World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Transdermal delivery of Telmisartan through rat skin from formulation containing synthetic and natural penetration enhancer

Sarika Pranam Patil [1, *], Miss Sayali Sanjay Nejkar [1], Miss Farnaz Anjum Ayyaz Mutwalli [1], Chand Abbas Mujawar [1], Ravina Ramesh Lapate [1], Anuja Atul Masule [1] and Trupti Pratik Durgawale [2]

[1] *Department of Pharmaceutical Chemistry, Dr. Shivajirao Kadam College of Pharmacy, Kasabe Digraj, Sangli, Maharashtra, 416 305, India.*
[2] *Department of Pharmaceutical Chemistry, Krishna Institute of Pharmacy, KVV Karad, Satara, Maharashtra, 415 539, India.*

World Journal of Biology Pharmacy and Health Sciences, 2025, 24(03), 057-064

Publication history: Received on 26 July 2024; revised on 05 August 2025; accepted on 08 September 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.24.3.0597

Abstract

Telmisartan, an angiotensin-II receptor antagonist, has shown promising effects when delivered through transdermal patches for effective hypertension management. This study aimed to develop a matrix-type transdermal therapeutic system for telmisartan using Hydroxypropyl methyl cellulose (HPMC) and Polyvinyl pyrrolidone (PVP) as polymers, with Dimethyl sulfoxide (DMSO) as a synthetic penetration enhancer and a combination of piperine and menthol as natural enhancers. Comparative permeability studies were conducted to assess the effectiveness of these enhancers. Drug release rates were evaluated across rat skin using a Franz diffusion cell over 6 hours, measuring parameters such as percentage cumulative drug release (% CDR), apparent permeability (Papp), flux (J), and enhancement ratio (ER). The study found that patches containing natural enhancers (piperine and menthol) had a significantly higher drug release rate (up to 18.46 ± 0.02 % CDR) compared to those with synthetic enhancers (up to 10.19 ± 0.01 % CDR). This suggests that natural penetration enhancers could be more effective in promoting drug release. Transdermal drug delivery bypasses hepatic first-pass metabolism, reduces side effects and gastrointestinal issues and improves patient compliance, making it a promising approach for enhancing drug delivery efficiency.

Keywords: Transdermal patch; Telmisartan; Natural Penetration Enhancer; Piperine; Menthol

1. Introduction

Transdermal drug delivery systems offer significant advantages, including controlled release, reduced side effects, improved efficacy, and painless administration. Utilizing the skin as a delivery route takes advantage of its accessibility and non-invasive nature, allowing for continuous and consistent drug administration. This method is especially beneficial for medications with short biological half-lives, ensuring a steady supply to the bloodstream and avoiding the fluctuations associated with pulsed drug entry. Despite challenges posed by the skin's barrier properties, advancements over the past two decades have made transdermal systems a key focus in drug delivery research due to their clinical benefits. Transdermal patches, designed to deliver drugs at predetermined rates, minimize variations between and within patients, ensuring consistent therapeutic effects. These patches vary in size and may contain multiple active ingredients, with higher concentrations allowing for extended-release periods. In transdermal matrix patches, the drug is dispersed within a polymer matrix, enabling controlled release based on the properties of the drug and matrix. Transdermal patches offer non-invasive, painless drug delivery, improving patient compliance and providing consistent plasma levels through controlled release. They bypass hepatic first-pass metabolism, enhancing bioavailability and reducing side effects. Patches are especially beneficial for pediatric and geriatric patients and allow easy dose

* Corresponding author: Sarika Pranam Patil

adjustment or termination by simply removing the patch. However, they are limited to drugs that can penetrate the skin, may cause irritation, have a slower onset of action, and offer less flexibility in dosing. Additionally, they may not be suitable for high-dose medications, can be affected by patient variability, and may detach under certain conditions [1-5].

Telmisartan, an angiotensin II receptor blocker (ARB), effectively lowers blood pressure by causing vasodilation and is commonly used for hypertension treatment. Despite its high permeability, Telmisartan's low solubility (Class II of the Biopharmaceutics Classification System) poses challenges for absorption in the gastrointestinal tract, requiring formulation strategies to improve its solubility and bioavailability. With a terminal elimination half-life of about 24 hours and an absolute bioavailability of 42% to 58%, Telmisartan reaches peak plasma concentration 0.5 to 4 hours after oral administration. However, its nonlinear oral bioavailability limits dose-proportional absorption. Transdermal delivery offers advantages over oral administration by bypassing first-pass metabolism, ensuring stable plasma levels, and improving patient compliance [6-8].

Penetration enhancers are compound that boost the absorption and effectiveness of drug. Synthetic penetration enhancers can have inconsistent drug delivery performance, leading to variability in effectiveness across individuals and over time. They may also raise environmental concerns due to non-biodegradability or harmful byproducts from their production. Additionally, regulatory approval for transdermal patches containing synthetic enhancers may be more stringent due to safety and efficacy concerns. In contrast, natural penetration enhancers are often safer, derived from renewable sources, and biocompatible, making them more sustainable and less likely to cause adverse effects. They also enjoy greater cultural acceptance, provide additional health benefits, and face fewer regulatory hurdles compared to synthetic counterparts [4,9]. With various types of penetration enhancers available, one of the effective and low-cost penetration enhancer piperine and menthol was selected. As piperine and menthol are one of the natural, safe and effective penetration enhancers having its easy partitioning, it can modulate membrane dynamics, thus helping to efficiently permeate drugs across barriers [10-12].

Thereby, taking into account the favorable impacts of these enhancers, it was deemed worth exploring comparative permeability studies to assess the effectiveness of these enhancers. In the present study, comparative permeability tests were conducted to evaluate the effectiveness of synthetic and natural penetration enhancers.

2. Materials and Methods

2.1. Material

Sample of Telmisartan was gladly bestowed by Alkem laboratories, Mumbai, India. Piperine was bought from Loba Chemie Pvt. Ltd. India. The research experiment was carried out using deionized double distilled water. All other chemicals and solvents were of analytical grade.

2.2. Methods

2.2.1. Determination of λ max

Preparation of standard stock solution

Standard stock solution of Telmisartan was prepared by diluting 10mg of reference drug in 100ml of saline phosphate buffer pH 7.4 solution

Calibration curve of Telmisartan

Different concentration 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml of solution was prepared from this standard stock solution. The stock solution is further diluted appropriately with saline phosphate buffer solution pH 7.4 to acquire a concentration of 10µg/ml. This was scanned from 200-400nm. The λ max was found at 238nm

Solvent evaporation method for preparation of patches[9]

The patches were prepared by solvent casting evaporation technique. The weighed amount of HPMC and PVP were dissolved in solvent system of dichloromethane (DCM) and methanol in proportion 8:2, out of which 8 ml of solvent system is used. This solution is stirred for 10 minutes using magnetic stirrer, till the solution become clear. After that weighed amount of drug, and penetration enhancer is dissolved in PEG 600 (plasticizer), this mixture is poured in above solution and again stirred for 10 minutes until the mixture becomes uniform. Then this mixture was sonicated for 10 minutes using ultra sonicator. The uniform solution was then poured into petri plate which was previously lubricated with glycerin and an inverted funnel was placed to control the evaporation of solvent and avoiding cracking of patches. These plates were kept aside for overnight. Dried patches were separated from the plate, cut and stored.

Table 1 Optimized formula for telmisartan transdermal patches

Formulation Batch	Drug mg	HPMC mg	PVP mg	Solvent (DCM: Methanol 8:2) ml	PEG 600 ml	DMSO ml	Piperine mg	Menthol mg
F1	100	350	50	8	0.5	0.5	-	-
F2	100	350	50	8	0.5	-	0.5	0.5

F1: Patch with synthetic penetration enhancer; F2: Patch with natural penetration enhancer

To determine the optimization criteria, preformulation studies were conducted and the pertinent scientific literature was reviewed. Two transdermal patches of Telmisartan were prepared by mixing of plasticizer (PEG600), Drug (Telmisartan), polymers (HPMC, PVP) and penetration enhancer (DMSO as a synthetic penetration enhancer and piperine with menthol as natural penetration enhancer) as shown in table no. 1. Prepared transdermal patches were evaluated for their physicochemical evaluation of thickness, folding endurance, and in vitro drug release through rat skin. The diffusion study was conducted in Franz diffusion cell

2.2.2. Folding endurance

Folding endurance include folding capacity of the patches. It was determined by folding the patch continuously until it breaks. Folding endurance= No. of times the patch is folded without breaking it [5].

2.2.3. Thickness of patch

In micro-meter method, thickness was determined by taking readings at multiple places of patch using Vernier caliper. Average thickness of these multiple observations was used to confirm that the thickness of patch was desired [5].

Ex-vivo permeation studies using Franz diffusion cell across rat skin:[13, 14]

Receptor fluid: Saline phosphate buffer pH 7.4 solution was utilized as a receptor fluid and was made according to Indian Pharmacopoeia Monograph.

Rat skin membrane model: Ex-vivo drug release was studied with the Franz diffusion cell method. Male Swiss albino rats weighing 140–160 g provided skin sample was used for study. Following the use of a mechanical hair clipper to shave the hair without causing any skin damage, a 5 × 5 cm skin patch was removed from the dorsal area of rat that was slaughtered. The removed rat skin was kept in storage at -80°C. To get rid of superfluous debris and leachable enzymes, the skin membrane was first hydrated for 30 minutes at room temperature (23 ℃) in the buffer solution (pH 7.4) It was then positioned so that the dermal side was in direct contact with the receptor media, sandwiched between the donor and receptor compartments of the cells. The receptor compartment held around 9 ml of phosphate buffer (pH 7.4). Temperature control was done with a thermostatic water bath controller set at 37 ± 0.5-C and stirred at 100 rpm throughout the experiment. Transdermal patch having, 0.9 cm diameter containing synthetic and natural penetration enhancers were applied on the donor side of diffusion cell, and at each 30 min time interval 2 ml aliquots were withdrawn from receiver chamber up to 6 h maintaining sink conditions throughout the experiment. The samples were then promptly subjected to spectrophotometric analysis at 238 nm and the cumulative amount of drug permeated was computed. From ex-vivo permeability studies data obtained in triplicate for each test and control samples were utilized to calculate permeability metrics like % CDR, apparent permeability (Papp), Flux (J) and enhancement ratio (ER) by using standard formulae [15-19]. The experiments were done in triplicates, and the average value reported.

Permeability coefficient (apparent permeability)

$$Papp\left(\frac{cm}{s}\right) = \left(\frac{VA}{[area \times time]}\right) \times \left(\frac{[Drug]acceptor}{[Drug]donar}\right)$$

Where, V_A= volume in acceptor chamber, Area= intestinal membrane surface area, Time= total transport time

$$Flux(J)\left(\frac{\frac{mg}{cm2}}{hr}\right) = \frac{mass\,diffusing}{surface\,area \times time}$$

3. Results

In the present study, transdermal patches of telmisartan were formulated to promote its transdermal delivery. Maximum absorbance of Telmisartan in saline phosphate buffer solution pH 7.4 was found to be 238nm. Figure no. 1 indicates UV absorbance of telmisartan. Calibration curve of Telmisartan in saline phosphate buffer pH 7.4 has been shown in figure no. 2 and data for the same has been given in table no. 2. Thickness of patches is measured by Vernier caliper at different spots of the patch and was observed to be 0.346 mm and 0.351 mm for F1 and F2 respectively. The patches remained intact even after multiple folding. The folding endurance was found to 108 for F1 and 113 for F2, which outline that the patches that were prepared have the ability to withstand mechanical pressure and also have good flexibility.

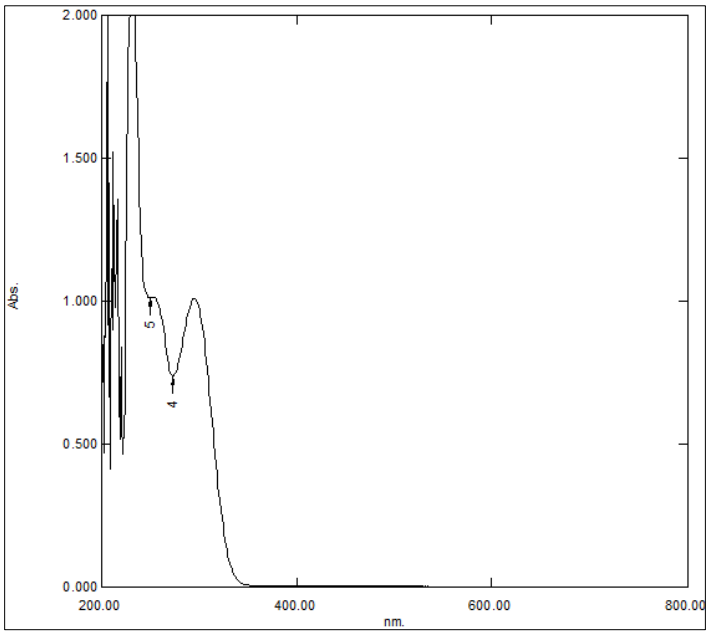

Figure 1 UV absorbance of telmisartan

Table 2 Data for calibration curve of Telmisartan in saline phosphate buffer pH 7.4

Conc.	Absorbance
2	0.266
4	0.478
6	0.662
8	0.865
10	1.09

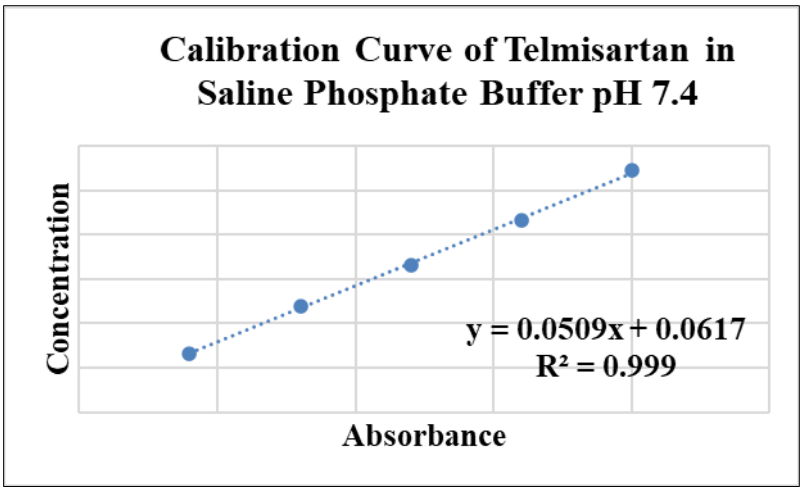

Figure 2 Calibration curve of Telmisartan in saline phosphate buffer pH 7.4

Ex-vivo permeation studies: The results of permeability behavior of telmisartan from both F1 and F2 patches are shown in table no. 3. Patch F1 has shown poor membrane permeability of 10.20 ± 0.01 % CDR only while patch F2 has shown significantly greater rat skin permeability of telmisartan that has been enhanced up to 18.50 ± 0.02 % CDR. Other permeability parameters such as Papp and J were also found to be increased significantly in F2 patch as compared to F1. Table no. 4 indicates the calculated values of permeability parameters % CDR, Papp and J upto 6 h in cases of both patches. Figure no. 3 shows comparison of % CDR of patch containing synthetic and natural penetration enhancer.

Table 3 %CDR of Telmisartan from F1 and F2 patch

Time (h)	F1 (Patch with synthetic penetration enhancer) *	F2 (Patch with natural penetration enhancer) *
0.5	1.11 ± 0.01	1.67 ± 0.015
1	1.56 ± 0.02	2.61 ± 0.01
1.5	2.23 ± 0.01	4.29 ± 0.015
2	3.06 ± 0.02	6.07 ± 0.015
2.5	3.67 ± 0.03	7.94 ± 0.04
3	4.32 ± 0.02	9.53 ± 0.015
3.5	4.86 ± 0.02	10.88 ± 0.02
4	6.12 ± 0.01	12.43 ± 0.015
4.5	6.92 ± 0.02	14.02 ± 0.015
5	8.25 ± 0.02	15.56 ± 0.01
5.5	9.24 ± 0.02	16.97 ± 0.01
6	10.20 ± 0.01	18.50 ± 0.02

Table 4 Observed response values with permeability profiles

Samples	% CDR	Papp×10^7cm/s	*J* mg/cm^2/hr
F1 (Patch with synthetic penetration enhancer)	10.20 ± 0.01	0.28	0.36
F2 (Patch with natural penetration enhancer)	18.50 ± 0.02	0.39	0.48

%CDR: percentage cumulative drug release; Papp: apparent permeability coefficient; J: flux i.e. amount of drug permeated through a unit area in a unit of time.

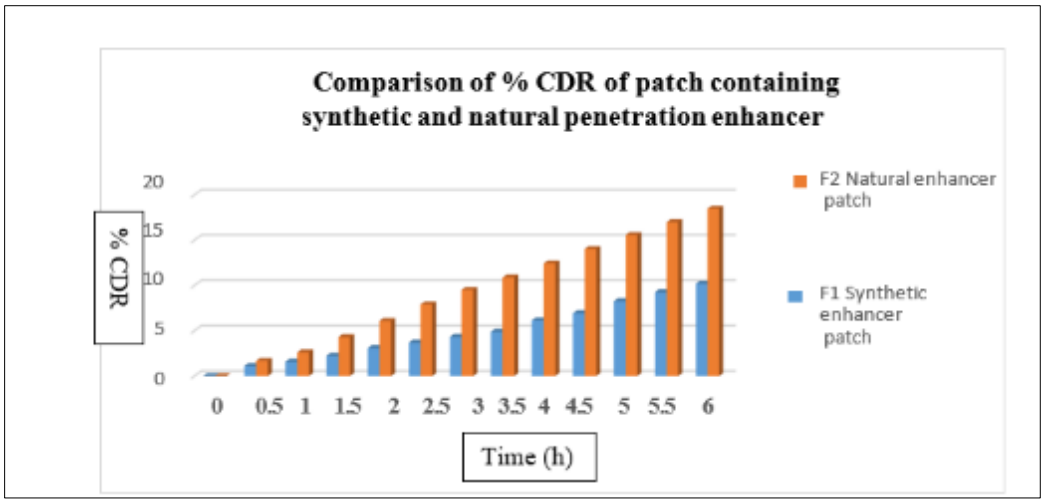

Figure 3 Comparison of % CDR of patch containing synthetic and natural penetration enhancer

4. Discussion

So, from current study it has been observed that, patch containing natural penetration enhancer has shown more significant drug permeation profile as compared to patch with synthetic penetration enhancer. This might be due to presence of piperine and menthol penetration enhancers. As piperine and menthol are one of the natural, safe and effective penetration enhancers having its easy partitioning, it can modulate membrane dynamics, thus helping to efficiently permeate drugs across skin barriers. Piperine enhances the permeability of the skin barrier by interacting with keratinocytes and altering their structure, it inhibits the activity of drug-metabolizing enzymes in the skin, and increasing the concentration of drugs that reach deeper skin layers. The mechanism of piperine to enhance skin permeation of drugs possibly involves partial extraction of the stratum corneum, interaction with the keratin of the stratum corneum, tight junction protein disruption [20,21].

Menthol disrupts the lipid structure of the stratum corneum, the outermost layer of the skin, and increasing permeability of drugs. menthol has vasodilator effects which increased blood flow to the skin and enhanced circulation can further promote the delivery of drugs by facilitating their diffusion through the skin's layers [22,23].

5. Conclusion

Telmisartan transdermal patches were successfully prepared by solvent evaporation technique, using synthetic and natural penetration enhancers. The chemical evaluation of patches was also performed. The results of ex vivo permeability study concluded that permeation of drug through rat skin using natural penetration enhancer is significantly greater than synthetic penetration enhancer. This is due to piperine and menthol mediated enhancement in the permeability profile of telmisartan which might be solely accountable for drugs permeability improvement.

Compliance with ethical standards

Acknowledgements

Authors are thankful to Principal, Dr. Shivajirao Kadam College of Pharmacy, Kasabe Digraj, Sangli, Maharashtra, India for providing laboratory facilities and constant encouragement.

Disclosure of conflict of interest

The author(s) declare(s) that they have no declaration of interests to disclose.

Statement of ethical approval

The institutional animal ethical committee (IAEC) of Dr. Shivajirao Kadam College of Pharmacy, Kasabe Digraj, Sangli, Maharashtra, India agreed the proposed protocol of present animal studies. The approval was recorded and protocol approval number is IAEC/SKCP/2025-26/129 (K)

References

[1] Ali S, Shabbir M, Shahid N. The structure of skin and transdermal drug delivery system-a review. Research journal of pharmacy and technology. 2015;8(2):103-9.

[2] Bird D, Ravindra NM. Transdermal drug delivery and patches—An overview. Medical Devices & Sensors. 2020 Dec;3(6): e10069.

[3] Rastogi V, Yadav P. Transdermal drug delivery system: An overview. Asian Journal of Pharmaceutics (AJP). 2012;6(3):161.4.

[4] Chivte VK, Tiwari SV, Nikalge AP. Bioenhancers: A brief review. Adv J Pharm Life Sci Res. 2017; 2:1-8.

[5] Vishwakarma AK, Panda P, Verma NK, Vishwakarma DK, Mishra JN. An overview on transdermal patches. Pharmacy Review & Research. 2017, 7 (1); 17-23.

[6] Ahad A, Al-Mohizea AM, Al-Jenoobi FI, Aqil M. Transdermal delivery of angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs) and others for management of hypertension. Drug delivery. 2016 Feb; 12;23(2):579-90.

[7] Bakheit AH, Abd-Elgalil AA, Mustafa B, Haque A, Wani TA. Telmisartan. Profiles of drug substances, excipients and related methodology. 2015 Jan; 1;40:371-429.

[8] Teaima M, Abdelmonem R, Adel YA, El-Nabarawi MA, El-Nawawy TM. Transdermal delivery of telmisartan: formulation, in vitro, ex vivo, iontophoretic permeation enhancement and comparative pharmacokinetic study in rats. Drug design, development and therapy. 2021 Nov; 10:4603-14.

[9] Das AS, Ahmed AB. Natural permeation enhancer for transdermal drug delivery system and permeation evaluation: A review. Asian J Pharm Clin Res. 2017;10(9):5-9.

[10] Bhise SB, Pore YV, Influence of co-administration of piperine on pharmacokinetic profile of ciprofloxacin. Indian Drugs 2002; 39 (3):166-168.

[11] Narade SB, Pore YV. Optimization of goat intestinal permeability of berberine chloride in presence of natural bioenhancer piperine using 32 full factorial design. International Journal of Biology, Pharmacy and Allied Sciences. 2022, 11(10): 4758-4778.

[12] Narade SB, Pore YV. Pharmacokinetic assessment of Natural Anticancer Berberine Chloride in presence and absence of some Herbal Bioenhancers in rabbit model. Research J. Pharm. and Tech. 2023; 16(11):5121-5129.

[13] Transdermal Delivery of Diclofenac Sodium Through Rat Skin From Various Formulations. AAPS PharmSciTech 2006; 7 (4) Article 88

[14] Formulation and evaluation of transdermal patches and to study permeation enhancement effect of eugenol Nirav S Sheth , Rajan B Mistry Journal of Applied Pharmaceutical Science 2011; 01 (03):96-101

[15] Narade SB, Pore YV, Optimization of ex vivo permeability characteristics of berberine in presence of quercetin using 32 full factorial design. Journal of Applied Pharmaceutical Science 2019; 9 (1):073-082.

[16] Narade SB, Pore YV, Effect of co-administration of quercetin on goat intestinal permeability of berberine chloride. Int J Pharma Sci Res. 2019; 10 (8):3915-3919.

[17] Narade SB, Pore YV, Assessment of permeability behavior of berberine chloride across goat intestinal membrane in presence of natural biopotentiator curcumin. Indian Drugs 2021; 58 (4): 23-27.

[18] Chakraborti CK, Sahoo S, Behera PK, Effect of different polymers on in vitro and ex-vivo permeability of ofloxacin from its mucoadhesive suspensions. Saudi Pharma J. 2015; 23 (2):195-201.

[19] Varma VNSK, Maheshwari MN, Navya M, Reddy SC, Shivkumar HG, Gowda DV, Calcipotriol delivery into the skin as emulgel for effective permeation. Saudi Pharm J. 2014;22(6): 591-599.

[20] Jantarat C, Sirathanarun P, Boonmee S, Meechoosin W, Wangpittaya H. Effect of Piperine on Skin Permeation of Curcumin from a Bacterially Derived Cellulose-Composite Double-Layer Membrane for Transdermal Curcumin Delivery. *Scientia Pharmaceutica*. 2018; 86(3):39.

[21] Patil, V.M.; Das, S.; Balasubramanian, K. Quantum chemical and docking insights into bioavailability enhancement of curcumin by piperine in pepper. *J. Phys. Chem. A* **2016**, *120*, 3643–3653.

[22] Fox LT, Gerber M, Plessis JD, Hamman JH. Transdermal Drug Delivery Enhancement by Compounds of Natural Origin. *Molecules*. 2011; 16(12):10507-10540.

[23] Gao, S.; Singh, J. *In vitro* percutaneous absorption enhancement of a lipophilic drug tamoxifen by terpenes. *J. Control. Release* 1998; 51:193–199.