98.79
F10	99.34	99.20	98.92	97.93	99.34	98.78	98.24	97.62
F11	99.55	99.49	99.42	99.32	99.55	99.18	98.95	98.37
F12	99.49	99.22	98.97	98.55	99.49	98.88	98.59	98.16
F13	99.86	99.81	99.72	99.61	99.86	99.57	99.26	98.86
F14	99.97	99.94	99.86	99.76	99.97	99.73	99.42	99.06
F15	99.29	99.19	99.06	98.94	99.29	98.72	98.51	98.13
F16	99.92	99.82	99.46	98.98	99.92	99.46	99.15	98.66
F17	99.27	99.05	98.82	98.20	99.27	98.66	98.22	97.79
F18	99.37	99.18	98.95	98.66	99.37	98.73	98.46	98.17
F19	98.95	98.65	97.95	96.89	98.95	98.40	97.80	97.56
F20	99.59	99.21	98.83	98.12	99.59	99.04	98.56	97.79

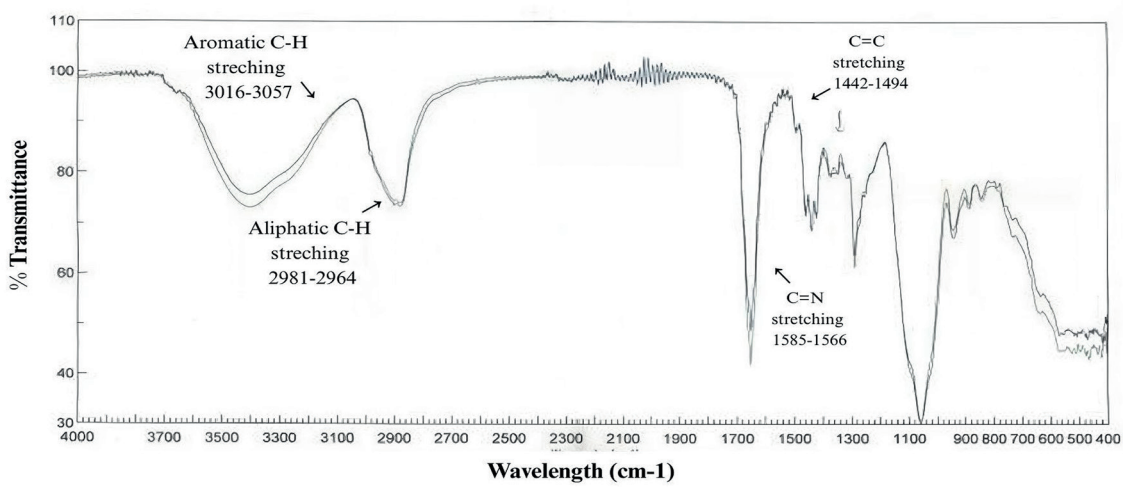

Figure 1. Overlapping image of the Mirtazapine spectra on the initial and day 180

It was determined that the formulations maintained their physical integrity and chemical stability at both 25 ± 2°C and 40 ± 2°C temperatures for 6 months. In line with these findings, it was concluded that transdermal films containing Mirtazapine can be stored at room temperature.

Six of the prepared formulations were tested for their *in vitro* performance. After studying Mirtazapine solubility in different dissolution media, pH 7.4 phos-

phate buffer was selected as the dissolution medium since it effectively simulates physiological environments and assures the Sink condition. The dissolution test was carried out in the Sotax AT-7 dissolution system. The quantitative analysis of the samples was made by using a validated HPLC method. The results were given in Table 4.

The dissolution profiles of the formulations were formed by plotting the % released drug vs. time and are given in Figure 2.

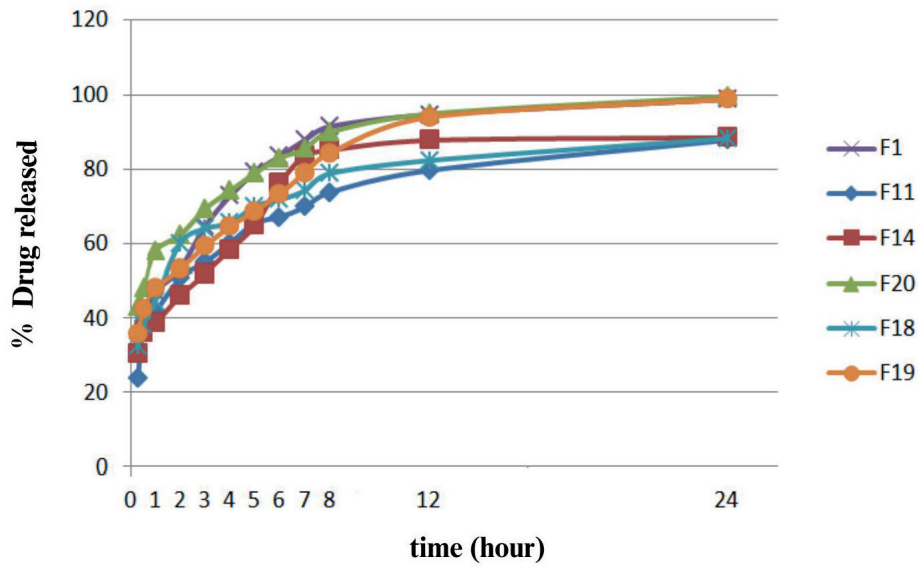

Figure 2. Dissolution profiles of the Mirtazapine transdermal films

Table 4. Dissolution results of Mirtazapine transdermal films

	F11		F14		F20		F1		F18		F19	
Time (hour)	**% released drug**	**SD (±)**	**% released drug**	**SD (±)**	**% released drug**	**SD (±)**	**% released drug**	**SD (±)**	**% released drug**	**SD (±)**	**% released drug**	**SD (±)**
0.25	23.88	0.070	30.62	0.07	43.07	0.048	30.69	0.063	32.41	0.049	35.92	0.059
0.5	39.01	0.036	36.33	0.069	48.10	0.043	39.29	0.062	38.33	0.053	42.52	0.105
1	41.83	0.082	38.67	0.039	57.87	0.069	47.13	0.062	44.66	0.075	48.1	0.090
2	50.78	0.081	46.03	0.092	62.20	0.065	53.19	0.051	60.00	0.054	53.12	0.088
3	54.84	0.135	51.95	0.049	69.22	0.070	64.54	0.086	63.92	0.051	59.17	0.079
4	60.00	0.151	58.28	0.165	74.11	0.064	72.73	0.092	65.37	0.193	64.47	0.088
5	65.37	0.127	64.82	0.107	78.85	0.040	79.06	0.085	69.98	0.191	68.67	0.082
6	67.02	0.082	76.10	0.182	82.98	0.028	83.46	0.075	71.70	0.169	73.28	0.083
7	69.70	0.097	83.67	0.202	85.39	0.024	87.8	0.062	74.17	0.171	78.99	0.055
8	73.69	0.103	85.05	0.169	89.93	0.031	91.44	0.072	78.78	0.159	84.29	0.040
12	79.61	0.044	87.73	0.077	94.89	0.019	94.68	0.076	82.29	0.14	93.99	0.057
24	87.80	0.053	88.49	0.038	99.50	0.017	98.74	0.075	88.28	0.066	98.81	0.039

The data obtained from the dissolution study were plotted in several kinetic models to determine the release kinetics of the transdermal films. The plotted data are presented in Table 5.

Table 5. Release kinetics of Mirtazapine from transdermal film formulations.

		F11	F14	F20	F1	F18	F19
Zero-order kinetics	**k0**	2.3104	2.5569	2.2454	2.6989	2.0971	2.6311
	r2	0.6971	0.6161	0.6724	0.6064	0.6270	0.7590
1st order kinetics	**k1**	0.0733	0.0864	0.1977	0.1734	0.0717	0.1717
	r2	0.9072	0.7092	0.9982	0.9523	0.9523	0.9880
Higuchi	**D**	14.0759	15.9044	13.8475	17.0668	13.1450	15.6225
	r2	0.9076	0.8362	0.8970	0.8505	0.8642	0.9387
Hixson Crowell	**kH**	0.0754	0.0869	0.1287	0.1301	0.0720	0.1280
	r2	0.8437	0.6794	0.9302	0.8393	0.7714	0.9426
Korsmeyer peppas	**n**	0.2963	0.2192	0.1857	0.2799	0.2799	0.1995
	r2	0.9212	0.9717	0.9751	0.9834	0.9839	0.9906

It was determined that when applied to kinetic models, the dissolution profile of the tested films conforms to the Korsmeyer-Peppas, which gave the highest determination coefficient. Depending on the "n" value, the profile fits different drug release mechanisms. The release of the prepared formulations is explained by diffusion in accordance with Fick's law, since the "n" value was obtained as ≤ 0.45. The transdermal films prepared in the study were designed to have a matrix structure. The drug release rate is not constant in matrix structured films; it is related to the concentration gradient, diffusion distance, and swelling degree, and most of the time the release occurs by the Fick diffusion mechanism (Fu & Kao, 2010; Siepmann & Siepmann, 2012).

It is well acknowledged that the quantification of the samples taken within the first hour of the dissolution studies of matrix transdermal films provides more distinctive data for evaluating the dissolution behavior (EMA/CHMP/QWP/608924/2014, 2014).

The dissolution studies were applied to the 6 formulations. The drug release rate wasn't constant, and the drug release didn't follow zero-order kinetics. It showed a distinctive initial burst and subsequently slowed. Particularly, F20, F11 and F19 ($R^2 \approx 0.99$) showed first-order release, meaning a concentration-dependent release rate existed. Korsmeyer Peppas was the best fit for all the formulations, explaining the concentration-dependent and diffusion-controlled kinetics. This substantiates that the release is mainly controlled by diffusion through the polymer matrix, but not by polymer erosion or relaxation.

An evaluation was made in line with the results of the dissolution studies, and 3 formulations were selected for the *in vitro* permeation studies. In the F11, F14 and F18 formulations, less than 45% of the drug amount in the formulation was released in the first hour, and it was observed that the drug release from these formulations continued more than 24 hours. In the designed transdermal film formulation, F11, F14 and F18 were selected to continue with *in vitro* permeation studies, as the preferred feature is that the release extends over a longer time. When the dissolution data is evaluated, release occurs faster in formulations such as F1 and F20 containing higher concentrations of HEC than the transdermal films containing the same amount of HPMC. Therefore, it was concluded that HEC has an increasing effect on the release rate. With an increase in the ratio of HEC, drug release increased, which can be explained by the high water solubility of the polymer due to the multiple hydroxyl groups in its structure. Increased porosity of the polymer matrix led to the rapid dissolution of the drug (Tudoroiu et al., 2025).

In *in vitro* permeation studies, a synthetic skin membrane that can simulate human skin was used. The Merck Strat-M® product, which correlates with working with human skin and is sensitive to penetration enhancers, was preferred (Haq et al., 2018). The *in vitro* permeation study of transdermal film formulations containing Mirtazapine was conducted in the Franz diffusion cell system using pH 7.4 phosphate buffer. The permeation study results were given in Table 6 and Figure 3.

Among the transdermal films tested, at the end of 24 hours, the highest Mirtazapine penetration through the Strat-M® membrane was determined in F14, the formulation containing no penetration enhancer, with a cumulative penetrated amount of 14.41% ($p<0.05$). F18 and F11 provided cumulative permeated amounts of 11.15% and 9.25%, respectively ($p<0.05$). Since the permeation performance was the highest in F14, oleic acid was incorporated into the formulation, and the F14OA formulation was created to study the permeation enhancement effect of oleic acid. The cumulative permeated Mirtazapine amount was 16.07% in F14OA (Table 6). Among the permeation tested formulations, optimal permeation performance was realized by the formulation that comprises the highest ratio of HPMC. This can be attributed to the likely formation of hydrophilic pores within the film structure and the following swelling of the polymer (Aho et al., 2017; Yener et al., 2010).

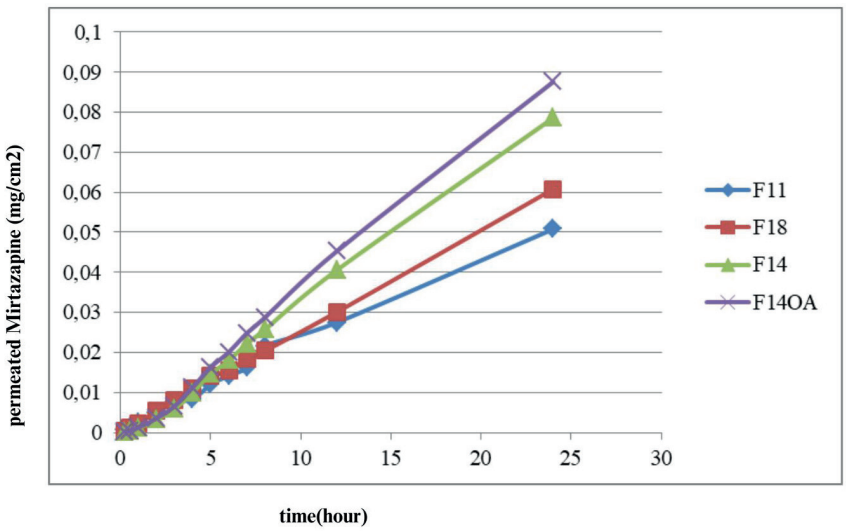

Figure 3. Permeation profiles of Mirtazapine from the different formulations through the Strat-M® membrane

The permeation studies were applied to the 3 formulations, and before reaching the steady-state, all of them had a short lag time of about 2 hours. Between the 4th and 12th hours, for all formulations the permeation increased linearly, showing steady-state flux. This type of kinetics, steady-state following a lag time, suggests Fickian diffusion.

The used non-animal-based, synthetic transdermal diffusion testing membrane was sensitive to the penetration enhancers and simulated Stratum corneum behavior to a comparable degree. Oleic acid incorporation into the F14OA formulation was resulted in improved permeation consistent with the previous studies (Kichou et al., 2023; Rowat et al., 2006; Satpute et al., 2025; Virani et al., 2024).

For all the formulations (F11, F18, F14, F14OA), the flux was calculated and given in Table 7. F14OA had the finest flux, 3.254 µg/cm^2.hour permeation. Recognizing the mandatory *in vivo* and clinical studies requirement, if the bioavailability is reachable by the transdermal drug delivery, it was calculated that 52.972 mg Mirtazapine containing transdermal film in a size of 85.61 cm^2 could present the equivalent treatment as a 15 mg oral tablet administration in a day.

Table 6. Mirtazapine quantity permeated through the Strat-M® membrane.

	F18			F14			F11			F14OA		
time (hour)	**permeated cumulative Mirtazapine quantity (mg/cm²)**	**% permeated cumulative**	**SD (±)**	**permeated cumulative Mirtazapine quantity (mg/cm²)**	**% permeated cumulative**	**SD (±)**	**permeated cumulative Mirtazapine quantity (mg/cm²)**	**% permeated cumulative**	**SD (±)**	**permeated cumulative Mirtazapine quantity (mg/cm²)**	**% permeated cumulative**	**SD (±)**
0.25	0.0005	0.09	0.005	0.0002	0.04	0.005	0.0007	0.13	0.019	0.0002	0.04	0.003
0.50	0.0011	0.20	0.009	0.0003	0.05	0.010	0.0011	0.19	0.014	0.0003	0.05	0.003
1	0.0023	0.42	0.015	0.0011	0.21	0.013	0.0026	0.48	0.022	0.0013	0.23	0.008
2	0.0053	0.98	0.014	0.0032	0.58	0.010	0.0049	0.90	0.015	0.0036	0.65	0.016
3	0.0081	1.49	0.034	0.0059	1.09	0.022	0.0076	1.38	0.063	0.0066	1.21	0.021
4	0.0110	2.03	0.020	0.0099	1.81	0.023	0.0083	1.84	0.024	0.0113	2.07	0.024
5	0.0141	2.58	0.017	0.0146	2.67	0.020	0.0120	2.19	0.018	0.0163	2.98	0.027
6	0.0154	2.82	0.020	0.0180	3.29	0.029	0.0142	2.60	0.015	0.0201	3.68	0.045
7	0.0183	3.36	0.023	0.0222	4.06	0.021	0.0162	2.96	0.017	0.0248	4.54	0.046
8	0.0204	3.75	0.041	0.0257	4.71	0.029	0.0216	3.97	0.014	0.0287	5.26	0.068
12	0.0301	5.52	0.036	0.0406	7.45	0.018	0.0275	5.04	0.026	0.0453	8.31	0.030
24	0.0608	11.15	0.051	0.0786	14.41	0.017	0.0508	9.25	0.025	0.0876	16.07	0.080

Table 7. Cumulative permeated Mirtazapine concentration at Steady-state, flux and permeability coefficient (n=6) (5th hour)

Formulation	Concentration (%)	SD±	Jss (μg/cm².hour)	SD±	P (cm/minute)	SD±
F11	2.19	0.018	2.386	0.011	0.0004	0.00001
F18	2.58	0.017	2.816	0.016	0.0005	0.00001
F14	2.67	0.020	2.913	0.021	0.0005	0.00001
F14OA	2.98	0.027	3.254	0.010	0.0006	0.00001

CONCLUSION

In the presented research study, stable Mirtazapine matrix-type transdermal film formulations were obtained with HMPC, HEC and PVP K30 as polymers and PEG 400 as the plasticizer. The prepared films proved to be of desired pharmaceutical quality and stability by physicochemical tests and FT-IR scanning.

It was found that the developed formulations released Mirtazapine for more than 24 hours. The best permeation profile was obtained in the F14 formulation, which cumulatively penetrated 14.41% ($p < 0.05$) through the synthetic membrane during 24 hours. F14OA, the oleic acid incorporated version of F14, has successfully increased the Mirtazapine permeation by 11.51% through the synthetic membrane during 24 hours.

As a result, Mirtazapine transdermal film formulations were designed and prepared in desired pharmaceutical quality, with an even improved permeation profile by incorporating oleic acid into the formulation as a penetration enhancer. Despite the promising results, certain limitations need to be noted. The study was conducted using an *in vitro* model to test the pharmaceutical quality of the formulations, and further *in vivo* tests are required to confirm the efficacy of the formulation as a human medicine. In light of these considerations, Mirtazapine transdermal film formulations are suggested to be able to improve patient compliance by creating an alternative to the oral use of Mirtazapine, which has limited oral bioavailability.

ACKNOWLEDGEMENTS

The present study was supported by the Research Fund of Istanbul University. Project No. 31926.

AUTHOR CONTRIBUTION STATEMENT

Initial literature survey, experimental design (ÖK, FGY, AK, EMY), sourcing for materials, laboratory work (ÖK), data acquisition and analysis, interpretation of result, writing and revision of the manuscript (ÖK, FGY, AK, EMY).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Aho, J., Halme, A., Boetker, J., Water, J. J., Bohr, A., Sandler, N.,...Baldursdottir, S. (2017). The effect of HPMC and MC as pore formers on the rheology of the implant microenvironment and the drug release *in vitro*. *Carbohydrate Polymers, 177,* 433-442. https://doi.org/10.1016/j.carbpol.2017.08.135

Bathe, R., & Kapoor, R. (2015). Transdermal Drug Delivery System: Formulation, Development and Evaluation-An overview. *IJBAR*, *6*(01). https://doi.org/10.7439/IJBAR.V6I1.1556

Benson, K. K., Zajic, L. B., Morgan, P. K., Brown, S. R., Hansen, R. J., Lunghofer,...Quimby, J. M. (2017). Drug exposure and clinical effect of transdermal mirtazapine in healthy young cats: a pilot study. *Journal of Feline Medicine and Surgery*, *19(10),* 998–1006. https://doi.org/10.1177/1098612X16667168

Berner, B., & John, V. A. (1994). Pharmacokinetic Characterisation of Transdermal Delivery Systems. *Clinical Pharmacokinetics, 26(2)*, 121-134. https://doi.org/10.2165/00003088-199426020-00005

Bird, D., & Ravindra, N. M. (2020). Transdermal Drug Delivery and Patches – An overview. *MEDICAL DEVICES & SENSORS, 3*(6), *e*10069. https://doi.org/10.1002/mds3.10069

Birsan, M., Apostu, M., Todoran, N., Antonoaea, P., Rusu, A., & Ciurba, A. (2018). Development of Dermal Films Containing Miconazole Nitrate. *Molecules, 23,* 1640. https://doi.org/10.3390/molecules23071640

British Pharmacopoeia (2023). CAT 842 Mirtazapine Assay Standard, Safety Data Sheet, Quality Standard.

Brown, M. B., Martin, G. P., Jones, S. A., & Akomeah, F. A. (2006). Dermal and Transdermal Drug Delivery Systems: Current and Future Prospects. *Journal of Drug Delivery Science and Technology, 13*(3), 175-187. https://doi.org/10.1080/10717540500455975

Buhles, W., Quimby, J. M., Labelle, D., & Williams, V. S. (2018). Single and Multiple Dose Pharmacokinetics of a Novel Mirtazapine Transdermal Ointment in Cats. *Journal of Veterinary Pharmacology and Therapeutics, 41*(5), 644-651. https://doi.org/10.1111/jvp.12691

Buzia, O. D., Paduraru, A. M., Stefan, C. S., Dinu, M., Cocos, D. I., Nwabudike, L. C., & Tatu, A. L. (2023). Strategies for Improving Transdermal Administration: New Approaches to Controlled Drug Release. *Pharmaceutics, 15*(4), 1183. https://doi.org/10.3390/pharmaceutics15041183

Carat, H. (2025). Transdermal Drug Delivery: Advantages and Opportunities for Improved Patient Compliance. *Pharmaceutica Analytica Acta, 16*(2). doi: 10.35248/2167-1044.25.16.813

Chandrashekar, N. S., & Shobha Rani, R. H. (2008). Physicochemical and Pharmacokinetic Parameters in Drug Selection and Loading for Transdermal Delivery. *Indian Journal of Pharmaceutical Sciences, 70*(1), 94-96. doi: 10.4103/0250-474X.40340

Cherukuri, S., Batchu, U. R., Mandava, K., Cherukuri, V., & Ganapuram, K. R. (2017). Formulation and Evaluation of Transdermal Drug Delivery of Topiramate. *International Journal of Pharmaceutical Investigation, 7*(1). https://doi.org/10.4103/jphi.jphi_35_16

Croom, K. F., Perry, C. M., & Plosker, G. L. (2009). Mirtazapine A Review of its Use in Major Depression and Other Psychiatric Disorders. *CNS Drugs, 23*(5), 427-452. https://doi.org/10.2165/00023210-200923050-00006

EMA/CHMP/QWP/608924/2014. Guideline on quality of transdermal patches. Committee for Medicinal Products for Human Use (CHMP). 2014.

Eronen, S. T., Kurko, T., Kivela, S. L., Paunio, T., Airaksinen, M., & Rantamaki, T. (2024). Sleep Medicines are Often Prescribed for Older Adults (≥75 years) without Appropriate Dosing Instructions: A Nationwide Retrospective Register Study in Finland. *Acta Psychiatrica Scandinavica, 149,* 350-360. https://doi.org/10.1111/acps.13661

Escobar-Chavez, J. J., Diaz-Torres, R., Rodriguez-Cruz, I. M., Dominguez-Delgado, C. L., Morales, R. S., Angeles-Anguiano, E. A., & Melgoza, L. M. (2012). Nanocarriers for Transdermal Drug Delivery. *Research and Reports in Transdermal Drug Delivery, 1*, 3-17. https://doi.org/10.2147/RRTD.S32621

Ezealisiji, K. E., Mbah, C. J., & Osadebe, P. O. (2015). Aqueous Solubility Enhancement of Mirtazapine: Effect of Cosolvent and Surfactant. *Pharmacology & Pharmacy, 6*, 471-476. https://doi.org/10.4236/pp.2015.610049

Fu, Y., & Kao, W. J. (2010). Drug Release Kinetics and Transport Mechanisms of Non- degredable and Degredable Polymeric Delivery Systems. *Expert Opinion on Drug Delivery, 7*(4), 429–444. https://doi.org/10.1517/17425241003602259

Guy, R. H., & Hadgraft, J. (1985). Transdermal Drug Delivery: a Simplified Pharmacokinetic Approach. *lnternational Journal of Pharmaceutics, 24,* 267-274. https://doi.org/10.1016/0378-5173(85)90026-2

Hanbali, O., Khan, H. M. S., Sarfraz, M., Arafat, M., Ijaz, S., & Hameed, A. (2019). Transdermal Patches: Design and Current Approaches to Painless Drug Delivery. *Acta Pharmaceutica, 69,* 197–215. https://doi.org/10.2478/acph-2019-0016

Haq, A., Goodyear, B., Ameen, D., Joshi, V., & Michniak-Kohn, B. (2018). Strat-M® synthetic membrane: Permeability comparison to human cadaver skin. *International Journal of Pharmaceutics, 547,* 432–437. https://doi.org/10.1016/j.ijpharm.2018.06.012

Harnett, A., Byrne, S., O'Connor, J., Lyons, D., & Sahm, L. J. (2023). Adult Patients with Difficulty Swallowing Oral Dosage Forms: A Systematic Review of the Quantitative Literature. *Pharmacy, 11*(5), 167. https://doi.org/10.3390/pharmacy11050167

He, H., Li, X., Yuan, D., Huang, X., Qiu Z., Hong, Y., He, J.,...Lu, S. (2025). Novel Therapeutic Deep Eutectic Solvents Based on Mirtazapine and Medium-chain Fatty acids for Enhancing the Transdermal Delivery of Mirtazapine. *International Journal of Pharmaceutics, 670*, 125133. https://doi.org/10.1016/j.ijpharm.2024.125133

Idrees, A., Rahman, N. U., Javaid, Z., Kashif, M., Aslam, I., Abbas, K., & Hussain, T. (2014). In vitro Evaluation of Transdermal Patches of Flurbiprofen with Ethyl Cellulose. *Acta Poloniae Pharmaceutica - Drug Research, 71*(2), 287-295. Retrieved from https://www.ptfarm.pl

Jeong, W. Y., Kwon, M., Choi, H. E., & Kim, K. S. (2021). Recent Advances in Transdermal Drug Delivery Systems: a review. *Biomaterials Research, 25*(1), 24. doi: 10.1186/s40824-021-00226-6

Kichou, H., Bonnier, F., Dancik, Y., Bakar, J., Michael-Jubeli, R., Carita, A. C., Perse, C.,...Munnier, E. (2023). Strat-M® Positioning for Skin Permeation Studies: A Comparative Study Including EpiSkin® RHE, and Human Skin. *International Journal of Pharmaceutics, 647*, 123488. https://doi.org/10.1016/j.ijpharm.2023.123488

Kriplani, P., Guarve, K., & Baghel, U. S. (2020). Formulation optimization and characterization of transdermal film of curcumin by response surface methodology. *Chinese Herbal Medicines, 13*(2), 274–285. https://doi.org/10.1016/j.chmed.2020.12.001

Laurn, P., & Arean, M. (2024). Advances in Transdermal Drug Delivery Systems for Systemic Disease Management. *JAPRSS, 1(1)*, 1-12. https://doi.org/10.70177/japrss.v1i1.12663

Liu, S., Li, H., Zhang, Y., Gong, K., & Fang, L. (2025). Combining Ion-pair Strategy and Chemical Enhancers to Develop Mirtazapine Long-acting Transdermal Patches for Depression Treatment. *Journal of Drug Delivery Science and Technology, 103,* 106435. https://doi.org/10.1016/j.jddst.2024.106435

mirataz.com/pi.(2025). Mirataz (Mirtazapine trans-

dermal ointment) product label. Retrieved from mirataz.com/pi. Access date: 13.09.2025.

Nandi, S., & Mondal, S. (2022). Fabrication and Evaluation of Matrix Type Novel Transdermal Patch Loaded with Tramadol Hydrochloride. *Turkish Journal of Pharmaceutical Sciences, 19*(5), 572–582. doi: 10.4274/tjps.galenos.2021.43678

Neupane, R., Boddu, S. H. S., Renukuntla, J., Babu, R. J., & Tiwari, A. K. (2020). Alternatives to Biological Skin in Permeation Studies: Current Trends and Posibilities. *Pharmaceutics, 12,* 152. https://doi.org/10.3390/pharmaceutics12020152

Nguyen, P. V. Q., Dangvu, T. T., Forest, G., Desjardins, S., Forget, M. F., Vu, T. T., Nguyen, Q. D.,...Desmarais, P. (2025). Mirtazapine for chronic insomnia in older adults: a randomised double-blind placebo-controlled trial-the MIRAGE study. *Age and Aging*, *54*(3), 2025. https://doi.org/10.1093/ageing/afaf050

Parhi, R., Sahoo, S. K., & Das, A. (2022). Applications of Polysaccharides in Topical and Transdermal Drug Delivery: A Recent Update of Literature. *Brazilian Journal of Pharmaceutical Sciences, 58,* e20802. https://doi.org/10.1590/s2175-97902022e20802

Parmar, K., Patel, M., Patel, M., Soni, T., & Suhagia, B. (2023). Development and Evaluation of Buspirone Hydrochloride Loaded Transdermal Patch Using Natural Polymers. *Hacettepe University Journal of the Faculty of Pharmacy, 43*(4), 310-322. https://doi.org/10.52794/hujpharm.1214109

Pastore, M. N., Kalia, Y. N., Horstmann, M., & Roberts, M. S. (2015). Transdermal patches: History, Development and Pharmacology. *British Journal of Pharmacology, 172*, 2179–2209. https://doi.org/10.1111/bph.13059

Patel, D., Chaudhary, S. A., Parmar, B., & Bhura, N. (2012). Transdermal Drug Delivery System: A Review. *The Pharma Journal, 1*(4), 66-75. Retrieved from https://www.thepharmajournal.com/archives/

Ping L. (2011). Modeling of Drug Release From Matrix Systems Involving Moving Boundaries: Approximate Analytical Solutions. *International Journal of Pharmaceutics, 418*(1), 18-27 https://doi.org/10.1016/j.ijpharm.2011.01.019

Poole, M., Quimby, J. M., Hu, T., & Labelle, D. (2019). A Double-blind, Placebo-controlled, Randomized Study to Evaluate the Weight Gain Drug, Mirtazapine Transdermal Ointment, in Cats with Unintended Weight Loss. *Journal of Veterinary Pharmacology and Therapeutics, 42*, 179–188. https://doi.org/10.1111/jvp.12738

Prabhu, P., Shah S., & Gundad, S. (2011). Formulation Development and Investigation of Domperidone Transdermal Patches. *International Journal of Pharmaceutical Investigation, 1*(4). doi: 10.4103/2230-973X.93008

RX Media Pharma, Interactive Drug Information Resource, 2023. Retrieved from the RX Media Pharma Database.

Ramadon, D., McCrudden, M. T. C., Courtenay, A. J., & Donnelly, R. F. (2022). Enhancement Strategies for Transdermal Drug Delivery Systems: Current Trends and Applications. *Drug Delivery and Translational Research, 12*, 758–791. doi: 10.1007/s13346-021-00909-6

Rowat, A. C., Kitson, N., & Thewalt, J. L. (2006). Interactions of Oleic acid and Model Stratum corneum Membranes as Seen by 2H NMR. *International Journal of Pharmaceutics, 307,* 225–231. https://doi.org/10.1016/j.ijpharm.2005.10.008

Saidin, N. M., Anuar, N. K., & Affandi, M. M. R. M.

M. (2018). Roles of Polysaccharides in Transdermal Drug Delivery System and Future Prospects. *Journal of Applied Pharmaceutical Science, 8*(03), 2018: 141-157. doi: 10.7324/JAPS.2018.8320

Satpute, R., Salve, P. S., Qutub, M., & Hussain, U. M. H. (2025). Enhanced systemic delivery of mirtazapine through transdermal drug-in-adhesive matrix: A sustained-release approach. *Next Nanotechnology, 8*, 100151. https://doi.org/10.1016/j.nxnano.2025.100151

Shivalingam, M. R., Balasubramanian, A., & Ramalingam, K. (2021). Formulation and Evaluation of Transdermal Patches of Pantoprazole Sodium. *International Journal of Applied Pharmaceutics, 13*(5), 287-291. doi: 10.22159/ijap.2021v13i5.42175

Siepmann, J., & Peppas, N. A. (2011). Higuchi Equation: Derivation, Applications, Use and Misuse. *International Journal of Pharmaceutics, 418*(1), 6-12. https://doi.org/10.1016/j.ijpharm.2011.03.051

Siepmann, J., & Siepmann F. (2012). Modeling of Diffusion Controlled Drug Delivery. *Journal of Controlled Release, 161,* 351–362. https://doi.org/10.1016/j.jconrel.2011.10.006

Singh, A., & Bali, A. (2016). Formulation and Characterization of Transdermal Patches for Controlled Delivery of Duloxetine Hydrochloride. *Journal of Analytical Science and Technology, 7,* 25. doi: 10.1186/s40543-016-0105-6

Tanwar, H., & Sachdeva, R. (2016). Transdermal Drug Delivery System: A Review. *IJPSR, 7*(6), 2274-2290. doi: 10.13040/IJPSR.0975-8232.7(6).2274-90

Tiwary, A. K., & Sapra, B. (2007). Innovations in Transdermal Drug Delivery: formulations and Techniques. Recent *Patents on Drug Delivery & Formulation, 1*, 23-36. doi: 10.2174/187221107779814087

Tudoroiu, E. E., Kaya, M. G. A., Dinu-Pirvu, C. E., Popa, L., Anuta, V., Ignat, M., Visileanu, E.,...Ghica, M. V. (2025). Development of Smart pH-Sensitive Collagen-Hydroxyethylcellulose Films with Naproxen for Burn Wound Healing. *Pharmaceuticals, 18*(5), 689. https://doi.org/10.3390/ph18050689

Velasco-Aguirre, C., & Sintov, A. C. (2019). Microemulsions and Nanoparticles as Carriers for Dermal and Transdermal Drug Delivery. *Journal of Pharmacology & Pharmaceutical Research, 2*(4), 1–12. doi: 10.31038/JPPR.2019241

Virani, A., Dholaria, N., Mohd, H., Albayati, N., & Michniak-Kohn, B. (2024). Effect of chemical penetration enhancers on the transdermal delivery of olanzapine in human skin in vitro. *AAPS Open, 10,* 4. doi: 10.1186/s41120-024-00092-1

Vlad, R. A., Pintea, A., Pintea, C., Redai, E. M., Antonoaea, P., Birsan, M., & Ciurba, A. (2025). Hydroxypropyl Methylcellulose—A Key Excipient in Pharmaceutical Drug Delivery Systems. *Pharmaceutics, 17, 784*. https://doi.org/10.3390/pharmaceutics17060784

Waghulde, S., Naik, P. P., Gorde, N., Juvatkar, P., Shirodkar, P. Y., & Kale, M. K. (2013). Development, Recent Inventions and Evaluation Techniques of Transdermal Drug Delivery System - A Review. *International Journal of Pharmaceutical and Phytopharmacological Research, 3*(2), 152-160. Retrieved from https://eijppr.com

Watanebe, N., Omori, I. M., Nakagawa, A., Cipriani, A., Barbui, C., Churcill, R., & Furukawa, T. A. (2011). Mirtazapine versus other Antidepressive Agents for Depression. *Cochrane Database Syst Rev, 12*. doi: 10.1002/14651858.CD006528.pub2

Wolff, H. M. (2000). Optimal Process Design for the Manufacture of Transdermal Drug Delivery Systems. *Pharmaceutical Science & Technology Today, 3*(5), 173-181. https://doi.org/10.1016/S1461-5347(00)00251-0

Wong, W. F., Ang, K. P., Sethi, G., & Looi, C. Y. (2023). Recent Advancement of Medical Patch for Transdermal Drug Delivery. *Medicina, 59,* 778. https://doi.org/10.3390/medicina59040778

Yener, G., Üner, M., Gönüllü, Ü., Yıldırım, S., Kılıç, P., Aslan, S. S., & Barla, A. (2010). Design of Meloxicam and Lornoxicam Transdermal Patches: Preparation, Physical Characterization, ex Vivo and in Vivo Studies. *Chemical and Pharmaceutical Bulletin, 58*(11), 1466—1473. https://doi.org/10.1248/cpb.58.1466

Zhan, X., Mao, Z., Chen, J., & Zhang, Y. (2015). Acrylate Copolymer: A Rate-Controlling Membrane in the Transdermal Drug Delivery System. *e Polymers, 15(1),* 55–63. doi: 10.1515/epoly-2014-0123