



Impact of various electromagnetic fields on the transdermal permeability of naproxen and the effect of active compound exposure on magnetic field properties

Rafał Rakoczy^a, Karolina Zyburtowicz-Ćwiartka^c, Maciej Konopacki^a, Anna Nowak^b, Kararzyna Piotrowska^d, Anna Muzykiewicz-Szymańska^b, Łukasz Kucharski^b, Marian Kordas^a, Paula Ossowicz-Rupniewska^{c,*}

^a West Pomeranian University of Technology in Szczecin, Faculty of Chemical Technology and Engineering, Department of Chemical and Process Engineering, Piastów Ave. 42, 71-065 Szczecin, Poland

^b Pomeranian Medical University in Szczecin, Department of Cosmetic and Pharmaceutical Chemistry, Powstańców Wielkopolskich Ave. 72, 70-111 Szczecin, Poland

^c West Pomeranian University of Technology in Szczecin, Faculty of Chemical Technology and Engineering, Department of Organic Chemical Technology and Polymer Materials, Piastów Ave. 42, 71-065 Szczecin, Poland

^d Pomeranian Medical University in Szczecin, Department of Physiology, Powstańców Wielkopolskich Ave. 72, 70-111 Szczecin, Poland

ARTICLE INFO

Keywords:

Electromagnetic Field
Active pharmaceutical ingredients
Nonsteroidal anti-inflammatory drugs
Naproxen
Transdermal drug delivery
Skin barrier

ABSTRACT

Transdermal drug delivery systems present a promising alternative to oral administration, though improving skin permeability of active pharmaceutical ingredients (APIs) remains challenging. This study examines how various electromagnetic fields (EMFs) affect the transdermal permeability of naproxen (NAP) and its physicochemical properties. Using pigskin as a model, NAP permeability was tested under oscillating, pulsed, static, and rotating magnetic fields (RMF), compared to a control group without EMF exposure. The results show significant differences in NAP permeability depending on EMF type, with RMF at 50 Hz yielding the highest cumulative permeation mass (CPM) of $1461.40 \pm 256.15 \mu\text{g}/\text{cm}^2$, compared to $267.57 \pm 41.74 \mu\text{g}/\text{cm}^2$ for the control. RMF 50 Hz also maximized steady-state flux (J_{ss}) and permeability coefficient (K_p), highlighting its potential for enhanced transdermal delivery. Conversely, static magnetic fields with negative polarization reduced permeation, showing a complex interaction between magnetic fields and skin permeability. The study also found that RMF treatments lowered NAP skin accumulation, improving permeation efficiency. Physicochemical analyses (FTIR, XRD, solubility, and lipophilicity) revealed that while EMF exposure did not significantly change NAP's crystal structure, it did affect solubility and partition coefficient. This research highlights the potential of optimizing EMF parameters to enhance transdermal drug delivery and provides insights into the physicochemical interactions between EMFs and active compounds. The findings suggest that rotating magnetic fields, particularly at 50 Hz, offer the most significant improvement in drug permeability, which could be beneficial for developing advanced transdermal delivery systems.

1. Introduction

Electromagnetobiology is a scientific discipline focused on exploring the effects of electromagnetic fields (EMF) on living organisms and cells. EMF comprises electric and magnetic fields, each playing a crucial role in biological processes [1–4]. An electric field (EF) arises from the presence of an electric charge and is characterized by the magnitude and

direction of the force it exerts on a charged particle. In contrast, a magnetic field (MF) is generated by electric currents and acts on moving electric charges and objects with a magnetic moment. The strength of an MF is directly proportional to the current flow in a conductor. Both static (constant over time) and alternating (time-varying) magnetic fields are utilized to enhance mass transfer processes. While static magnetic fields (SMF) do not transmit energy to living cells, they can alter the energy

* Corresponding author at: West Pomeranian University of Technology in Szczecin, Faculty of Chemical Technology and Engineering, Department of Chemical Organic Technology and Polymeric Materials, Piastów Ave. 42, 71-065 Szczecin, Poland.

E-mail address: possowicz@zut.edu.pl (P. Ossowicz-Rupniewska).

<https://doi.org/10.1016/j.ejpb.2025.114715>

Received 22 October 2024; Received in revised form 21 March 2025; Accepted 3 April 2025

Available online 23 May 2025

0939-6411/© 2025 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

levels of specific molecules. However, rotating magnetic fields (RMF) have been shown to increase process intensity by generating hydrodynamic states that enhance mixing and mass transfer, as demonstrated in applications involving magnetic particles and magnetically supported mixers [5].

Transdermal drug delivery systems (TDDS) have become a significant area of research and development due to their potential to provide controlled release of therapeutic agents through the skin. These systems offer numerous advantages, such as bypassing the gastrointestinal tract, avoiding first-pass metabolism, and enhancing patient compliance through non-invasive administration. However, the efficacy of TDDS can be limited by the *stratum corneum*, the outermost layer of the skin, which acts as a primary barrier to drug permeation [6–13]. Recent advancements in biomedical engineering have explored the use of electromagnetic fields (EMFs) to enhance transdermal drug delivery. EMFs are known to influence biological systems at the cellular and molecular levels, potentially increasing the permeability of the skin and facilitating the transport of active pharmaceutical ingredients (APIs). Various types of EMFs, including oscillating, pulsed, static, and rotating magnetic fields, have been studied for their effects on drug permeability and bioavailability [12,14–20].

Previous research has demonstrated that both pulsed and constant electromagnetic fields can enhance the permeability of active pharmaceutical ingredients (APIs) through the skin. For example, pulsed electromagnetic fields (PEMF) have been shown to increase the permeability of drugs such as 5-aminolevulinic acid [16], naltrexone [21], and dipeptide [14]. Furthermore, magnetophoretic drug permeation enhances drug movement through the skin by inducing rotation and movement of charged particles under the influence of EMF. Our earlier studies have shown that rotating magnetic fields (RMF) significantly enhance the permeability of various APIs, including caffeine, ibuprofen, naproxen, ketoprofen, and paracetamol, through porcine skin. These findings highlight the potential of RMF to increase drug transport efficiency, making it a valuable tool in developing innovative transdermal drug delivery systems [22,23].

Naproxen ((+)-(S)-2-(6-Methoxynaphthalen-2-yl)propanoic acid) (NAP) is one of the nonsteroidal anti-inflammatory drugs, a derivative of 2-arylpropionic acid. It is recommended for the treatment of gout, osteoarthritis, and other similar conditions. Naproxen has anti-inflammatory and analgesic effects and is used to relieve mild to moderate pain, including headache, toothache, muscle pain and menstrual pain. It is usually administered orally, less frequently locally, intravenously or rectally. Commercially available in the form of tablets and capsules with prolonged and controlled release, as well as in the form of gels and suppositories [24–26]. It serves as an ideal candidate for investigating the impact of EMFs on transdermal drug delivery. Its relatively low molecular weight and favourable physicochemical properties make it suitable for transdermal administration. However, the potential for EMFs to enhance skin permeation has not been thoroughly explored.

This study aims to evaluate the impact of different types of magnetic fields on the transdermal permeability of naproxen. The fields used in our experiments include an oscillating magnetic field with a frequency of 45–65 Hz and a maximum induction of 26–35 mT; a pulsating magnetic field with a frequency of 65 Hz, a maximum induction of 26 mT, and a pulse duration of 1–10 s; a positive polarity static magnetic field with a DC voltage of 5–25 V and a maximum induction of 4–21 mT; a negative polarity static magnetic field with a DC voltage of 5–25 V and a maximum negative induction of 3–15 mT; and a rotating magnetic field with a frequency of 10–50 Hz and a maximum induction of 33–45 mT. Additionally, this research will explore how these fields affect the physicochemical properties of naproxen, including solubility, crystal structure, lipophilicity, thermal stability, and phase transition temperatures. The study will also determine the permeability of naproxen from 1 % ethanol solutions through porcine skin.

By systematically examining the effects of various EMFs on the

transdermal transport of naproxen, this research aims to provide valuable insights into the optimization of TDDS for enhanced drug delivery. Understanding the interaction between EMFs and biological tissues, particularly in the context of transdermal drug delivery, can pave the way for innovative therapeutic strategies. This study contributes to the growing body of knowledge in this field and opens up new possibilities for improving the efficiency and effectiveness of transdermal drug delivery systems.

2. Materials and methods

2.1. Materials

A commercially available active substance from the group of nonsteroidal anti-inflammatory drugs was used for the research – naproxen of purity $\geq 98\%$ was provided by AmBeed (Arlington Hts, IL, USA). Acetonitrile (for HPLC, gradient grade ($\geq 99.9\%$)) and PBS tablets were acquired from Sigma-Aldrich (Steinheim am Albuch, Germany). Methanol (for HPLC ($\geq 99.9\%$)) was supplied by Honeywell (Charlotte, NC, USA). Orthophosphoric acid ($\geq 99\%$) and potassium dihydrogen phosphate (analytical grade) were obtained from Merck (Darmstadt, Germany). All reagents and solvents were obtained from commercial suppliers and used as received without further purification. A local slaughterhouse provided porcine skin.

2.2. Magnetic field exposure

In this study, various types of electromagnetic fields were applied to naproxen for an 8-hour exposure, ensuring consistency with *in vitro* permeation testing (IVPT) conditions. A sample of NAP was exposed to a magnetic field, and the properties of the compound were examined. The control sample was naproxen, not exposed to a magnetic field.

The naproxen used for physicochemical characterization tests was in solid form and was directly exposed to the electromagnetic field without ethanol to specifically evaluate the effect of electromagnetic fields on the active pharmaceutical ingredient itself. Subsequent FTIR, DSC, and XRD analyses were conducted immediately after exposure to capture potential structural or thermal modifications.

The experiments involved the following types of magnetic fields:

- Oscillating Magnetic Field: This field had a supply current frequency of 45–65 Hz and a maximum magnetic induction of 26–35 mT.
- Pulsating Magnetic Field (oscillating magnetic field operating in ON-OFF mode): This field was characterized by a supply current frequency of 65 Hz, a maximum magnetic induction of 26 mT, and a pulse duration of 1–10 s (ON-OFF mode).
- Positive Polarity Static Magnetic Field: This field used a direct current supply voltage of 5–25 V and had a maximum magnetic induction of 4–21 mT.
- Negative Polarity Static Magnetic Field: This field also used a direct current supply voltage of 5–25 V but had a maximum negative magnetic induction of 3–15 mT.
- Rotating Magnetic Field: This field had a supply current frequency of 10–50 Hz and a maximum magnetic induction of 33–45 mT.

Fig. 1 illustrates the experimental setup, which included reactors equipped with electromagnetic field generators. The system consisted of several reactors, allowing for simultaneous experimentation using oscillating, pulsating, positive and negative polarity static, and rotating magnetic fields, as well as a control trial. All reactors were connected to a temperature stabilization system to prevent temperature fluctuations during the process.

The main component of the magnetically assisted reactor is the magnetic field (MF) generator, which produces both direct current (DC) and alternating current (AC) magnetic fields. The magnet assembly consists of three identical pairs of coils, symmetrically spaced apart

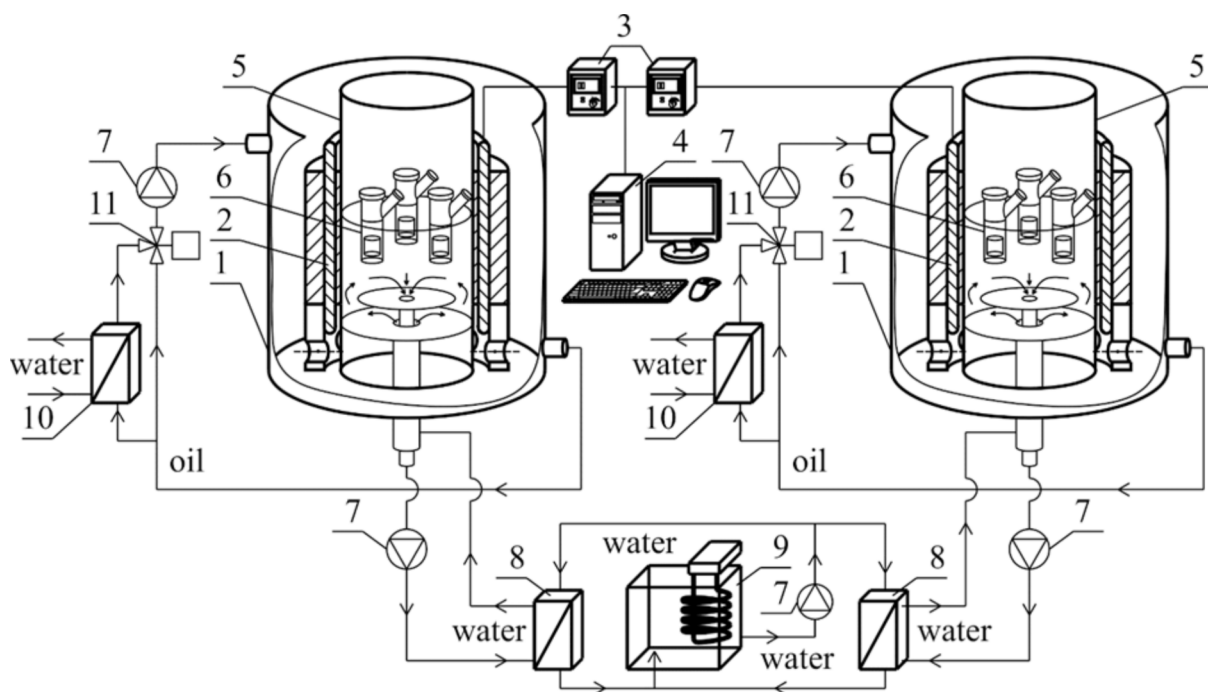


Fig. 1. Schematic of magnetically assisted reactor: 1) tank, 2) induction motor, 3) inverter, 4) PC, 5) cultivation tank, 6) Franz diffusion cell, 7) pump, 8) plate heat exchanger, 9) thermostat, 10) oil heat exchanger, 11) control valve.

(requiring the purchase of generators). It is assumed that each winding has at least one pair of poles. Each coil can be powered individually or in combination with others in various configurations. This flexibility allows the generators to produce different types of magnetic fields, including oscillating (OMF), pulsating (PMF), static (SMF), and rotating (RMF) magnetic fields. The winding connection diagram for the designed setup is shown in Fig. 2.

The magnetic field (MF), as a manifestation of the electromagnetic field, can be considered as the space surrounding a magnet or a material through which current flows. It is generated by moving electrical charges and is characterized by its effect on charged particles, on which it exerts a force. The physical quantity used to describe a magnetic field is magnetic induction, which determines the field's intensity. Generally, the greater the magnetic induction, the stronger the influence of the MF. As mentioned above, MFs can be divided into two main types: direct current magnetic fields (DCMF) and alternating current magnetic fields (ACMF). DCMFs do not change with time or change very slowly, so they have no frequency (the MF vector remains constant in time and space). An example of a constant current MF is a static magnetic field (SMF). In contrast, ACMFs vary with frequency. An example of this type of MF is an oscillating magnetic field (OMF), characterized by an external MF vector that changes as a sine wave over time at each point in space. The vector of this field oscillates with the frequency of the current flowing through the coil. Additionally, the superposition of three OMFs, each 120° out of phase, produces a rotating magnetic field (RMF). This field has a constant intensity over time but continuously changes direction at every point in the domain (RMF is variable in space). Such a field is created, for example, in the stator and rotor windings when the windings are supplied with current, enabling engine rotation. The OMF is generated by periodically switching the oscillating field on and off.

Each reactor is comprised of a stainless steel tank containing induction stators for squirrel cage motors. The stator assemblies were powered by alternating current (for oscillating, pulsed, and rotating fields) or direct current (for static magnetic fields). For the former, a frequency converter (inverter) connected to a computer-controlled the operational parameters. In the case of static magnetic fields, the stators were connected to power supplies. Inside the generators, plexiglass

processing chambers held the sample holders. These holders were placed in a water bath with circulating water samples flowing through the heat exchanger system. The heat exchanger was supplied with hot water from a precision thermostat, maintaining a constant water temperature with deviations of about 0.1 °C. The stator windings were cooled with silicone oil, which absorbed the excess heat generated by the stators during operation. The silicone oil circulates in an external loop equipped with a heat exchanger supplied by tap water. The oil flow in the external loop was controlled by a three-way valve connected to a temperature sensor and controller, ensuring a stable oil temperature.

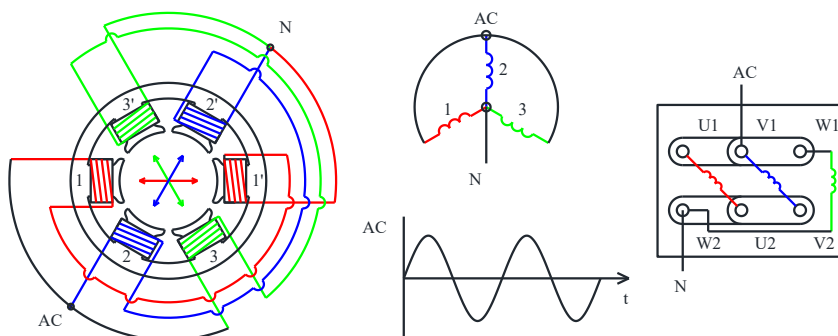
Similarly, naproxen permeability was tested using a simple formulation (1 % solution of the active substance in 70 % EtOH). In this case, the tests used Franz diffusion chambers (Phoenix DB-6, ABL&E-JASCO, Wien, Austria) which were placed in appropriate electromagnetic field generators.

The study utilized diffusion chambers with an area of 1 cm² and an acceptor chamber with a volume of 10 cm³, filled with PBS solution (pH 7.4) maintained at a constant temperature of 37.0 ± 0.1 °C. Porcine skin, 0.05 cm thick and with appropriate impedance, served as the permeable membrane. Each donor chamber received 1 ml of the active pharmaceutical ingredient (API) at a concentration of 1 % in 70 % ethanol. The experiments were conducted 8 h, with samples collected at intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h. The API content in the samples was measured using HPLC (standard curve method). *Ex vivo* permeability studies utilized porcine abdominal skin, which was commercially acquired as a byproduct from routine food processing at a local slaughterhouse. Since the skin samples were not specifically collected for research but obtained as regular food industry waste material, ethical approval was not necessary under applicable local regulations.

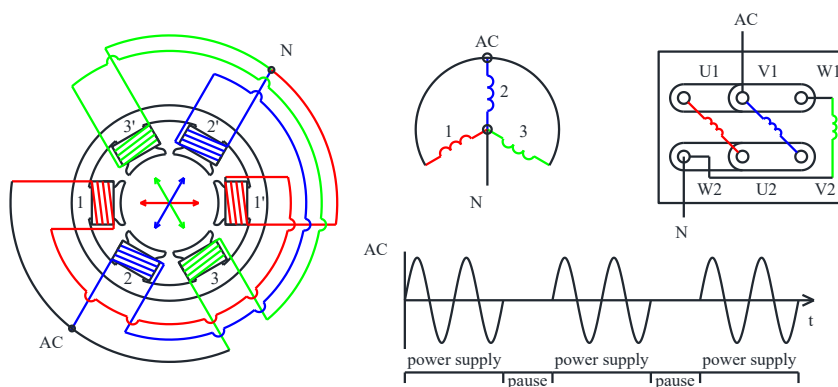
The accumulation of NAP in the skin following its penetration after 8 h was assessed using previously established methods [27–30]. The supernatant was collected and analyzed via HPLC. The concentration of NAP in the skin was determined by dividing the amount of drug retained in the skin by the mass of the skin sample and is expressed as the mass of ibuprofen per unit mass of the skin (µg/g).

The HPLC system, from Knauer (Berlin, Germany), included a model 2600 UV detector, a Smartline model 1050 pump, and a Smartline model

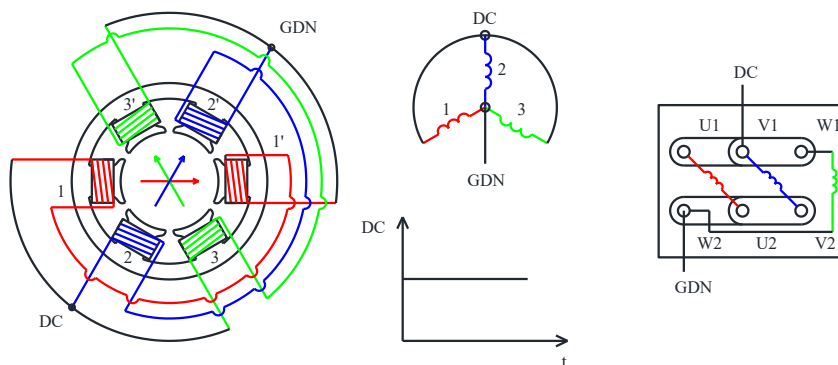
Oscillating Magnetic Field (OMF)



Pulsating Magnetic Field (oscillating magnetic field operating in ON-OFF mode; PMF)



Positive and Negative Polarity Static Magnetic Field (SMF)



Rotating Magnetic Field (RMF)

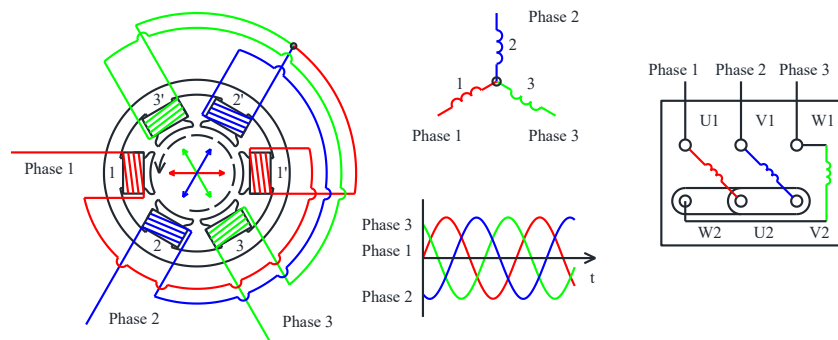


Fig. 2. Schematic of the experimental setup with reactors equipped with electromagnetic field generators.

3950 autosampler, all controlled by ClarityChrom 2009 software. A chromatographic column (125 × 4 mm) packed with Hyperisil ODS (C18), with a particle size of 5 µm, was used. The mobile phase consisted of 0.02 mol/dm³ potassium dihydrogen phosphate-acetonitrile-methanol (45/45/10, v/v/v), adjusted to pH 2.5 with orthophosphoric acid. The spectrophotometric detector was set at 220 nm, with a flow rate of 1 cm³/min. The column temperature was maintained at 25 °C, and the injection volume was 20 µL.

Fick's laws of diffusion were applied to characterize the kinetic profile of *in vitro* infinite dose steady-state percutaneous absorption. Permeation parameters such as flux (J_{ss}), the diffusion coefficient (K_p), and the time required to reach steady-state permeation (lag time – L_T) were determined.

2.3. Spectroscopic and physicochemical properties

Naproxen exposed to an electromagnetic field was examined using infrared spectroscopy. Data were collected on a Thermo Scientific (Waltham, Massachusetts, United States) Nicolet 380 spectrometer equipped with a diamond plate. The spectra were recorded in the transmission mode in the range of 4000–400 cm^{−1} at a resolution of 4 cm^{−1}.

Identification of the crystalline phases of the tested substances was carried out by X-ray powder diffraction (XRD) analysis using an Aeris X Rays ON X-ray diffractometer from Malvern Panalytical Ltd. (Malvern, Great Britain). Cu-Kα radiation ($\lambda = 1.54056 \text{ \AA}$) was used for measurements in the range of 2θ angles from 7 to 90°.

To examine the thermal stability of the tested compounds, thermogravimetric (TG) analysis was performed using the Netzch Proteus Thermal 209 F1 Libra (Selb, Germany). The tests were performed in a nitrogen atmosphere with a flow of 10 cm³/min and an air atmosphere with a 25 cm³/min flow. The temperature range was from 25 °C to 1000 °C, and the heating rate was set at 10 °C/min. The sample weight was 5.2 ± 0.2 mg, and aluminium oxide (Al₂O₃) crucibles were used for testing.

The phase transition temperature was determined by differential scanning calorimetry (DSC) on a TA Instruments model DSC 250 (New Castle, Delaware, United States). Aluminium hermetic crucibles with a lid were used for the tests, and the sample weight was in the range of 8–9 mg. The analysis was carried out in a nitrogen atmosphere and was carried out in 3 cycles: heating – cooling – heating. The temperature range was set individually for each analyzed compound, heated to a temperature at least 10 °C lower than the beginning of decomposition, and determined based on TG analysis. Naproxen was heated to 140 °C, cooled to −90 °C and then heated again to 140 °C. The temperature program range for naproxen, ketoprofen and salicylic acid was from −90 °C to 190 °C, and for NAP from −90 °C to 170 °C.

The specific rotation $[\alpha]$ was examined using an AUTOPOL IV polarimeter from Rudolph Research Analytical (Hackettstown, New Jersey, United States) at 25 °C at a wavelength of 590 nm. A measuring cell with a length of 50 mm was used. The determinations were carried out for solutions in anhydrous ethanol at a 5 mg/ml concentration.

The solubility of substances in water was determined by assessing the concentration of saturated solutions. For this purpose, 2 ml of deionized water was added to 15–20 mg of the substance. The samples were mixed on a magnetic stirrer for 24 h at 25 °C. After this time, the samples were filtered using a cellulose syringe filter made of cellulose esters (MCE – cellulose acetate/cellulose nitrate, 25 mm, 0.45 µm). The concentration of the substance was determined using high-performance liquid chromatography (HPLC) on a SHIMADZU Nexera-i LC-2040C 3D High Plus Liquid Chromatograph HPLC (Kyoto, Japan) with a DAD/FLD detector, equipped with an autosampler. The mobile phase was a mixture of 50 % acetonitrile and 50 % deionized water. The flow rate was 1 cm³/min, and the column temperature was 25 °C. A Phenomenex (Torrance, California, United States) Kinetex F5 column with a porosity of 2.6 mm and dimensions of 150 × 4.6 mm was used. The injection volume was 50

µL. Each measurement was performed three times, and the results were averaged. The results were analyzed using LabSolutions/LC Solution System. The spectra of NAP were recorded at a wavelength of 230 nm. Substance concentrations were calculated based on peak area analysis using the calibration curve method.

The n-octanol/water partition coefficient was used to determine the lipophilicity of a given sample using the shake-flask method. For this purpose, 5 ml of water saturated with octanol and 5 ml of octanol saturated with water were added to 10 mg of the substance and stirred on a magnetic stirrer for 3 h at 25 °C. The aqueous layer was collected using a syringe, and the prepared sample was placed in a centrifuge for 10 min (6000 RPM). The appropriate amount of the substance was carefully collected, and its concentration in the aqueous phase was determined using HPLC (analogous to the solubility test). The octanol/water partition coefficient n was calculated using the formula [22]:

$$\log P = \log \left(\frac{C_{okt}}{C_w} \right) = \log \frac{C_0 - C_w}{C_w}$$

where:

C_{okt} – concentration of the solute in the octanol layer (mg/cm³),
 C_w – concentration of the dissolved substance in the aqueous layer (mg/cm³),
 C_0 – total concentration of the substance used in the test (mg/cm³).

2.4. Fluorescent microscopy

The skin samples excised from the Franz diffusion cell were fixed in 4 % buffered paraformaldehyde (CHEMPUR, Poland) for 24 h. Subsequently, these samples underwent a dehydration process using a graded series of alcohols, ranging from 50 % to 99.9 %, followed by xylene treatment (all reagents purchased in Merck). The dehydrated samples were then embedded in paraffin blocks. Thin sections, approximately 5 µm in thickness, were obtained using a rotary microtome and placed onto Poly-L-lysine covered slides (ThermoFisher Scientific, Waltham, MS, USA). To visualize naproxen in the tissue sections, the slides were rehydrated, beginning with xylene and gradually decreasing concentrations of alcohols (99.9 % to 70 %) and ending with a rinse in deionized water. After deparaffinization, the sections were mounted with a fluorescent medium (Fluorescent Mounting Medium DAKO, Carpinteria, CA, USA). The Neu reagent (2-aminoethyl diphenylborinate, 1 % in methanol) was employed to detect FA and its derivatives. The sections were analyzed using a confocal microscope (FV-1000 Olympus, Hamburg, Germany) equipped with a 405 nm diode laser, 488 and 553 Argon lasers, an Olympus IX81 inverted microscope, and FV10-ASW 4.2 Viewer software (version 4.2b, Olympus).

2.5. Statistical analysis

Results are reported as the mean ± standard deviation (SD). A one-way analysis of variance (ANOVA) was utilized for statistical analysis. For the cumulative mass after 24 h of permeation, the Tukey test ($\alpha < 0.05$) was employed to assess the significance of differences between individual groups. Additionally, the Mann-Whitney test was used to estimate significant differences in cumulative mass between samples exposed to a magnetic field and those not, considering all time points of acceptor fluid uptake. Statistical analyses were performed using Statistica 13 PL software (StatSoft, Krakow, Poland).

3. Results and discussion

3.1. Permeability of NAP during the exposition of EMF

Due to its numerous advantages, transdermal drug delivery is an appealing alternative to the oral route. However, this method faces

significant challenges, mainly related to the limited passage of active pharmaceutical ingredients (API) through the protective skin barrier. This study presents findings on the use of an electromagnetic field to enhance the permeability of NAP through the skin. The research investigated NAP permeability through pigskin under conditions with (MF – Magnetic Field) and without (Control) exposure to various magnetic fields. The cumulative amount of NAP in the acceptor fluid at various time points exposed to different types of EMFs is illustrated in Fig. 3.

The present study utilized non-perfused tissue as a model to assess the permeability of the tested substances. While this approach provides a controlled environment for evaluating passive diffusion processes, it does not fully replicate the physiological conditions of perfused skin, where additional transport mechanisms are present. However, the fact that diffusion was observed in non-perfused tissue strongly suggests that, under *in vivo* conditions, the permeability would be even greater. In perfused tissue, the presence of an active microcirculation can enhance substance transport by maintaining a concentration gradient between the skin layers and the systemic circulation. This effect is well known in transdermal drug delivery and is often described in the context

of osmotic-driven transport. The continuous removal of absorbed molecules by capillary blood flow prevents local saturation and sustains the driving force for diffusion, which is not present in static, non-perfused systems. Thus, while our results provide a conservative estimate of permeability, they likely underestimate the true absorption potential *in vivo*. Moreover, previous studies have demonstrated that diffusion coefficients determined in *ex vivo*, non-perfused models tend to be lower than those obtained in living tissue due to the absence of convective transport contributions.

Table 1 presents a comprehensive comparison of the effects of various magnetic field treatments on the permeation of a substance through a membrane over an 8-hour period. The key parameters analyzed include cumulative permeation mass (CPM), steady-state flux (J_{ss}), permeability coefficient (K_p), lag time (L_T), diffusion coefficient (D), skin partition coefficient (K_m), percentage of the applied dose permeated ($Q\%_{24h}$), and enhancement factors ($EF_{0.5h}$ and EF_{8h}).

The CPM reflects the total amount of substance that permeated through the membrane over the 8-hour experiment. Control samples showed a CPM of $267.57 \pm 41.74 \mu\text{g}/\text{cm}^2$, while various magnetic field treatments significantly altered this parameter. Particularly, RMF 50 Hz

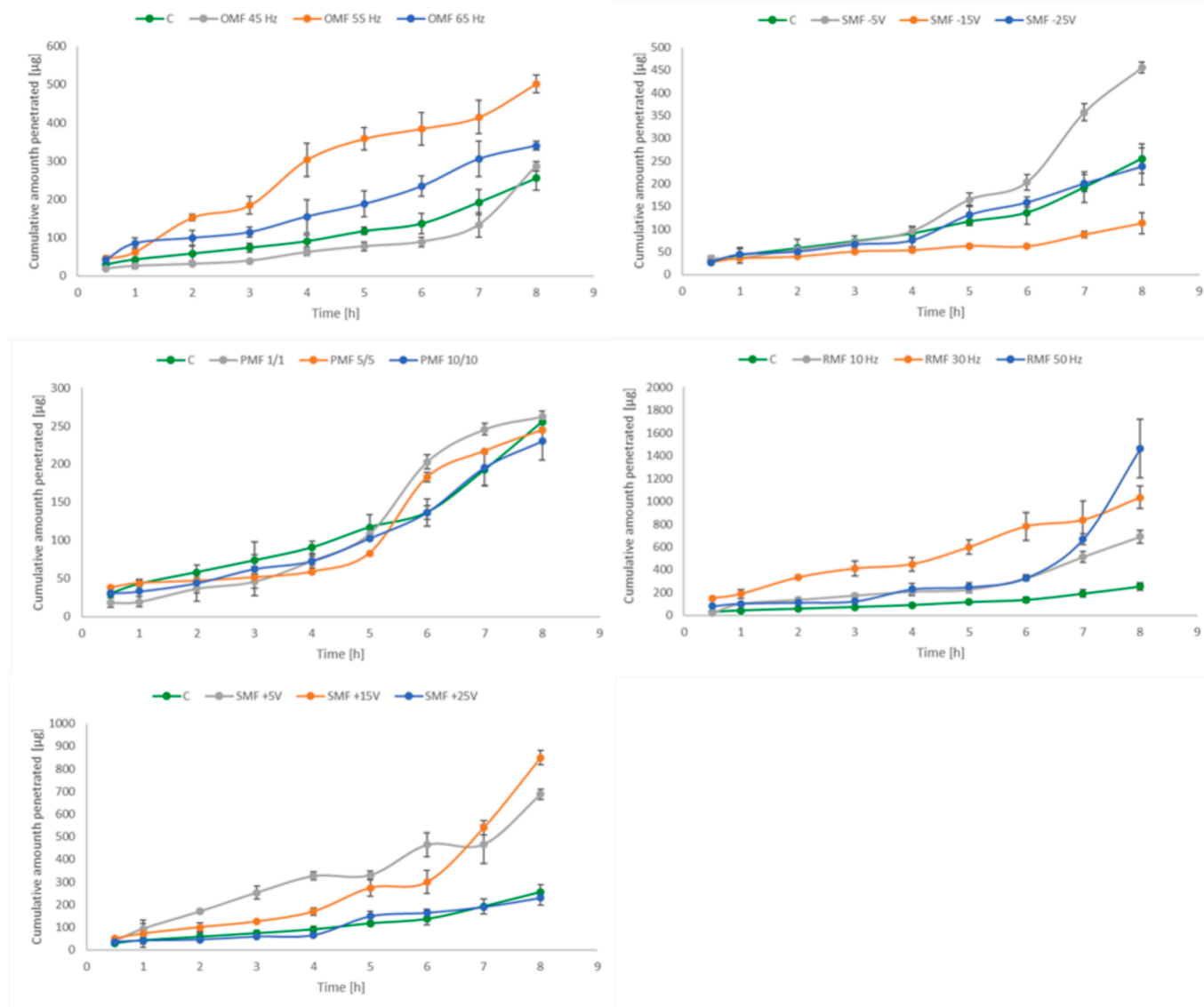


Fig. 3. Time course of the cumulative mass of naproxen exposed to different EMFs during the 8-hour permeation: A) oscillating magnetic field; B) pulsed magnetic field; C) static magnetic field with positive polarization; D) static magnetic field with negative polarization; E) rotating magnetic field; in green, a control sample without exposure to the electromagnetic field (Mean $\pm$ SD, $n = 3$).

Table 1
Permeability parameters of naproxen under various electromagnetic field conditions. OMF – oscillating magnetic field; PMF – pulsed magnetic field; SMF+ – static magnetic field with positive polarization; SMF– – static magnetic field with negative polarization; RMF – rotating magnetic field. All values are presented as mean ± SD, where n = 3. In this case, CPM was used as a one-way ANOVA, followed by Tukey’s post hoc test.* Value is higher significantly to control (the samples without exposure to the electromagnetic field) * $\alpha > 0.050$.

Sample	CPM, $\mu\text{g cm}^{-2}$	J_{ss} , $\mu\text{g cm}^{-2}\text{h}^{-1}$	$K_p \cdot 10^3$, $\text{cm}\cdot\text{h}^{-1}$	L_T , h	$D \cdot 10^4$, $\text{cm}^2\cdot\text{h}^{-1}$	K_m	$Q\%_{24h}$	$EF_{0.5h}$	EF_{8h}
Control	267.57 ±41.74	59.41 ±5.96	5.94 ±0.56	3.72 ±0.24	1.16 ±0.08	2.65 ±0.19	2.55 ±0.42	1.0	1.0
OMF 45 Hz	303.20 ±12.97	107.07 ±2.41	10.71 ±0.24	5.12 ±0.17	0.81 ±0.03	6.58 ±0.25	3.03 ±0.12	0.5	1.1
OMF 55 Hz	501.35 ±23.80 *	58.42 ±1.54	5.84 ±0.54	x	x	x	5.01 ± 0.29	1.2	1.9
OMF 65 Hz	340.27 ±12.02 *	53.09 ±1.69	5.31 ±0.69	1.48 ±0.26	2.82 ±0.08	0.94 ±0.11	3.40 ±0.12	1.1	1.3
PMF 1/1	262.36 ± 16.18	50.38 ±13.01	5.04 ±0.13	2.43 ±0.13	1.71 ±0.08	1.47 ±0.81	2.62 ±0.22	0.5	1.0
PMF 5/5	244.81 ± 14.08	51.92 ±3.02	5.19 ±0.30	2.99 ±0.21	1.40 ±0.09	1.86 ±0.22	2.45 ±0.14	1.0	0.9
PMF 10/10	229.98 ±7.47	44.06 ±1.17	4.41 ±0.16	2.73 ±0.37	1.53 ±0.18	1.44 ±0.98	2.30 ±0.07	0.8	0.9
SMF +5 V	687.41 ±236.49 *	162.10 ±7.60	16.21 ±0.76	3.09 ±0.12	1.34 ±0.21	6.01 ±0.16	6.87 ±0.24	1.0	2.6
SMF +15 V	849.54 ±32.10 *	334.77 ±1.68	33.48 ±0.82	5.20 ±0.17	0.81 ±0.03	20.88 ±0.58	8.49 ±0.21	1.3	3.2
SMF +25 V	229.87 ±32.87	33.05 ±1.61	3.31 ±0.16	1.11 ±0.14	0.37 ±0.02	0.44 ±0.08	2.29 ±0.33	0.9	0.9
SMF –5V	455.77 ±11.85	92.69 ±1.86	9.27 ±0.19	3.54 ±0.32	1.18 ±0.17	3.93 ±0.09	4.56 ±0.12	0.9	1.7
SMF –15 V	113.32 ±23.12 *	25.48 ±1.73	2.35 ±0.17	3.55 ±0.31	1.17 ±0.11	1.08 ±0.07	1.13 ±0.09	0.7	0.4
SMF –25 V	238.27 ±40.98	36.05 ±2.89	3.60 ±0.29	1.43 ±0.27	2.91 ±0.28	0.62 ±0.06	2.38 ±	0.7	0.9
RMF 10 Hz	689.58 ± 54.31 *	181.94 ± 16.42	18.19 ±1.64	4.19 ±0.13	0.99 ±0.03	9.17 ±1.06	6.90 ±0.54	0.5	2.6
RMF 30 Hz	1035.84 ± 97.81 *	127.45 ± 13.45	12.74 ± 0.73	x	x	x	10.36 ± 0.98	4.0	3.9
RMF 50 Hz	1461.40 ± 256.15 *	556.41 ±11.51	56.64 ±1.15	5.54 ±0.10	0.75 ±0.01	37.75 ±8.40	14.61 ±0.56	2.1	5.5

CPM – cumulative permeation mass after 8 h of experiment; J_{ss} –steady-state flux; K_p –permeability coefficient; L_T –lag time; D–diffusion coefficient; K_m –skin partition coefficient; Q—the percentage of the applied dose; EF— enhancement factor; * $L_T < 0$.

resulted in the statistically significant highest CPM of $1461.40 \pm 256.15 \mu\text{g}/\text{cm}^2$, demonstrating a substantial enhancement in permeation compared to the control ($p = 0.00134$). Conversely, treatments like SMF +25 V and SMF –15 V showed reduced CPMs of $229.87 \pm 32.87 \mu\text{g}/\text{cm}^2$ ($p = 0.28637$) and $113.32 \pm 23.12 \mu\text{g}/\text{cm}^2$ ($p = 0.43456$), respectively, indicating a decrease in permeation under these conditions.

The J_{ss} indicates the rate of substance permeation per unit area at a steady state. The control sample had a J_{ss} of $59.41 \pm 5.96 \mu\text{g}/\text{cm}^2\text{h}$. Significant increases were observed under treatments such as RMF 50 Hz ($556.41 \pm 11.51 \mu\text{g}/\text{cm}^2\text{h}$) and SMF +15 V ($334.77 \pm 1.68 \mu\text{g}/\text{cm}^2\text{h}$), suggesting that these treatments greatly enhance the flux of the permeating substance. On the other hand, the SMF –15 V treatment significantly reduced the J_{ss} to $25.48 \pm 1.73 \mu\text{g}/\text{cm}^2\text{h}$.

K_p , representing the permeability of the membrane, showed trends similar to those of CPM and J_{ss} . The highest K_p was observed in the RMF 50 Hz treatment ($56.64 \pm 1.15 \times 10^{-3} \text{ cm}/\text{h}$), while SMF –15 V resulted in the lowest K_p ($2.35 \pm 0.17 \times 10^{-3} \text{ cm}/\text{h}$). This pattern aligns with the variations in both CPM and J_{ss} , further underscoring the influence of different magnetic field treatments on membrane permeability.

L_T , the time taken to reach steady-state permeation, varied widely among treatments. The control had an L_T of $3.72 \pm 0.24 \text{ h}$, whereas RMF 50 Hz reduced L_T to $5.54 \pm 0.10 \text{ h}$, suggesting a faster onset of permeation. Certain treatments like OMF 55 Hz and RMF 30 Hz showed negative L_T values (denoted by x), indicating an almost immediate onset of permeation, which could be associated with very rapid diffusion or minimal resistance by the membrane.

The diffusion coefficient, D, was highest for RMF 50 Hz ($37.75 \pm 8.40 \times 10^{-4} \text{ cm}^2/\text{h}$) and lowest for SMF –25 V ($0.62 \pm 0.06 \times 10^{-4} \text{ cm}^2/\text{h}$), highlighting significant differences in how these treatments affect the rate of diffusion through the membrane. The control sample

exhibited a D value of $1.16 \pm 0.08 \times 10^{-4} \text{ cm}^2/\text{h}$. K_m , which reflects the affinity of the substance for the membrane, was notably high for SMF +15 V (20.88 ± 0.58) and RMF 50 Hz (37.75 ± 8.40), indicating a strong interaction between the substance and the membrane under these conditions. The control K_m was 2.65 ± 0.19 , placing it in the mid-range of observed values.

$Q\%_{24h}$, the percentage of the applied dose that permeated through the membrane, showed the highest values in treatments with RMF 50 Hz ($14.61 \pm 0.56 \%$) and RMF 30 Hz ($10.36 \pm 0.98 \%$), indicating efficient permeation. The control exhibited a moderate Q% of $2.55 \pm 0.42 \%$, with the lowest observed in SMF –15 V ($1.13 \pm 0.09 \%$).

The enhancement factors (EF) after 0.5 and 8 h provide insight into the relative increase in permeation due to treatment. RMF 50 Hz again showed the most pronounced enhancement ($EF_{8h} = 5.5$), while the lowest enhancement was seen with SMF –15 V ($EF_{8h} = 0.4$). The control’s enhancement factors were set as the baseline ($EF_{0.5h} = 1.0$, $EF_{8h} = 1.0$).

Overall, the study demonstrates that different magnetic fields can significantly modulate the permeation properties of the substance through the membrane. Particularly, RMF 50 Hz proved to be the most effective in enhancing permeation across all parameters, suggesting its potential application in transdermal delivery systems, as confirmed by our previous studies [22,23,31]. This could be due to the magnetic field’s ability to increase molecular motion and reduce membrane resistance, leading to higher permeation rates. In contrast, treatments such as SMF –15 V and SMF +25 V appear to reduce permeation, indicating potential inhibitory effects under certain conditions. This could be due to the magnetic field stabilizing the membrane structure or aligning molecules in a way that reduces their ability to permeate. These findings underscore the importance of optimizing magnetic field

parameters to achieve desired permeation outcomes.

The influence of magnetic fields on diffusion processes has been a subject of growing interest, particularly in systems where charged or polar molecules are involved [32–35]. While a magnetic field does not alter the fundamental mechanism of diffusion, it can modify the diffusion rate by affecting molecular motion and interactions within the medium. In our study, we observed that the application of a magnetic field resulted in measurable changes in the diffusion profile, suggesting an enhancement (or hindrance) of molecular transport depending on the field parameters.

One possible explanation for these effects is the interaction of the magnetic field with dipolar or charged molecules, which may lead to alignment effects or changes in local viscosity, indirectly influencing diffusion kinetics. Previous studies have reported similar phenomena, where external magnetic fields altered molecular mobility in polymeric or biological systems.

Furthermore, it is important to consider potential heating effects due to induced eddy currents, especially in systems containing conductive components. These eddy currents can generate localized heating, leading to changes in the diffusion coefficient by decreasing medium viscosity or increasing molecular kinetic energy. However, in our experimental conditions, any temperature-related changes were controlled to minimize their impact, ensuring that the observed effects were primarily due to magnetic interactions rather than thermal artifacts.

The findings align with previous research, suggesting that while a magnetic field does not change the intrinsic nature of diffusion, it can modulate the rate and efficiency of the process. Further studies will be required to quantify these effects in different materials and determine their potential applications in controlled-release systems or magnetically-assisted drug delivery technologies.

3.2. Accumulation in skin

Fig. 4 provides data on skin accumulation of a substance following various magnetic field treatments, along with the corresponding

standard deviations (SD). The skin accumulation for the control sample is 3671.02 $\mu\text{g/g}$ skin, serving as a baseline for comparison. This value represents the amount of substance accumulated in the skin without any magnetic field treatment.

The data presented in Fig. 4 reveal statistically significant variations in skin accumulation of the substance (in $\mu\text{g/g}$ skin) following different magnetic field treatments, highlighting the relationship between magnetic field parameters and permeability. The control group, which received no magnetic field treatment, exhibited a skin accumulation of 3671.02 $\mu\text{g/g}$ skin⁻¹, serving as a baseline for comparison.

Oscillating Magnetic Field (OMF) treatments showed a general decrease in skin accumulation compared to the control. Specifically, OMF 45 Hz resulted in a skin accumulation of 3031.89 $\mu\text{g/g}$ skin ($p = 0.03826$), while OMF 55 Hz further reduced accumulation to 2693.31 $\mu\text{g/g}$ skin ($p = 0.00327$). Despite the enhanced permeability observed in previous data for these treatments, this decrease suggests that the substance permeated more rapidly through the skin, leaving less to accumulate. At OMF 65 Hz, skin accumulation increased slightly to 3070.03 $\mu\text{g/g}$ skin ($p = 0.09854$), which may indicate a reduction in permeability or a balance between permeation and retention at this frequency.

Pulsed Magnetic Field (PMF) treatments (1/1, 5/5, 10/10) showed relatively stable skin accumulation, ranging from 2871.84 to 3050.25 $\mu\text{g/g}$ skin ($p = 0.19743$, $p = 0.01333$ and $p = 0.03133$, respectively), with PMF 10/10 showing the lowest variability ($SD = 76.42$). This consistency suggests that PMF does not significantly alter the balance between skin retention and permeation compared to the control, indicating a moderate influence on the substance's behaviour in the skin.

In contrast, Static Magnetic Field (SMF) treatments demonstrated a more variable impact on skin accumulation, dependent on the voltage applied. SMF +5 V led to a significant decrease in skin accumulation to 2401.16 $\mu\text{g/g}$ skin (0.00136) despite having a high permeability coefficient, which indicates that this treatment facilitates efficient permeation with reduced retention in the skin. However, at SMF +15 V, skin accumulation increased to 2683.78 $\mu\text{g/g}$ skin ($p = 0.00132$), reflecting a moderate retention level despite enhanced permeability. Notably, SMF +25 V caused a significant rise in skin accumulation to 3509.31 $\mu\text{g/g}$

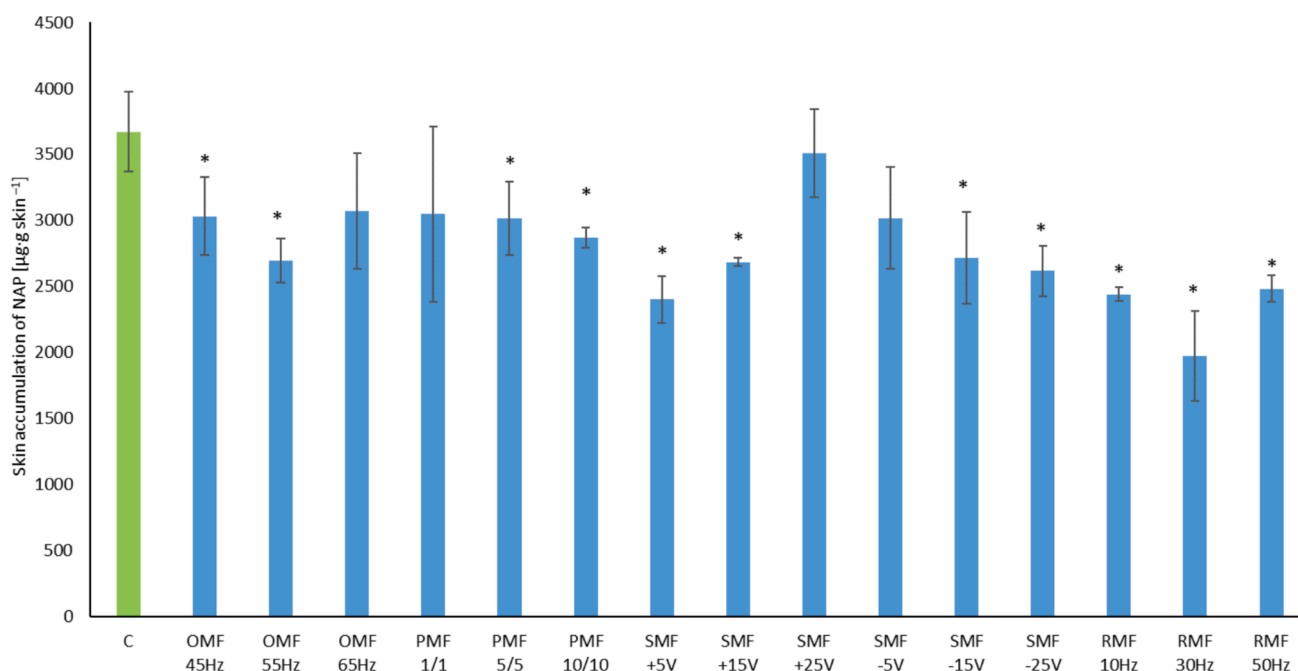


Fig. 4. Skin accumulation of naproxen during control and exposure to different EMFs during the 8-hour permeation. OMF – oscillating magnetic field; PMF – pulsed magnetic field; SMF+ – static magnetic field with positive polarization; SMF- – static magnetic field with negative polarization; RMF – rotating magnetic field. The column in green is a control sample without exposure to the electromagnetic field. All values are presented as mean $\pm$ SD, where $n = 3$. One-way ANOVA followed by Tukey's post hoc test. * Value is higher significantly to control (without exposure to the electromagnetic field) * $\alpha > 0.050$.

skin (0.51629), closely matching the control value, suggesting that this treatment may slow down the permeation process, thereby increasing retention within the skin.

Negative polarity SMF treatments (−5V, −15 V, −25 V) showed varying results, with skin accumulations of 3017.29 $\mu\text{g/g}$ skin ($p = 0.06178$), 2719.75 $\mu\text{g/g}$ skin ($p = 0.01538$), and 2619.31 $\mu\text{g/g}$ skin ($p = 0.00370$), respectively. The SMF-5 V treatment retained a substantial amount of the substance in the skin. SMF −25 V showed one of the

lowest accumulations, indicating that negative polarity affects the permeation-retention balance differently depending on the applied voltage.

Rotating Magnetic Field (RMF) treatments exhibited the lowest skin accumulation values among all treatments. RMF 10 Hz resulted in an accumulation of 2442.11 $\mu\text{g/g}$ skin ($p = 0.00061$), with a higher standard deviation indicating variability in response. RMF 30 Hz produced the lowest accumulation at 1972.93 $\mu\text{g/g}$ skin ($p = 0.00180$), which

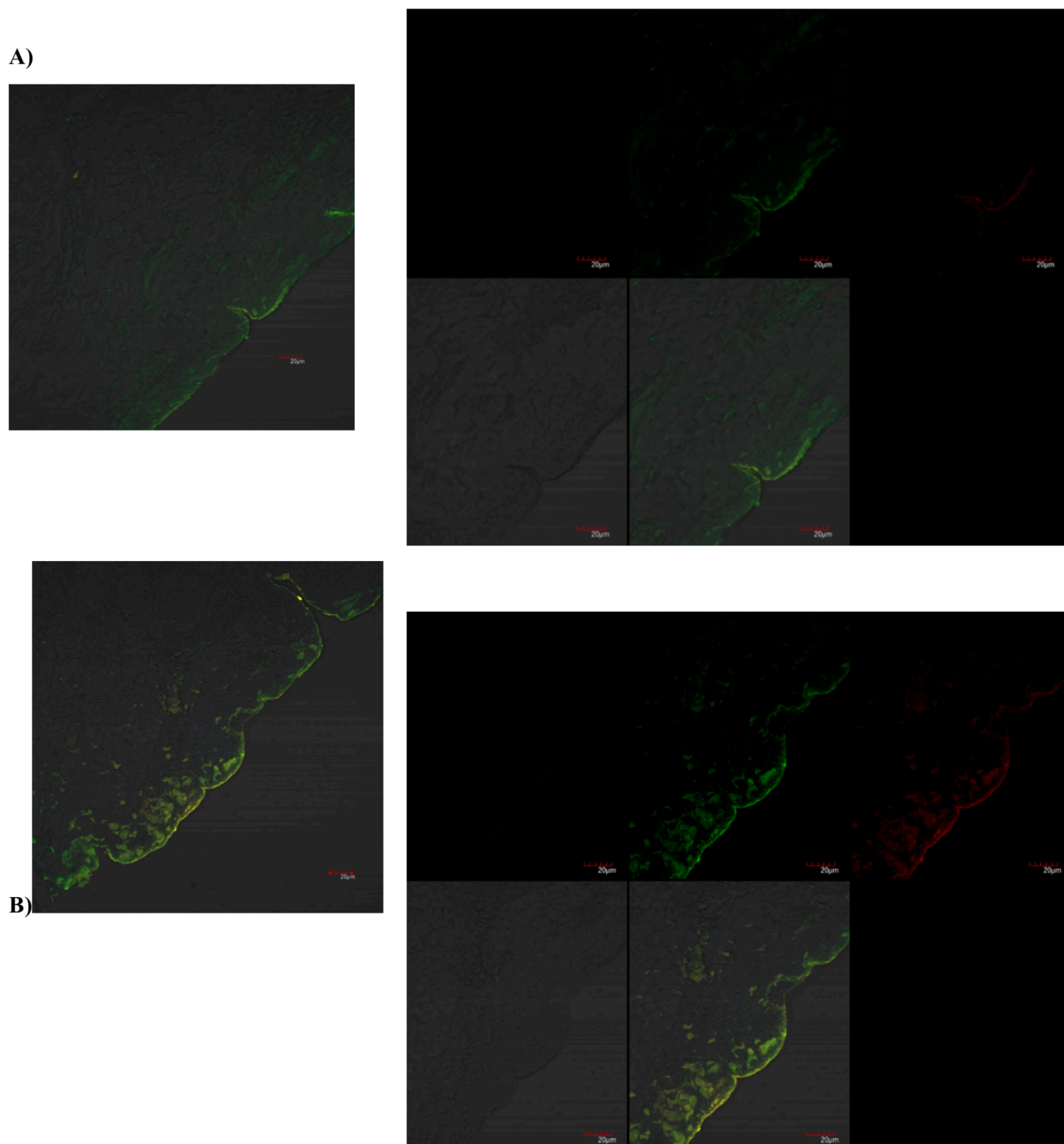


Fig. 5. Confocal microscopic images of vertical sections of porcine skin 24 h after applying the alcohol solution containing NAP: A) without and B) with exposure to an electromagnetic field (RMF 50 Hz). NAP is visible throughout the skin, with the highest concentration in the upper layers, particularly along the stratum corneum (green colour).

corresponds with high permeability values from previous data, suggesting rapid permeation with minimal retention in the skin. Finally, RMF 50 Hz resulted in moderate accumulation ($2484.01 \mu\text{g/g}$ skin, $p = 0.00093$), still lower than the control, confirming that RMF treatments generally enhance permeation, thereby reducing retention in the skin.

3.3. Microscopic examination

Fig. 5 presents confocal microscopic images of porcine skin cross-sections taken 24 h after the application of an alcohol solution containing FA. In panel A, where no electromagnetic field was applied, NAP is distributed throughout the skin, with a notable accumulation in the stratum corneum (SC). In contrast, panel B shows the skin exposed to an electromagnetic field (RMF 50 Hz), where the NAP distribution is more homogeneous across the skin layers, though still most prominent along the SC. These findings suggest that the application of an electromagnetic field can influence the permeation pattern of NAP, potentially enhancing its diffusion across deeper skin layers.

3.4. Evaluation of selected spectroscopic and physicochemical properties of NAP after exposition of EMF

Given the limited existing data on the effects of EMFs on active compounds, this research aimed to elucidate any potential changes in NAP when subjected to various magnetic fields. The identity and structural integrity of the compound were verified using Fourier-transform infrared (FTIR) spectroscopy. At the same time, additional analyses included X-ray diffraction (XRD), solubility in water and phosphate-buffered saline (PBS), specific rotation, thermal stability, phase transition temperatures, and the octanol/water partition coefficient (log P).

3.4.1. Spectroscopic analysis

FTIR spectroscopy was employed to confirm the identity of NAP before and after EMF exposure. The analysis revealed no significant changes in the FTIR spectra across the different samples, indicating that the fundamental molecular structure of NAP remained intact despite exposure to various magnetic field conditions. Detailed comparisons of the FTIR spectra are provided in Figs. S1–S17 of the [Supplementary Data](#), further supporting the lack of structural alterations.

3.4.2. X-ray diffraction (XRD)

Fig. S18 presents a compilation of XRD patterns for naproxen before and after exposure to oscillating, pulsed, static, and rotating magnetic fields, while Figs. S19–S34 display the individual diffraction patterns.

XRD analysis confirmed the crystalline structure of the examined substances, with naproxen identified in each sample. Several reflections were recorded at 2θ angles of approximately 12.5° , 13° , 16.5° , 19° , 22° , 24° , and 28.5° for each sample. Minor variations in the intensities of these reflections were observed among the samples. The effects of the electromagnetic fields led to slight alterations in the crystalline forms of the compounds compared to the control sample.

3.4.3. Solubility in water and partition coefficient

The solubility of naproxen in water at 25°C and its lipophilicity, represented by the octanol/water partition coefficient (log P), were assessed under various EMF conditions. The results indicate that both solubility and lipophilicity are sensitive to changes in EMF parameters, reflecting their potential influence on drug distribution and permeability.

The solubility of naproxen in water, a critical factor for its bioavailability, varied across different EMF treatments, although the variations were relatively small. The control sample exhibited a solubility of $25.08 \pm 0.12 \text{ mg/L}$, which serves as the reference point for comparison.

Oscillating Magnetic Field (OMF) treatments demonstrated slight

fluctuations in solubility. At 45 Hz, solubility was slightly lower than the control at $24.96 \pm 0.05 \text{ mg/L}$, indicating a minimal reduction. However, increasing the frequency to 55 Hz led to a modest increase in solubility to $25.69 \pm 0.02 \text{ mg/L}$. This trend suggests that OMF at 55 Hz may enhance the aqueous solubility of naproxen, possibly by influencing molecular interactions or the hydration shell around the drug molecules. At 65 Hz, solubility decreased again to $24.26 \pm 0.12 \text{ mg/L}$, slightly below the control, indicating a potential threshold beyond which further increases in frequency may reduce solubility.

Pulsed Magnetic Field (PMF) treatments generally increased the solubility of naproxen compared to the control. PMF 1/1 yielded a solubility of $25.21 \pm 0.11 \text{ mg/L}$, similar to the control. As the pulse width increased, so did solubility, with PMF 5/5 showing $26.03 \pm 0.16 \text{ mg/L}$ and PMF 10/10 reaching $26.60 \pm 0.07 \text{ mg/L}$, the highest among PMF treatments. These results suggest that PMF may enhance the solubility of naproxen by altering its crystalline structure or by inducing a more favourable interaction with the solvent.

Static Magnetic Field (SMF) treatments displayed a diverse impact on solubility. SMF +5 V significantly increased solubility to $27.10 \pm 0.04 \text{ mg/L}$, the highest recorded value, indicating that a positive voltage can enhance water solubility substantially. Conversely, SMF +15 V and +25 V exhibited slightly lower solubilities of $25.89 \pm 0.04 \text{ mg/L}$ and $25.16 \pm 0.04 \text{ mg/L}$, respectively, suggesting a nonlinear relationship between voltage intensity and solubility. Negative SMF treatments (-5V , -15V , -25V) generally resulted in slightly lower solubility values compared to their positive counterparts, with SMF -5V showing a solubility of $27.11 \pm 0.07 \text{ mg/L}$, similar to SMF +5 V, but SMF -25V decreased to $24.48 \pm 0.04 \text{ mg/L}$. This indicates that the polarity and magnitude of the SMF can have complex, sometimes opposing, effects on solubility.

Rotating Magnetic Field (RMF) treatments also influenced solubility, though the effects were less pronounced. RMF 10 Hz and 30 Hz maintained solubility close to the control at $25.62 \pm 0.15 \text{ mg/L}$ and $25.76 \pm 0.03 \text{ mg/L}$, respectively. However, RMF 50 Hz increased solubility to $26.64 \pm 0.06 \text{ mg/L}$, suggesting that higher rotation frequencies may positively affect solubility by inducing more significant structural or dynamic changes in the solution.

The lipophilicity of naproxen, expressed as the log P value, is crucial for understanding its distribution in biological systems and its ability to permeate lipid membranes. Previous studies suggested that the log P of drugs might increase under a rotating magnetic field with specific parameters (50 Hz, $B_{\text{max}} = 34 \text{ mT}$) [22,23]. In this study, the log P values for naproxen exposed to different EMF conditions exhibited slight variations (see Table 2). The control sample exhibited a log P value of 2.115 ± 0.01 , indicating moderate lipophilicity.

OMF treatments revealed minor but notable changes in log P values. At 45 Hz, the log P slightly decreased to 2.097 ± 0.01 , suggesting a

Table 2

Solubility in water (25C) and lipophilicity of naproxen with or without exposure MFs.

Sample	Solubility in water [mg/l]	Log P
Control	25.08 ± 0.12	2.115 ± 0.01
OMF 45 Hz	24.96 ± 0.05	2.097 ± 0.01
OMF 55 Hz	25.69 ± 0.02	2.181 ± 0.01
OMF 65 Hz	24.26 ± 0.12	2.197 ± 0.01
PMF 1/1	25.21 ± 0.11	2.175 ± 0.02
PMF 5/5	26.03 ± 0.16	2.128 ± 0.01
PMF 10/10	26.60 ± 0.07	2.150 ± 0.01
SMF +5 V	27.10 ± 0.04	2.186 ± 0.02
SMF +15 V	25.89 ± 0.04	2.233 ± 0.02
SMF +25 V	25.16 ± 0.04	2.193 ± 0.03
SMF -5V	27.11 ± 0.07	2.234 ± 0.04
SMF -15V	25.64 ± 0.02	2.165 ± 0.01
SMF -25V	24.48 ± 0.04	2.196 ± 0.01
RMF 10 Hz	25.62 ± 0.15	2.126 ± 0.01
RMF 30 Hz	25.76 ± 0.03	2.141 ± 0.01
RMF 50 Hz	26.64 ± 0.06	2.184 ± 0.01

minor reduction in lipophilicity. Interestingly, at 55 Hz and 65 Hz, the log P values increased to 2.181 ± 0.01 and 2.197 ± 0.01 , respectively. This increase implies that higher OMF frequencies may enhance the lipophilicity of naproxen, possibly by promoting interactions that favour its partitioning into lipid environments.

PMF treatments also impacted lipophilicity, although the effects were relatively modest. PMF 1/1 and PMF 5/5 resulted in log P values of 2.175 ± 0.02 and 2.128 ± 0.01 , respectively, showing a slight decrease from the control. PMF 10/10 further reduced lipophilicity to a log P of 2.150 ± 0.01 , indicating that increasing pulse width might slightly diminish naproxen's preference for lipid phases.

SMF treatments exhibited more pronounced effects on lipophilicity. SMF +5 V and +15 V increased the log P values to 2.186 ± 0.02 and 2.233 ± 0.02 , respectively, indicating enhanced lipophilicity. These results suggest that positive voltage SMF conditions might promote the partitioning of naproxen into lipid environments. Conversely, SMF +25 V resulted in a log P of 2.193 ± 0.03 , slightly lower than SMF +15 V, indicating a potential threshold beyond which further increases in voltage may not continue to enhance lipophilicity. Negative SMF treatments exhibited varied effects, with SMF -5V showing the highest log P of 2.234 ± 0.04 , similar to SMF +15 V, while SMF -15 V and -25 V decreased log P to 2.165 ± 0.01 and 2.196 ± 0.01 , respectively. These results suggest that the direction of the magnetic field and its intensity can significantly modulate the lipophilicity of naproxen.

RMF treatments led to a moderate increase in lipophilicity, with RMF 50 Hz showing a log P of 2.184 ± 0.01 , slightly higher than the control. RMF 10 Hz and 30 Hz produced log P values of 2.126 ± 0.01 and 2.141 ± 0.01 , respectively, lower than the control, indicating a mild reduction in lipophilicity at lower RMF frequencies.

The solubility and lipophilicity of naproxen are sensitive to electromagnetic field conditions, with both parameters showing variations that could influence the drug's permeability and distribution. Increased solubility often correlates with reduced lipophilicity, as seen in several SMF and RMF treatments, suggesting a shift towards more hydrophilic behaviour. These findings provide insights into how EMF parameters can be optimized to modulate the physicochemical properties of drugs, potentially enhancing their therapeutic efficacy and delivery.

3.4.4. Thermal properties and stability

The thermal properties and stability of naproxen were investigated before and after exposure to various magnetic fields, with results presented in Figs. S35–S66. The analysis revealed minor differences in phase transition temperatures between samples. The lowest onset melting temperature ($T_{DS\text{Onset}}$) was 156.07°C for the sample exposed to a static field with negative polarity and 15 V voltage (SMF -15 V), while the highest value of 156.76°C was recorded for the sample exposed to a static field with negative polarity and 25 V voltage (SMF -25 V). The maximum melting temperatures ($T_{DS\text{Cmax}}$) ranged from 158.45°C (SMF +15 V) to 160.80°C (OMF 55 Hz). The melting enthalpy (ΔH_m) was lowest for the naproxen sample exposed to an oscillating magnetic field with a frequency of 55 Hz (OMF 55 Hz), at 131.17 J/g , while the highest value of 189.26 J/g was noted for the control sample (Control). These differences may suggest changes in the crystalline structure of naproxen samples following magnetic field exposure.

The thermal stability of naproxen samples was evaluated based on melting temperature (T_f), onset degradation temperature (T_{onset}), 5 % degradation temperature ($T_{d5\%}$), 50 % degradation temperature ($T_{d50\%}$), and temperature of maximum degradation rate (T_{max}). The lowest melting temperature of 156.8°C was observed for the sample exposed to a rotating magnetic field with a frequency of 30 Hz (RMF 30 Hz), whereas the highest value of 157.7°C was observed for the control sample (Control), SMF -25 V, and RMF 10 Hz. Onset degradation temperatures ranged from 252.8°C (RMF 50 Hz) to 255.3°C (SMF +15 V and SMF -25 V). The lowest 5 % degradation temperature of 221.0°C was recorded for the control sample (Control), while the highest $T_{d5\%}$ value of 224.4°C was found for the SMF -5V sample. The 50 %

degradation temperatures ranged from 270.6°C (Control and RMF 50 Hz) to 272.3°C (PMF 5/5). The maximum degradation rate occurred at temperatures between 284.5°C (SMF -15 V) and 287.5°C (SMF +15 V), indicating differences in thermal stability likely due to variations in sample amounts or thermobalance accuracy rather than the direct effect of the applied magnetic field. The least thermal stability was exhibited by naproxen samples exposed to a rotating magnetic field with a frequency of 50 Hz (RMF 50 Hz) and the control sample, while the highest stability was observed in the sample exposed to a static magnetic field with positive polarity and 15 V DC voltage (SMF +15 V).

4. Conclusion

This study investigated the impact of various electromagnetic fields (EMFs) on the permeability, skin accumulation, and physicochemical properties of naproxen (NAP). The findings demonstrate significant variations in the effectiveness of different EMF treatments, highlighting the potential for optimizing transdermal delivery systems using EMFs. The results suggest that magnetic field treatments, particularly rotating magnetic fields (RMF), can significantly enhance the permeation of substances through membranes by increasing flux, permeability, and diffusion rates while reducing lag times. These effects are likely due to increased molecular motion and altered membrane properties under these conditions. However, static magnetic fields (SMF) with certain polarities and intensities can have the opposite effect, reducing permeation by stabilizing the membrane structure or altering molecular interactions. These findings highlight the potential for using magnetic fields to control and optimize transdermal drug delivery and other permeation processes. Magnetic field treatments have been shown to significantly influence the balance between skin accumulation and the permeability of a substance. High permeability often correlates with lower skin accumulation, as seen in RMF and certain SMF treatments, where the substance permeates more efficiently through the skin, leaving less behind. Conversely, lower permeability treatments, such as SMF +25 V, are associated with higher skin accumulation, likely due to reduced permeation rates that allow the substance to be retained longer within the skin layers.

This study demonstrates that EMFs can be strategically employed to modulate NAP's permeability and physicochemical properties, potentially optimizing transdermal drug delivery systems. RMF 50 Hz stands out as a particularly effective treatment, suggesting its practical application for enhancing drug permeation. However, the impact of EMFs on skin accumulation and physicochemical properties indicates that careful consideration and optimization of EMF parameters are crucial for achieving the desired therapeutic outcomes in transdermal delivery. Further research is needed to explore the mechanisms behind these effects and to fine-tune EMF conditions for specific drug delivery applications.

CRedit authorship contribution statement

Rafał Rakoczy: Supervision, Project administration, Funding acquisition, Conceptualization. **Karolina Zyburtowicz-Ćwiartka:** Formal analysis. **Maciej Konopacki:** Formal analysis. **Anna Nowak:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Katarzyna Piotrowska:** Formal analysis. **Anna Muzykiewicz-Szymańska:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Łukasz Kucharski:** Formal analysis. **Marian Kordas:** Visualization, Formal analysis. **Paula Ossowicz-Rupniewska:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Data curation, Conceptualization.

Ethics approval

Not applicable.

Funding

This research was funded by National Science Centre [Projekt NCN OPUS 25 NR UMO-2023/49/B/ST8/00605].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpb.2025.114715>.

Data availability

No data was used for the research described in the article.

References

- [1] R. Rakoczy, M. Konopacki, J. Lechowska, M. Bubnowska, A. Hürter, M. Kordas, K. Fijałkowski, Gas to liquid mass transfer in mixing system with application of rotating magnetic field, *Chem. Eng. Process. - Process Intensif.* 130 (2018) 11–18, <https://doi.org/10.1016/j.cep.2018.05.013>.
- [2] L. Liu, B. Huang, Y. Lu, Y. Zhao, X. Tang, Y. Shi, Interactions between electromagnetic radiation and biological systems, *iScience* 27 (2024) 109201. doi: 10.1016/j.isci.2024.109201.
- [3] H. Lai, Exposure to static and extremely-low frequency electromagnetic fields and cellular free radicals, *Electromagn. Biol. Med.* 38 (2019) 231–248, <https://doi.org/10.1080/15368378.2019.1656645>.
- [4] B. Gholipour Hamedani, B. Goliaei, S.P. Shariatpanahi, M. Nezamtaheri, An overview of the biological effects of extremely low frequency electromagnetic fields combined with ionizing radiation, *Prog. Biophys. Mol. Biol.* 172 (2022) 50–59, <https://doi.org/10.1016/j.pbiomolbio.2022.04.008>.
- [5] B. Greenebaum, F.S. Barnes (Eds.), *Bioengineering and Biophysical Aspects of Electromagnetic Fields*, Third edition, CRC Press, Boca Raton, 2018.
- [6] M.R. Prausnitz, R. Langer, Transdermal drug delivery, *Nat. Biotechnol.* 26 (2008) 1261–1268, <https://doi.org/10.1038/nbt.1504>.
- [7] A. Alkilani, M.T. McCrudden, R. Donnelly, Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the Stratum Corneum, *Pharmaceutics* 7 (2015) 438–470, <https://doi.org/10.3390/pharmaceutics7040438>.
- [8] P.L. Lam, R. Gambari, Advanced progress of microencapsulation technologies: in vivo and in vitro models for studying oral and transdermal drug deliveries, *J. Control. Release* 178 (2014) 25–45, <https://doi.org/10.1016/j.jconrel.2013.12.028>.
- [9] A. Haq, B. Goodyear, D. Ameen, V. Joshi, B. Michniak-Kohn, Strat-M® synthetic membrane: permeability comparison to human cadaver skin, *Int. J. Pharm.* 547 (2018) 432–437, <https://doi.org/10.1016/j.ijpharm.2018.06.012>.
- [10] H.A.E. Benson, Skin structure, function, and permeation, in: H.A.E. Benson, A. C. Watkinson (Eds.), *Topical and Transdermal Drug Delivery*, John Wiley & Sons Inc, Hoboken, NJ, USA, 2012, pp. 1–22, <https://doi.org/10.1002/9781118140505.ch1>.
- [11] R.H. Guy, J. Hadgraft, eds., *Transdermal Drug Delivery*, 1st ed., CRC Press, 2002, doi: 10.1201/9780203909683.
- [12] Y.S.R. Krishnaiah, V. Satyanarayana, R.S. Karthikeyan, Effect of the solvent system on the in vitro permeability of nicardipine hydrochloride through excised rat epidermis, *J. Pharm. Pharm. Sci.* 5 (2002) 123–130.
- [13] M.R. Prausnitz, S. Mitragotri, R. Langer, Current status and future potential of transdermal drug delivery, *Nat. Rev. Drug Discov.* 3 (2004) 115–124, <https://doi.org/10.1038/nrd1304>.
- [14] S. Namjoshi, Y. Chen, J. Edwards, H.A.E. Benson, Enhanced transdermal delivery of a dipeptide by dermaportation, *Biopolymers* 90 (2008) 655–662, <https://doi.org/10.1002/bip.21033>.
- [15] H. Benson, Transdermal drug delivery: penetration enhancement techniques, *CDD* 2 (2005) 23–33, <https://doi.org/10.2174/1567201052772915>.
- [16] S. Namjoshi, R. Caccetta, J. Edwards, H.A.E. Benson, Liquid chromatography assay for 5-aminolevulinic acid: application to in vitro assessment of skin penetration via Dermaportation, *J. Chromatogr. B* 852 (2007) 49–55, <https://doi.org/10.1016/j.jchromb.2006.12.040>.
- [17] A. Alexander, S. Dwivedi, T.K. Ajazuddin, S. Giri, S. Saraf, D.K.T. Saraf, Approaches for breaking the barriers of drug permeation through transdermal drug delivery, *J. Control. Release* 164 (2012) 26–40, <https://doi.org/10.1016/j.jconrel.2012.09.017>.
- [18] S.N. Murthy, S.M. Sammeta, C. Bowers, Magnetophoresis for enhancing transdermal drug delivery: mechanistic studies and patch design, *J. Control. Release* 148 (2010) 197–203, <https://doi.org/10.1016/j.jconrel.2010.08.015>.
- [19] A. Nanda, S. Nanda, N. Khan Ghilzai, Current developments using emerging transdermal technologies in physical enhancement methods, *CDD* 3 (2006) 233–242, doi: 10.2174/15672010677731091.
- [20] T.W. Wong, Electrical, magnetic, photomechanical and cavitation waves to overcome skin barrier for transdermal drug delivery, *J. Control. Release* 193 (2014) 257–269, <https://doi.org/10.1016/j.jconrel.2014.04.045>.
- [21] G. Krishnan, J. Edwards, Y. Chen, H.A.E. Benson, Enhanced skin permeation of naltrexone by pulsed electromagnetic fields in human skin in vitro, *J. Pharm. Sci.* 99 (2010) 2724–2731, <https://doi.org/10.1002/jps.22024>.
- [22] P. Ossowicz-Rupniewska, A. Nowak, M. Konopacki, M. Kordas, L. Kucharski, J. Klebko, E. Świątek, R. Rakoczy, Increase of ibuprofen penetration through the skin by forming ion pairs with amino acid alkyl esters and exposure to the electromagnetic field, *Eur. J. Pharm. Biopharm.* 188 (2023) 15–25, <https://doi.org/10.1016/j.ejpb.2023.05.003>.
- [23] R. Rakoczy, A. Nowak, M. Konopacki, M. Kordas, L. Kucharski, P. Ossowicz-Rupniewska, Exposure to a rotating magnetic field as a method of increasing the skin permeability of active pharmaceutical ingredients, *Eur. J. Pharm. Biopharm.* (2023) S0939641123000590, <https://doi.org/10.1016/j.ejpb.2023.02.017>.
- [24] N.M. Davies, K.E. Anderson, Clinical pharmacokinetics of naproxen: clinical pharmacokinetics 32 (1997) 268–293, doi: 10.2165/00003088-199732040-00002.
- [25] T. Benbow, J. Campbell, Microemulsions as transdermal drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs): a literature review, *Drug Dev. Ind. Pharm.* 45 (2019) 1849–1855, <https://doi.org/10.1080/03639045.2019.1680996>.
- [26] L. Kumar, S. Verma, M. Singh, T. Chalotra, P. Utreja, Advanced drug delivery systems for transdermal delivery of non-steroidal anti-inflammatory drugs: a review, *CDD* 15 (2018) 1087–1099, <https://doi.org/10.2174/1567201815666180605114131>.
- [27] E. Janus, P. Ossowicz, J. Klebko, A. Nowak, W. Duchnik, L. Kucharski, A. Klimowicz, Enhancement of ibuprofen solubility and skin permeation by conjugation with L-valine alkyl esters, *RSC Adv.* 10 (2020) 7570–7584, <https://doi.org/10.1039/D0RA00100G>.
- [28] A. Puri, S. Bhattacharjee, W. Zhang, M. Clark, O. Singh, G. Doncel, A. Banga, Development of a transdermal delivery system for Tenofovir Alafenamide, a prodrug of Tenofovir with potent antiviral activity against HIV and HBV, *Pharmaceutics* 11 (2019) 173, <https://doi.org/10.3390/pharmaceutics11040173>.
- [29] J. Kuntsche, H. Bunjes, A. Fahr, S. Pappinen, S. Rönkkö, M. Suhonen, A. Urtti, Interaction of lipid nanoparticles with human epidermis and an organotypic cell culture model, *Int. J. Pharm.* 354 (2008) 180–195, <https://doi.org/10.1016/j.ijpharm.2007.08.028>.
- [30] M. Khiao In, K.C. Richardson, A. Loewa, S. Hedtrich, S. Kaessmeyer, J. Plendl, Histological and functional comparisons of four anatomical regions of porcine skin with human abdominal skin, *Anat. Histol. Embryol.* 48 (2019) 207–217, <https://doi.org/10.1111/ahe.12425>.
- [31] A. Nowak, P. Ossowicz-Rupniewska, M. Konopacki, A. Muzykiewicz-Szymańska, L. Kucharski, R. Rakoczy, Assessing the influence of a rotating magnetic field on ibuprofen permeability from diverse pharmaceutical formulations, *Sci. Pharm.* 92 (2023) 4, <https://doi.org/10.3390/scipharm92010004>.
- [32] V. Zablotskii, T. Polyakova, A. Dejneka, Effects of high magnetic fields on the diffusion of biologically active molecules, *Cells* 11 (2021) 81, <https://doi.org/10.3390/cells11010081>.
- [33] M. Waskaas, Short-term effects of magnetic fields on diffusion in stirred and unstirred paramagnetic solutions, *J. Phys. Chem.* 97 (1993) 6470–6476, <https://doi.org/10.1021/j100126a023>.
- [34] Y. Kinouchi, S. Tanimoto, T. Ushita, K. Sato, H. Yamaguchi, H. Miyamoto, Effects of static magnetic fields on diffusion in solutions, *Bioelectromagnetics* 9 (1988) 159–166, <https://doi.org/10.1002/bem.2250090207>.
- [35] P. Jiang, J. Wang, L. Hou, Y. Fautrelle, X. Li, Controlling and adjusting the concentration distribution during solidification process using static magnetic fields, *J. Mater. Sci. Technol.* 50 (2020) 86–91, <https://doi.org/10.1016/j.jmst.2020.03.002>.