Bulgarian Chemical Communications, Volume 56, Issue 3 (pp. 342-347) 2024 *DOI: 10.34049/bcc.56.3.HM-M*

Development of transdermal cellulose-based patches for Alzheimer's treatment and investigation of penetration behavior

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Received June 3, 2024; Accepted: August 17, 2024

Transdermal patch drug delivery systems deliver the drug to the body through the skin and provide a controlled release. The present study aims at developing transdermal patches for Alzheimer's treatment and to improve the penetration characteristics of transdermal patches. Donepezil hydrochloride drug active substance selected in this study is commonly used to treat Alzheimer's disease. HEC (hydroxyethyl cellulose) and CHI (chitosan) were used as polymer-based matrix and natural additives as penetration enhancers for the transdermal patches. The effectiveness of the patches prepared using different plasticizer materials was investigated. Synthesized films under *in vitro* conditions were characterized by UV spectrophotometry, SEM, FTIR and Zetasizer. The drug release kinetics were determined using the zero-order, first-order, Higuchi and Korsmeyer-Peppas kinetic models by analyzing samples taken at certain time intervals using a UV spectrophotometer.

The results in this study confirm that synthesized films can be potential materials for developing treatments for Alzheimer's disease. This project aims to contribute to the healthcare sector by developing unique patch formulations with high stability in order to provide solutions to the problems encountered in the oral treatment of Alzheimer's disease, reducing the negative effects of existing commercial patches and improving their features.

Keywords: Drug delivery; Transdermal patch; Donepezil hydrochloride; Penetration; Alzheimer

INTRODUCTION

Alzheimer's disease is a progressive condition affecting memory, thinking and behavior. Alzheimer's, which affects millions of people worldwide, creates a significant social and economic burden and requires effective treatment strategies [1]. Existing oral medications for Alzheimer's disease have limitations, including issues with adherence, absorption and side effects, highlighting the need for alternative treatment methods and innovative therapeutic approaches, such as transdermal drug delivery systems [2].

Transdermal drug delivery is a method of administering drugs through the skin for systemic distribution [3]. The drug penetrates through the skin layers to reach the systemic circulation, providing a controlled release of the drug [4]. Transdermal patch systems are designed to deliver therapeutically effective amounts of drugs, providing controlled and sustained drug release [5]. Transdermal drug delivery system types are reservoir, matrix and microneedle patch systems. Reservoir systems consist of a drug reservoir that is surrounded by a rate-controlling membrane. The drug is released from the reservoir through the membrane at a controlled rate, ensuring consistent delivery over time. Advancements in nanotechnology, microneedle patches, and transdermal systems hold promise for further enhancing Alzheimer's treatment options. The non-invasive nature of transdermal patches enhances patient compliance and comfort, particularly in the context of chronic conditions like Alzheimer's [6].

Donepezil is a cholinesterase inhibitor that works by increasing the levels of acetylcholine in the brain, a neurotransmitter that is crucial for memory and learning. The traditional oral formulation of donepezil presents challenges such as gastrointestinal side effects and consistent dosing difficulties, which may impact treatment efficacy [7]. The development of a transdermal patch for delivering donepezil addresses the limitations of the oral formulation and offers a new approach to enhancing treatment outcomes for individuals with Alzheimer's disease.

Challenges in transdermal drug delivery require the use of penetration enhancers. Penetration enhancers play a significant role in improving drug permeation through the skin, minimizing the limitations posed by the skin's natural barriers, and thus increasing the efficiency of transdermal drug delivery [8-11]. Penetration enhancers work with disrupting the skin's barrier function, facilitating drug permeation through mechanisms such as lipid extraction, protein denaturation and alteration of intercellular lipids. Penetration enhancers should

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increase drug permeation by biocompatible and sustainable substances that minimize skin irritation and adverse effects [12].

The present study aims at improving the penetration properties of the synthesized transdermal patches by developing a transdermal formulation for the controlled release of donepezil, one of the important active ingredients in the treatment of Alzheimer's disease.

MATERIALS AND METHOD

Materials

The list of purchased chemicals used in this study is given in Table 1. In films prepared based on HEC and CHI polymer, propylene glycol and glycerine are used as plasticizers; natural oils as a penetration enhancer and donepezil HCl which is widely used in Alzheimer's patients, as a drug.

Transdermal patch preparation

Transdermal patches were prepared by the solvent casting method. All chemicals in the formulation, penetration enhancers and donepezil HCl were dissolved in distilled water and mixed by a magnetic stirrer until they became homogeneous to ensure proper dissolution and uniformity. The formulation of the transdermal patches is summarized in Table 2. To obtain patches, the solution was poured onto Petri dishes and left to dry at room temperature.

Drug permeation studies using the Franz diffusion cell

Franz diffusion cell consists of a donor and a receptor chamber separated by a membrane mimicking the biological barrier, enabling the measurement of drug permeation.

Experimental setup: The cell is designed to maintain physiological conditions, including temperature, pH and ionic strength to simulate the *in vivo* environment. This ensures that the drug release behavior closely resembles its performance in real-life applications.

Membrane selection: The choice of membrane in the Franz diffusion cell is critical, as it determines the relevance of the *in vitro* results to *in vivo* scenarios. Factors such as permeability, selectivity, and compatibility with the drug are essential considerations in membrane selection.

After the patches dried, drug release studies were started in the Franz diffusion cell. Transdermal patch samples were placed on the lid of the Franz cell. Cellulose acetate membrane filters, with a diameter of 47 mm and a pore size of 0.45 µm, were prepared and placed in pH 7.4 buffer solution to mimic the skin. The prepared patches were placed on the cellulose acetate membrane filter in the section between the diffusion cell cover and the receiver chamber. The top of the Franz cell was covered with parafilm to prevent evaporation and foreign objects. The Franz diffusion cell, shaking at 110 rpm, was kept at 37°C to represent body temperature. Drug release was achieved in the Franz cell for 24 h. Samples were collected at specific time intervals and analyzed using a UV-vis spectrophotometer. SEM, FT-IR and zeta potential analyzes were performed for the selected patch.

Table 1. Materials and supplier companies

Materials	Supplier
Hydroxyethyl cellulose	Dafmed Company
Propylene glycol	Genesus Company
Glycerine	Tekkim Chemical Company
Donepezil HCl	Abdi İbrahim Medicine Company

Table 2. Formulation of the transdermal patches

Film No	HEC (g)	CHI (g)	Propylene Glycol (g)	Glycerine (g)	Gelatine (g)	$CaCl_2$ (g)	Dimethyl Sulfoxide (g)	Arlasolve (g)	Lysofix (g)	St. John's Wort Oil (g)	Rosehip Oil (g)	Argan Oil (g)	Avocado Oil (g)	Sesame Oil (g)	Grape Seed Oil (g)	Donapezil HCl (g)
1	0.5	-	0.6	0.02	0.02	-	0.5	0.1	-	0.3	-	-	-	-	-	0.1
2	0.4	0.1	0.5	-	0.02	0.03	0.6	-	0.1	-	0.3	-	-	-	-	0.1
3	0.4	0.1	0.5	-	0.02	0.03	0.6	-	0.1	-	-	0.3	-	-	-	0.1
4	0.4	0.1	0.5	-	0.02	0.03	0.6	-	0.1	-	-	-	0.3	-	-	0.1
5	0.4	0.1	0.5	-	0.02	0.03	0.6	-	0.1	-	-	-	-	0.3	-	0.1
6	0.5	0.1	0.5	0.02	0.02	-	0.5	-	-	-	-	-	-	-	0.4	0.1

RESULTS AND DISCUSSION

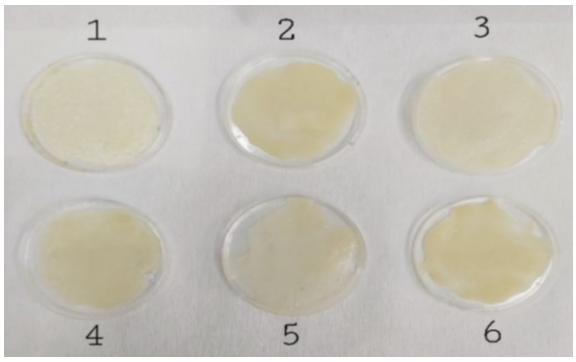

Fig. 1. Images of the transdermal patches

Kinetic behavior of drug release

Images of the transdermal patches are shown in Fig. 1. Drug release kinetic behavior graphs provide information about the drug release mechanism and kinetics. Understanding drug release kinetics is significant in predicting the *in vivo* behavior of the formulated drug. Different kinetic models can be used to fit experimental data and interpret drug release kinetics. The choice of carrier material significantly influences drug release kinetics. Factors such as porosity, surface area and degradation rate of the carrier material play a crucial role in determining the release profile of the drug. The morphology of the carrier, including its shape, size and internal structure can impact the diffusion and release of the drug. The kinetics of donepezil HCl drug release were determined using the zero-order, first-order, Higuchi equation and Korsmeyer-Peppas equation. The equations of the kinetic models are given in Table 3.

Table 3. Release kinetic models

Release Kinetics Modeling	
Zero-order Model	$Q=Q_o+k*t$
First-order Model	$Q/Q_o=1-e^{(-k*t)}$
Higuchi Model	$Q=k*t^{1/2}$
Korsmeyer-Peppas Model	$Q/Q_o=k*t^{n}$

Q is the amount of drug dissolved over time, Q_0 is the initial amount of drug in solution, k is the zero-order release constant expressed in units of concentration/time. R^2 regression coefficient values were found using kinetic model equations.

The highest R^2 regression coefficient values were observed in Korsmeyer-Peppas and Higuchi release kinetics. In conclusion, it was determined the patches fit the Korsmeyer-Peppas model and the release mechanism was examined through this model. The results are shown in Table 4.

Table 4. Regression coefficient values

Film No	Zero-order Kinetic Model	First-order Kinetic Model	Higuchi Kinetic Model	Korsmeyer – Peppas Kinetic Model
1	0.9833	0.8388	0.9454	0.991
2	0.9887	0.8179	0.9861	0.988
3	0.9827	0.8016	0.9787	0.9778
4	0.9754	0.7835	0.9834	0.9834
5	0.9724	0.7715	0.9899	0.9843
6	0.9908	0.8129	0.9875	0.9946

The controlled release behavior of donapezil was characterized by the Korsmeyer-Peppas equation. The emission exponent (n) values obtained from the slope of the log % emission plot against log t show that the release mechanism is working. Table 5 presents the (n and k) values of the films obtained using the Korsmeyer-Peppas model equation.

Table 5. Korsmeyer-Peppas release kinetic values

Film No	n	k
1	0.5841	0.0079
2	0.6313	-0.1787
3	0.5956	-0.0546
4	0.587	-0.0463
5	0.657	-0.2535
6	0.6723	-0.2984

The graphs are shown in Figs. 2, 3, 4 and 5. Film formulations exhibit a non-Fickian mechanism, as indicated by their n release exponent values falling within the range of $0.45<n<0.89$.

Non-Fickian release kinetics are characterized by a release rate that is not solely dependent on the concentration gradient, as observed in Fickian diffusion. Instead, the release mechanism may be influenced by factors such as swelling, erosion, or other complex drug release processes. Non-Fickian release kinetics enable the development of controlled release formulations that can modulate the drug release rate over an extended period. This has implications for improving patient compliance and therapeutic efficacy.

Zeta potential analysis

Zeta potential analysis indicates the stability of the dispersion and the potential for interactions with other particles or surfaces. Changes in pH and ionic strength can significantly impact the zeta potential of nanoparticles, influencing their stability and drug release properties. Among six films, film 1 has the highest drug release percentage. The zeta potential analysis result for film 1 is shown in Figure 6.

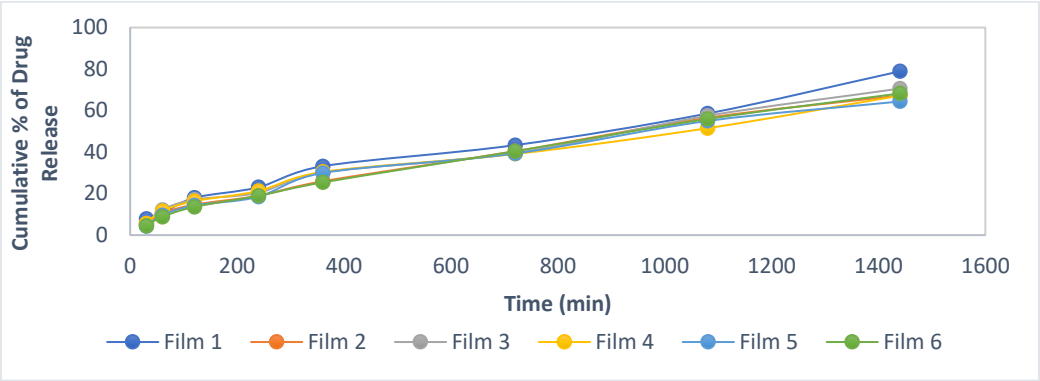

Fig. 2. Zero-order kinetic model

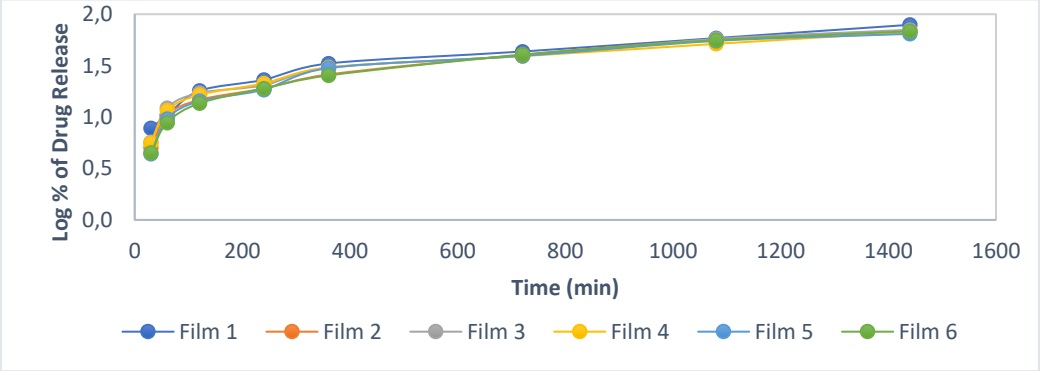

Fig. 3. First-order kinetic model

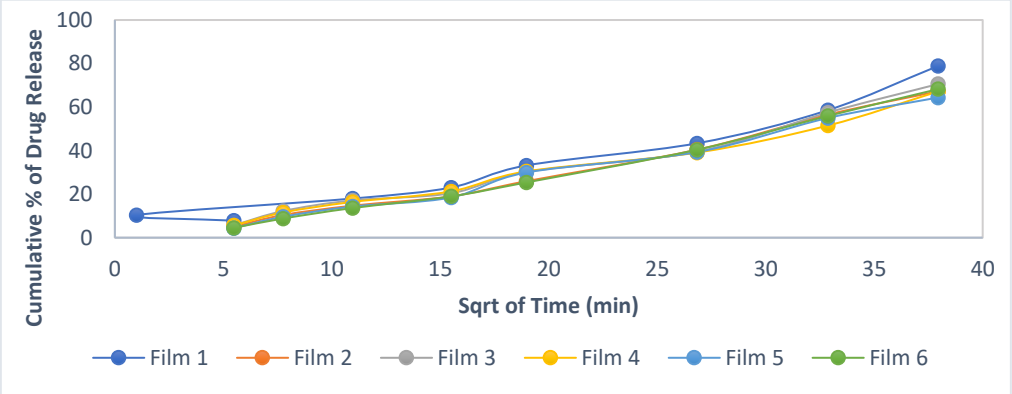

Fig. 4. Higuchi kinetic model

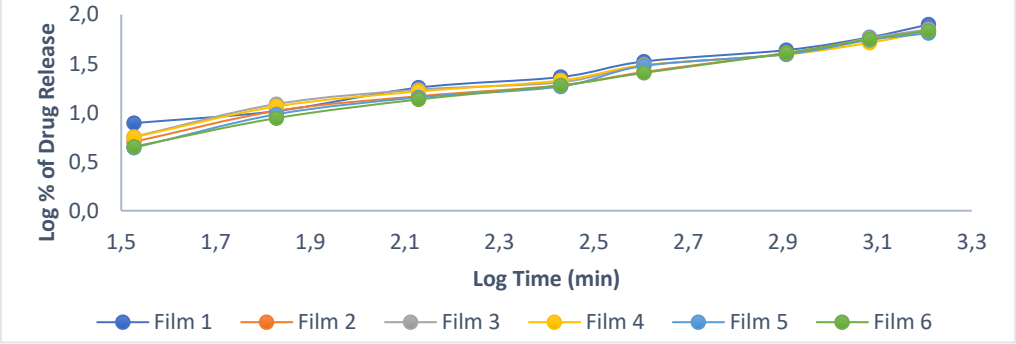

Fig. 5. Korsmeyer-Peppas kinetic model

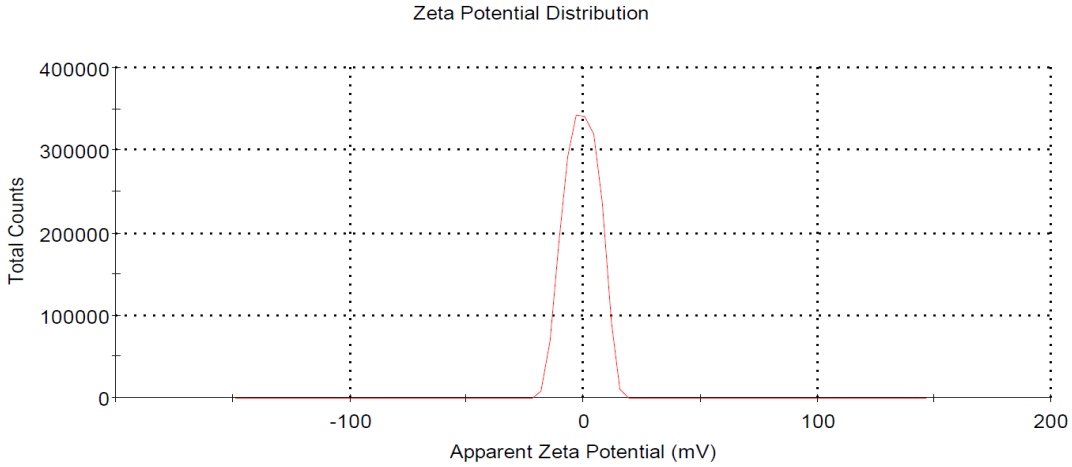

Fig. 6. Zero potential graph for film 1

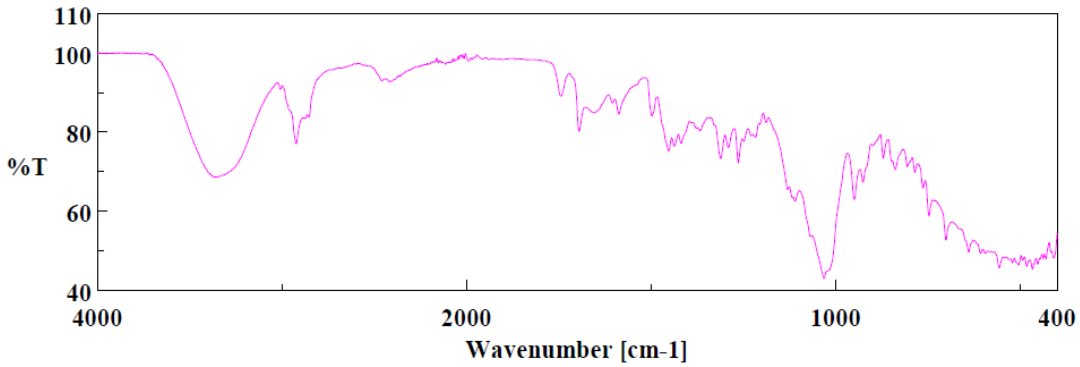

Fig. 7. FTIR analysis for film 1

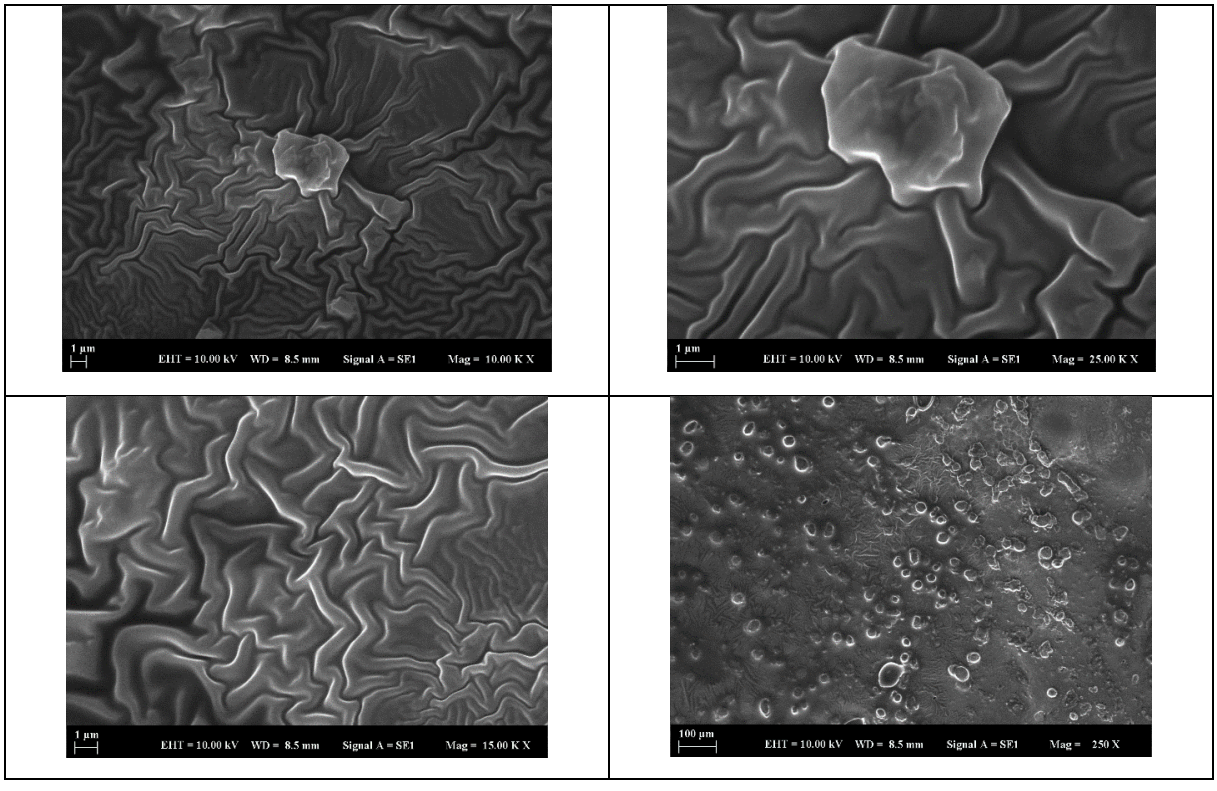

Fig. 8. FTIR analysis for film 1

FTIR (Fourier transform infrared) spectroscopy analysis

FTIR analysis provides information on drug-polymer interactions, diffusion processes, and the influence of environmental factors on drug release, aiding in the design of optimized drug delivery systems and this technique allows real-time monitoring of drug release. The FTIR analysis for film 1 is shown in Figure 7.

SEM (scanning electron microscopy) analysis

Scanning electron microscopy (SEM) is a powerful imaging technique that uses a focused beam of electrons to generate high-resolution images of the surface of a sample. It provides detailed information about the topography, morphology, and composition of materials at the nanoscale (Fig. 8).

CONCLUSION

In this thesis study, six different transdermal patches were successfully synthesized by adding different types and amounts of plasticizers, substances and penetration enhancers in varying ratios. Different release rates were achieved with the added plasticizers, flexibility and pore structure were observed to be different and the characterization results confirmed these. Drug release rates of all patches were examined in a pH 7.4 environment for 24 h. As a result of analyses using UV spectroscopy; the film with the highest release rate is film number 1 with 78.89%. In general, it can be said that the amount of drug release increases due to the increase in the amount of plasticizer in the patch. The drug release rates for other patches are 67.24% for film 2, 70.58% for film 3, 67.18% for film 4, 64.38% for film 5 and 68.25% for film 6. These findings establish a correlation between the substances in varying ratios and the resulting drug release rates, emphasizing the importance of formulation optimization for transdermal patches.

Scanning electron microscopy (SEM) analyses were also carried out at different magnification rates and scales. Accordingly, the most homogeneous structure of the films and the pore structure in the films containing St. John's wort oil were clearly seen.

Stability studies performed with the Zetasizer device showed that there was no significant change in films kept at room temperature.

According to the analysis results obtained with the FTIR device, the polymers in the films accurately meet the wavelengths specified in the literature. This reveals that the synthesized patches are mostly homogeneously distributed which is confirmed by analysis.

Acknowledgement: *This study was supported by the Research Fund of the Yıldız Technical University (Project No: FDK-2023-5572).*

REFERENCES

1. L. Huang, T. Su, X. Li, *Curr. Top Med. Chem.,* **13** (15),1864 (2013).
2. P. Anand, B. Singh, *Arch. Pharm. Res*., **36**(4), 375 (2013).
3. S. Sadab, S. Sahu, S. Patel, R. Khan, B. Khare, B. Thakur, S. P. K. Jain, *Asian Journal of Dent. and Health Sci.*, **2**(4), 40 (2022).
4. D. Ramadon, M. T. McCrudden, A. J. Courtenay, R. F. Donnelly, *Drug Delivery and Translational Research*, 1-34 (2021).
5. X. Wang, in: *SHS Web of Conferences, EDP Sciences,* **144**, 01006 (2022).
6. A. Hanbali, O.A. Khan, H.M.S. Sarfraz, M. Arafat, M. Ijaz, A. Hameed, *Acta Pharm.,* **69**(2). 197 (2019).
7. Y. Acar, E. Akyol, *The Online Journal of Sci. and Tech.,* **11**(1), 31 (2021).
8. L. Chen, L. Ma, S. Yang, X. Wu, X. Dai, S. Wang, X. Shi, *Journal of Trad. Chinese Med. Sci.,* **6 (**4), 347 (2019).
9. S. Chakraborty, N. Gupta, K. T. Sastri, M. Sharadha, P. Chand, H. Kumar, V. Jain, *Journal of Drug Del. Sci. and Tech.,* **73**(1), (2022).
10. L. Bartosova, J. Bajgar, *Curr Med Chem,* **19**(1), (2012).
11. K. Purushotham, K. A. Vijetha, *GSC Biological and Pharmaceutical Sciences,* **22**(2), 245 (2023).
12. D. Ekşi, E. Akyol, I. Küçük, *Bulg. Chem. Commun.,* **55 (**3), 289 (2023).