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Enhancement of Losartan Transdermal Transport Through Incorporation into Chitosan Nanoparticles

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Abstract
Losartan, an antihypertensive agent, has low oral bioavailability. Therefore, developing a design for transdermal delivery of losartan is interesting. This study aims to enhance losartan in vitro transport by incorporating it into chitosan nanoparticles. Transdermal transport studies were conducted using two experimental groups: the pretreatment group using oleic acid and propylene glycol, and the group without pretreatment. The results showed that losartan incorporated into chitosan nanoparticles resulted in a significantly higher amount of drug being transported than the losartan solution (control) in both experimental groups. In the experiment without pretreatment, the amount of losartan from the control could not be detected in the receptor compartment until 28 hours. In contrast, losartan was detected at 16 hours of transport from chitosan nanoparticles. In pretreatment, chitosan nanoparticles exhibited 6.6-fold higher losartan transport than the control. In addition, losartan chitosan nanoparticles showed significant increases in steady-state flux and transport efficiency by 3.3 and 6.6 times higher than the control, respectively. It can be concluded that the incorporation of losartan into chitosan nanoparticles can increase its transdermal transport.

Keywords: Chitosan, losartan, nanoparticles, transdermal

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Peningkatan Transpor Transdermal Losartan Melalui Inkorporasi ke Dalam Nanopartikel Kitosan

Abstrak
Losartan sebagai antihipertensi memiliki bioavailabilitas oral yang rendah. Oleh karena itu, pengembangan desain untuk penghantaran losartan transdermal menjadi hal yang menarik. Penelitian ini bertujuan untuk meningkatkan transport losartan secara in vitro dengan menginkorporasikannya ke dalam nanopartikel kitosan. Studi transport transdermal dilakukan dengan menggunakan dua kelompok percobaan, yaitu kelompok pra-perlakuan menggunakan asam oleat dan propilen glikol, dan kelompok tanpa pra-perlakuan. Hasil penelitian menunjukkan bahwa losartan yang diinkorporasikan ke dalam nanopartikel kitosan menunjukkan jumlah obat yang ditransport secara signifikan lebih tinggi daripada larutan losartan (kontrol) pada kedua kelompok percobaan. Dalam percobaan tanpa pra-perlakuan, jumlah losartan dari kontrol tidak dapat dideteksi pada kompartemen reseptor hingga 28 jam, sedangkan losartan dapat terdeteksi pada 16 jam transport dari nanopartikel kitosan. Dalam percobaan dengan pra-perlakuan, losartan dari nanopartikel kitosan menunjukkan transport 6,6 kali lipat lebih tinggi daripada kontrol. Selain itu, nanopartikel kitosan losartan menunjukkan peningkatan signifikan dalam fluks *steady state* dan efisiensi transport masing-masing sebesar 3,3 dan 6,6 kali lebih tinggi daripada kontrol. Dapat disimpulkan bahwa inkorporasi losartan ke dalam nanopartikel kitosan dapat meningkatkan transport transdermalnya.

Kata Kunci: chitosan, losartan, nanopartikel, transdermal

1. Introduction

Among the various drug administrations, the development of the transdermal delivery system is a challenge due to several benefits including the ability to minimize drug side effects, keep the uniformity of pharmacokinetic profiles, increase patient compliance by reducing the frequency of drug doses, prevent first pass metabolism and avoid drug degradation against enzymes as well as pH differences during in the gastrointestinal tract thus increasing the bioavailability of the drug.[1–12] In addition, transdermal drug delivery can be used for patients with digestive problems. To develop a transdermal drug delivery system, it is necessary to understand the skin's structure.

The function of the skin is to protect the body from the penetration of chemicals or microorganisms in the environment and prevent water loss. The presence of the stratum corneum in the epidermis of the skin acts as the main barrier preventing foreign materials from crossing the skin. Stratum corneum is mainly composed of about 70% keratin, providing hydrophilic properties. Lipids in small amounts are also part of the skin components.[13,14] Penetration of drugs into the skin can occur through two main routes, namely trans-epidermal and trans-appendageal. Most drugs penetrate the skin via the trans-epidermal route, including intracellular and intercellular routes. The hydrophilic drugs may cross the skin via the intracellular route due to the same drug properties as keratin, a component of stratum corneum, whereas the lipophilic drugs pass through the skin via the intercellular route. However, the intracellular pathway is not easily traversed by drugs such as losartan potassium.

Losartan is an antihypertensive drug providing low oral bioavailability, which is available commercially as losartan potassium.[15] To increase the bioavailability of losartan, the development of losartan carriers to be applied as transdermal drug delivery systems is a challenge. The hydrophilic nature of losartan potassium makes it difficult to pass through the skin. As a stratum corneum component, keratin is a hydrophilic, tightly packed part that is not easily traversed by even hydrophilic chemicals. Therefore, this study aims to increase the transport of losartan through the skin by incorporating chitosan into nanoparticles.

Nanoparticle development as part of nanotechnology in transdermal drug delivery systems is a promising carrier to be developed to increase drug efficacy, as exhibited in previous studies.[4,16–32] Conventional dosage forms and drug limitations to achieve the target of action due to several barriers existing in the physiological body could be the reason for the low therapeutic effect of the drug. Therefore, it is necessary to develop a potential way to design drug carriers as performed in this study. The urgency of this research is to overcome the problem of low oral bioavailability of losartan via the development of a transdermal delivery system by forming chitosan nanoparticles as a carrier. Chitosan as a carrier can increase the fluidity of the skin stratum corneum. In addition, the pretreatment using oleic acid and propylene glycol can improve skin permeability and lead to an increase in transported drugs across the skin. In the present research, an in vitro transdermal study was carried out on losartan nanoparticles using Franz diffusion cells with two experimental groups, including one with and without pretreatment using oleic acid and propylene glycol. The amount of drug transported was analyzed using HPLC.

2. Materials and methods

2.1. Materials

Losartan potassium was purchased from PT Kalbe Pharma. Chitosan and sodium tripolyphosphate (Na TPP) were obtained from Sigma Aldrich. Acetonitrile for HPLC originated from E Merck and Wistar male rats with a weight of 110-190 g and an age of 1.5-2.5 months were obtained from the Faculty of Pharmacy, Ahmad Dahlan University.

2.2. Methods

2.2.1. Preparation of losartan nanoparticles

Preparation of losartan nanoparticles was conducted by mixing a solution of losartan potassium in water with a 0.15 M chitosan solution in acetate buffer pH 4 at a speed of 350 rpm using a magnetic stirrer at room temperature for 10 minutes. Subsequently, 14% of Na TPP solution in water was added, and mixing was continued for 30 minutes, followed by sonication for 20 minutes. Afterward, centrifugation was carried out at 14000 rpm for 45 minutes at 10°C to separate the losartan nanoparticles in the precipitate. Thereafter, the sediment was collected and dried using a freeze-dryer for further experiments.[33]

2.2.2. Preparation of diffusion cells using rat skin membrane

Wistar male rats aged 1.5-2.5 months and weighing 110-190 g were conditioned in a chamber containing chloroform. Afterward, the rat skin was taken from the dorsal part, and the fat was removed using a scalpel. Hair was also removed from the skin using an electric clipper. Subsequently, the skin was cut into a circular shape with a diameter of about 2 cm, followed by rinsing the skin using 0.15 M phosphate buffer saline

(PBS) pH 7.4. Thereafter, the skin was set on the Franz diffusion cells containing 20.0 mL of 0.15M PBS pH 7.4. The stratum corneum of the skin should face the sample in the donor compartment.[34]

2.2.3. Sample preparation for in vitro transdermal delivery studies

A certain amount of losartan nanoparticle powder containing losartan amount equivalent to the control group was dispersed in water, followed by mixing using a vortex for approximately 15 minutes before sonication to produce a dispersion at a concentration of 2 mg/ml. After 20 minutes of sonication, the samples were put into the donor compartment. There were two experimental groups, namely the experiment with pretreatment using oleic acid and propylene glycol and the group without pretreatment. In each experiment, there were losartan nanoparticles as samples and a control, namely, losartan solution.

2.2.4. In vitro transdermal transport studies

Briefly, the Franz diffusion cells were placed on a Thermolyne with a magnetic stir bar rotating at 700 rpm. The donor compartment contained 2 ml of losartan solution or dispersion of losartan-chitosan nanoparticles in water. Sampling was carried out at 0 hour of the experiment before filling the dispersion sample in the donor compartment, the further sampling was conducted at predetermined time points, namely 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28 hours. One ml sample was taken from the acceptor compartment and replaced with 0.15 M PBS pH 7.4, with the same volume and temperature. The amount of transported losartan was analyzed using HPLC.[34]

2.2.5. Quantification of losartan using HPLC

The amount of losartan in the acceptor compartment was quantified using HPLC with the mobile phase of 0.05M acetic buffer pH 4 and acetonitrile with a ratio of 3:2. Lichrospher RP 18 250-4 (5 µm) was used as the fixed phase, and UV spectrum at a wavelength of 223 nm was used as a detector. The column was conditioned with the selected method for 30 minutes before sample injection.[35]

2.2.6. Statistical analyses

The steady-state flux and transport efficiency between formulations with and without oleic acid-propylene glycol pretreatment were compared using an independent sample t-test (SPSS 17) at a 95% confidence level.

3. Result

Several HPLC chromatograms showing losartan peaks are depicted in Figure 1, where the target drug was detected at a retention time of approximately 9.14 minutes, close to the validation results of this HPLC method 35. The validation parameters, including limit of detection (LOD), limit of quantification (LOQ), recovery, and random error, were 27.3 ng/ml, 91.1 ng/ml, 106.4%, and 3.7%, respectively. This method has a good linearity (r=0.9998) in a low concentration range of 50-1000 nm, showing a calibration equation of y=121.13 x + 674.57, in which y and x are the area under the curve of the chromatogram peak (mV minutes) and concentration (ng/ml), respectively.

Based on the analysis of transdermal transport without pretreatment using oleic acid and propylene glycol, as indicated in Figure 2, the results showed that during 28 hours of experiment, the losartan incorporated in the chitosan nanoparticle could be transported almost 2000 ng, whereas the control potassium solution indicated an amount of practically zero. The experiment without pretreatment of nanoparticle formulation provided significantly higher transported losartan than the control formulation, namely, losartan solution.

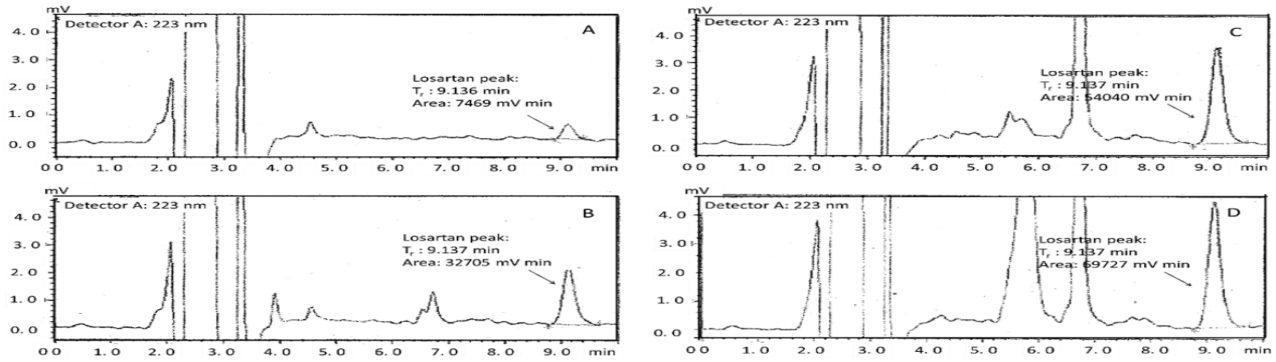

Figure 1. A typical HPLC chromatogram of receptor medium on losartan transdermal transport. The donor compartment contained losartan solution with 10% oleic acid in propylene glycol pretreatment. A, B, C, and D are losartan peaks after 12, 20, 24, and 28 hours of permeation studies, respectively.

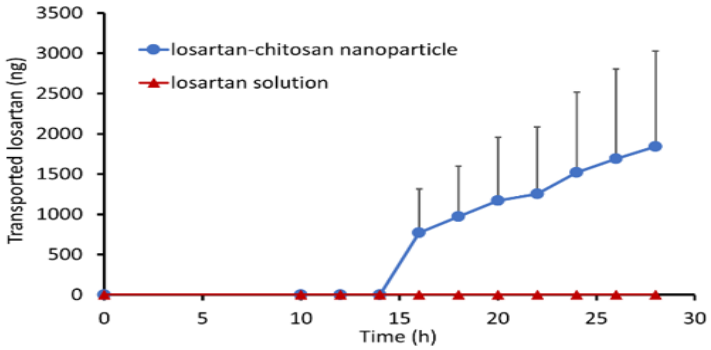

Figure 2. Amount of transported losartan during 28 hours of experiment, in the case of control (losartan solution) (red triangle) and losartan nanoparticles (blue circle) without pretreatment using oleic acid and propylene glycol. Data are presented as mean ± SD (n = 3).

In case of the losartan transport study using pretreatment, the results of losartan transdermal transport exhibited the amount of drug transported 6.6-fold higher than losartan solution, as shown in Figure 3. It was indicated that the transport of the drug incorporated into nanoparticles was significantly higher than the control.

The flux of losartan nanoparticles indicated a higher value compared to the control, both with and without pretreatment, as indicated in Table 1. In the pretreatment group, the losartan incorporated into the chitosan nanoparticles showed significantly improved steady-state flux and transport efficiency by 3.3-fold and 6.7-fold, respectively, higher than the control. Furthermore, in the experiment without pretreatment, the losartan from the losartan solution could not be detected in the receptor compartment, whereas the steady-state flux of losartan derived from the chitosan nanoparticle was 50,04 ng h^{-1} cm^{-2}.

4. Discussion

Continuing the study of formulation and characterization of losartan nanoparticles, which was performed in a previously published research article[33], a transport study of losartan nanoparticles was carried out in the present study to evaluate the capability of nanoparticles with chitosan as a carrier of the drug, namely losartan, to cross the skin to reach the systemic circulation. Within this research, a transport study was conducted using two groups of experiments, including the pretreatment group using 10% of oleic acid in propylene glycol on the rat skin as an animal model, and the second group was the experiment without pretreatment.

As shown in Figure 2, in the experiment without pretreatment, losartan incorporated into the nanoparticle formulation provides significantly higher losartan that can be transported than the control formulation, namely, losartan solution. The hydrophilic nature of losartan makes it difficult for the drug to pass through the skin due to the properties of the skin, which consists mostly of lipid lamella, present in the interstitial cells of the skin. This part is the main route for transporting lipophilic drugs, whereas the hydrophilic part of the skin consists of keratin, having a dense structure that is difficult for foreign substances to pass through.

Losartan nanoparticles provide a higher amount of drug transport compared to the control due to the ability of chitosan as a carrier of losartan nanoparticles to increase the fluidity and moisture content of keratin as

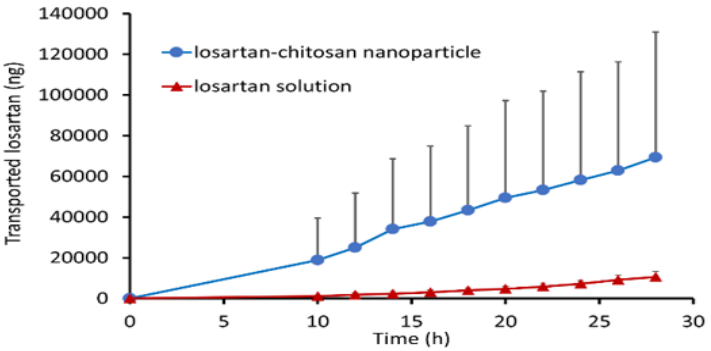

Figure 3. Amount of transported losartan during 28 hours of experiment, in the case of control (losartan solution) (red triangle) and losartan nanoparticles (blue circle) with pretreatment using oleic acid and propylene glycol. Data are presented as mean ± SD (n = 3).

Table 1. Flux and transport efficiency of losartan solution (control) and losartan nanoparticles with and without pretreatment using oleic acid and propylene glycol (PG). Data are presented as mean ± SD (n = 3).

Formulation	Oleic acid-propylene Glycol pre-treatment	Flux ($ng\ h^{-1}\ cm^{-2}$)	Transport efficiency (%)
Losartan solution	No	There is no detected losartan in the receptor compartment	
Losartan-chitosan nanoparticles	No	50.04 + 30.31	0.05 + 0.03
Losartan solution	Yes	418.94 + 103.67	0.26 + 0.07
Losartan-chitosan nanoparticles	Yes	1384.49 + 914.75	1.73 + 1.54

a component of stratum corneum, resulting in the ease of nanoparticles to cross the skin. Moisture absorption can reduce the viscosity (η) of the skin, thereby increasing the diffusion coefficient (D) according to the Stokes-Einstein equation, $D=RT/6\pi\eta rN$. The equation correlating lag time (T lag) with D, namely $T\ lag = h^2/6D$, shows that increasing the diffusion coefficient will decrease the lag time. This explains that chitosan produces benefits in transdermal permeation, not only in increasing flux but also in reducing lag time (T lag).[36]

The illustration of the mechanism is shown in Figure 4. This mechanism is likely due to the possible interaction between the NH3+ groups of chitosan with the SH-groups of cysteine as part of the keratin component.[37] In addition, chitosan can act as a permeation enhancer through its ability to enhance skin hydration. Under normal conditions, the water content of the skin is 15-20%, whereas during hydration, the water content can reach a higher value. This process causes swelling of the skin, resulting in changes in the stratum corneum, making it more flexible for the drug or carrier transport, resulting in the improvement of drug permeation across the skin.[38–40] Previous research published by Zhou et al demonstrated the mechanism of interaction between chitosan and keratin with transdermal transport experiments using rat skin, followed by observations of the stratum corneum and skin keratin using Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), and Fourier Transform Infrared Spectroscopy (FTIR). The results exhibited a change in the structure of the keratin to be more flexible based on SEM analysis. In the analysis using DSC, chitosan showed the ability to decrease the melting point of the α-helix microcrystals in keratin. In addition, based on FTIR analysis, there was a shift in the absorption spectrum of amide from keratin.[41]

Furthermore, the results of losartan transdermal transport with pretreatment using oleic acid and propylene glycol also indicated that the transport of the drug incorporated into nanoparticles was significantly higher than control, as shown in Figure 3. The function of the addition of oleic acid and propylene glycol is to maximize the transport of losartan incorporated into chitosan nanoparticles to cross the skin and reach systemic circulation. Chitosan nanoparticles can be easily transported across the skin with the pretreatment using oleic acid, providing the ability to scrape the keratin present in the stratum corneum, resulting in the enhancement of the skin fluidity. Previous studies exhibited that penetration into the skin of several drugs could be improved by oleic acid.[42–50]

Trommer and Neubert demonstrated that oleic acid indicated interactions with the hydrocarbon chain of the lipid bilayer, leading to changes in the polar head, thereby facilitating the transport of hydrophilic substances.[51] Propylene glycol at a concentration of 1 – 10% leads to the solvation of stratum corneum via the hydrogen bond formation, resulting in the enhancement of skin flexibility.

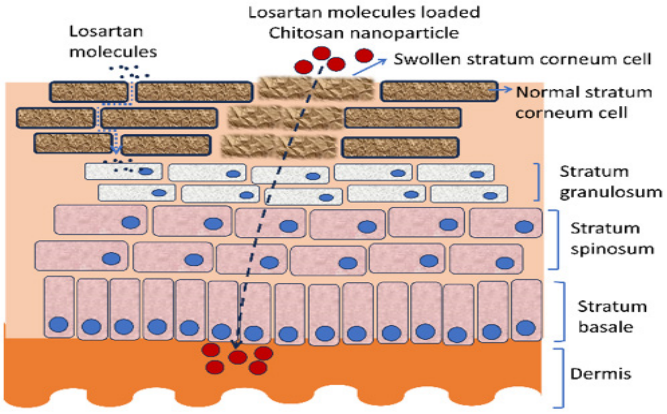

Figure 4. Illustration mechanism of skin transport of chitosan nanoparticles containing losartan via enhancement of the fluidity of stratum corneum 4

The combination of oleic acid and propylene glycol causes an increase in the fluidity of the stratum corneum, resulting in the ease with carrier passes through the skin. Two possible mechanisms that occur due to the use of a combination of oleic acid and propylene glycol are increased lipid fluidity and the formation of lacunae in the stratum corneum, resulting in increased skin permeability for drug transport.[52] A previous study showed that the combination of oleic acid and propylene glycol caused an increase in drug flux, namely propranolol.[53] In the present study, Figure 3 indicates an increase in drug transport in both groups, namely losartan control and nanoparticles with pretreatment, compared to the experiment without pretreatment (Figure 2). The amount of transported drug of the losartan nanoparticles showed a significant increase compared to the control. Based on the results, the amount of losartan transported in the experiment without pretreatment was much lower than the amount of losartan transported with pretreatment. This is likely due to the structure of the stratum corneum, which is still quite stiff and compact. Although chitosan can also increase keratin fluidity, the impact is not as big as if oleic acid and propylene glycol were added. The higher transport of nanoparticles is likely due to the different transport mechanisms. Endocytosis is a route that allows nanoparticles to cross the stratum corneum, whereas the losartan solution, showing molecular size, is difficult to transport via the endocytosis route. Losartan molecules in control permeate by passive diffusion, thereby the amount of transported drug is less than the nanoparticles.[54]

Based on Table 1, the losartan nanoparticles flux showed a higher value than the control, in both experimental groups, with and without pretreatment. The positive charges of chitosan nanoparticles provide the advantage of being transported via the transdermal route, due to the presence of negative charges on the skin, and thereby the nanoparticles can easily attach to the skin. This is in line with research conducted by Wu et al., indicating transport studies using different nanoparticle charges, including anionic and cationic. The results showed that the cationic nanoparticles indicated a higher ability to be transported across the stratum corneum compared to anionic nanoparticles.[55] Based on the transport efficiency data in Table 1, losartan nanoparticles provide a higher amount of transported drug during 28 h of experiment compared to the control at the same donor concentration, thereby the expected application area in further studies, namely in vivo, is considered feasible to achieve a steady state plasma concentration.

Pretreatment with oleic acid and propylene glycol not only affects the flux and transport efficiency but also the transport profile. Without pretreatment, the transport profile of the losartan nanoparticles showed a delayed time to reach the receptor compartment, as shown in Figure 2. It is due to the nanoparticles accumulated in the skin before being distributed to the receptor media. This condition is supported by the data that the transported drug increases from the last accumulation state to the first steady state point, resulting in a much lower calculation lag time compared to that observed directly from the profile. In the oleic acid pretreatment group, the skin's capacity to accumulate nanoparticles was reduced; therefore, the nanoparticles containing the drug directly penetrated the skin without waiting for the accumulation of the drug in the skin. The ability of oleic acid to disrupt lipid lamellae decreases the viscosity of intercellular pathways, thereby increasing the diffusion coefficient.

The effect of chitosan on skin fluidization due to increased water absorption is likely to appear in the skin at the surface of the donor compartment, resulting in a high input of nanoparticles into the skin, while the release of nanoparticles from the skin to the media receptor is delayed. On the other hand, fluidization of the skin in the experimental setting of the losartan solution does not occur in all lines of the skin, resulting in the same rate of drug movement from the donor medium into the skin and from the skin into the receptor compartment.

5. Conclusion

Within the present study, in vitro transdermal transport studies of losartan nanoparticles were performed. Losartan incorporated into nanoparticles with chitosan as a carrier could be transported through the skin, as shown by the improvement of drug amount, which can be detected in the receptor compartment compared to the control. Chitosan as a carrier in nanoparticles provides the ability to reduce the rigidity of the skin stratum corneum, resulting in the improvement of fluidity of the skin, thereby increasing the flux as well as transport efficiency of losartan. Based on these results, chitosan nanoparticle is a potential carrier for transdermal delivery of losartan.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Regenthal R, Voskanian M, Baumann F, Teichert J, Brätter C, Aigner A, Abraham G. Pharmacokinetic evaluation of a transdermal anastrozole-in-adhesive formulation. Drug Des Devel Ther 2018; 12: 3653–64.
2. Trivedi R, Umekar M, Kotagale N, Bonde S, Taksande J. Design, evaluation and in vivo pharmacokinetic study of a cationic flexible liposomes for enhanced transdermal

delivery of pramipexole. J Drug Deliv Sci Technol 2021; 61: 102313.
3. Morsi NM, Aboelwafa AA, Dawoud MHS. Improved bioavailability of timolol maleate via transdermal transfersomal gel: Statistical optimization, characterization, and pharmacokinetic assessment. J Adv Res 2016; 7: 691–701.
4. Burki FA, Shah KU, Razaque G, Shah SU, Nawaz A, Saeed MD, Rehman MU, Bibi H, Alfatama M, Elsayed TM. Optimization of Chitosan-Decorated Solid Lipid Nanoparticles for Improved Flurbiprofen Transdermal Delivery. ACS Omega 2023; 8: 19302–10.
5. Baek J-S, Cho C-W. Transdermal delivery of tadalafil using a novel formulation. Drug Deliv 2016; 23: 1571–7.
6. 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 Des Devel Ther 2021; 15: 4603–14.
7. Pandey SS, Patel MA, Desai DT, Patel HP, Gupta AR, Joshi SV, Shah DO, Maulvi FA. Bioavailability enhancement of repaglinide from transdermally applied nanostructured lipid carrier gel: Optimization, in vitro and in vivo studies. J Drug Deliv Sci Technol 2020; 57: 101731.
8. El-Tokhy FS, Abdel-Mottaleb MMA, Abdel Mageed SS, Mahmoud AMA, El-Ghany EA, Geneidi AS. Boosting the In Vivo Transdermal Bioavailability of Asenapine Maleate Using Novel Lavender Oil-Based Lipid Nanocapsules for Management of Schizophrenia. Pharmaceutics 2023; 15: 490.
9. Naguib MJ, Elsayed I, Teaima MH. Simultaneous Optimization of Oral and Transdermal Nanovesicles for Bioavailability Enhancement of Ivabradine Hydrochloride. Int J Nanomedicine 2021; 16: 2917–31.
10. Mo L, Lu G, Ou X, Ouyang D. Formulation and development of novel control release transdermal patches of carvedilol to improve bioavailability for the treatment of heart failure. Saudi J Biol Sci 2022; 29: 266–72.
11. Mazhar D, Haq NU, Zeeshan M, Ain QU, Ali H, Khan S, Khan SA. Preparation, characterization, and pharmacokinetic assessment of metformin HCl loaded transfersomes co-equipped with permeation enhancer to improve drug bioavailability via transdermal route. J Drug Deliv Sci Technol 2023; 84: 104448.
12. Alsaqr A, Rasoully M, Musteata FM. Investigating Transdermal Delivery of Vitamin D3. AAPS PharmSciTech 2015; 16: 963–72.
13. Abdo JM, Sopko NA, Milner SM. The applied anatomy of human skin: A model for regeneration. Wound Med 2020; 28: 100179.
14. Gorzelanny C, Mess C, Schneider SW, Huck V, Brandner JM. Skin Barriers in Dermal Drug Delivery: Which Barriers Have to Be Overcome and How Can We Measure Them? Pharmaceutics 2020; 12: 684.
15. Sica DA, Gehr TWB, Ghosh S. Clinical Pharmacokinetics of Losartan. Clin Pharmacokinet 2005; 44: 797–814.
16. Lio DCS, Liu C, Oo MMS, Wiraja C, Teo MHY, Zheng M, Chew SWT, Wang X, Xu C. Transdermal delivery of small interfering RNAs with topically applied mesoporous silica nanoparticles for facile skin cancer treatment. Nanoscale 2019; 11: 17041–51.
17. Nair RS, Morris A, Billa N, Leong C-O. An Evaluation of Curcumin-Encapsulated Chitosan Nanoparticles for Transdermal Delivery. AAPS PharmSciTech 2019; 20: 69.
18. Jeong WY, Kim S, Lee SY, Lee H, Han DW, Yang SY, Kim KS. Transdermal delivery of Minoxidil using HA-PLGA nanoparticles for the treatment in alopecia. Biomater Res 2019; 23: 16.
19. Zou J-J, Le J-Q, Zhang B-C, Yang M-Y, Jiang J-L, Lin J-F, Wu P-Y, Li C, Chen L, Shao J-W. Accelerating transdermal delivery of insulin by ginsenoside nanoparticles with unique permeability. Int J Pharm 2021; 605: 120784.
20. Xiang H, Xu S, Li J, Pan S, Miao X. Particle Size Effect of Curcumin Nanocrystals on Transdermal and Transfollicular Penetration by Hyaluronic Acid-Dissolving Microneedle Delivery. Pharmaceuticals 2022; 15: 206.
21. Dilawar N, Ur-Rehman T, Shah KU, Fatima H, Alhodaib A. Development and Evaluation of PLGA Nanoparticle-Loaded Organogel for the Transdermal Delivery of Risperidone. Gels 2022; 8: 709.
22. Lan X, She J, Lin D, Xu Y, Li X, Yang W, Lui VWY, Jin L, Xie X, Su Y. Microneedle-Mediated Delivery of Lipid-Coated Cisplatin Nanoparticles for Efficient and Safe Cancer Therapy. ACS Appl Mater Interfaces 2018; 10: 33060–9.
23. Uchida N, Yanagi M, Hamada H. Transdermal Delivery of Anionic Phospholipid Nanoparticles Containing Fullerene. Nat Prod Commun 2022; 17: 1934578X221078444.
24. Uchida N, Yanagi M, shimoda K, Hamada H. Transdermal Delivery of Small-Sized Resveratrol Nanoparticles to Epidermis Using Anionic Phospholipids. Nat Prod Commun 2020; 15: 1934578X20951443.
25. Zhang P, Zhang Y, Liu C-G. Polymeric nanoparticles based on carboxymethyl chitosan in combination with painless microneedle therapy systems for enhancing transdermal insulin delivery. RSC Adv 2020; 10: 24319–29.
26. Talib S, Ahmed N, Khan D, Khan GM, Rehman A ur. Chitosan-chondroitin based artemether loaded nanoparticles for transdermal drug delivery system. J Drug Deliv Sci Technol 2021; 61: 102281.
27. Zhang K, Zhuang Y, Zhang W, Guo Y, Liu X. Functionalized MoS2-nanoparticles for transdermal drug delivery of atenolol. Drug Deliv 2020; 27: 909–16.
28. Zeng L, Tao C, Liu Z, Zhang J, Zhang M, Zhang J, Fang S, Ma X, Song H, Zhou X. Preparation and Evaluation of Cubic Nanoparticles for Improved Transdermal Delivery of Propranolol Hydrochloride. AAPS PharmSciTech 2020; 21: 266.
29. Shahraeini SS, Akbari J, Saeedi M, Morteza-Semnani K, Abootorabi S, Dehghanpoor M, Rostamkalaei SS, Nokhodchi A. Atorvastatin Solid Lipid Nanoparticles as a Promising Approach for Dermal Delivery and an Anti-inflammatory Agent. AAPS PharmSciTech 2020; 21: 263.
30. Zaid Alkilani A, Nimrawi S, Al-Nemrawi NK, Nasereddin J. Microneedle-assisted transdermal delivery of amlodipine besylate loaded nanoparticles. Drug Dev Ind Pharm 2022; 48: 322–32.
31. Gu Y, Yang M, Tang X, Wang T, Yang D, Zhai G, Liu J. Lipid nanoparticles loading triptolide for transdermal

delivery: mechanisms of penetration enhancement and transport properties. J Nanobiotechnology 2018; 16: 68.
32. Ali HS, Namazi N, Elbadawy HM, El-Sayed AA, Ahmed SA, Bafail R, Almikhlafi MA, Alahmadi YM. Repaglinide–Solid Lipid Nanoparticles in Chitosan Patches for Transdermal Application: Box–Behnken Design, Characterization, and In Vivo Evaluation. Int J Nanomedicine 2024; 19: 209–30.
33. Efiana NA, Nugroho AK, Martien R. Formulation of Losartan Nanoparticles with Chitosan as a Carrier. J ILMU KEFARMASIAN Indones 2013; 11: 7–12.
34. Binarjo A, Nugroho A. Improvement of Losartan Transdermal Permeation using Oleic Acid Pretreatment: in Vitro Observation and in Vivo Prediction. Pharm Sci Res 2019 Apr 30; 6. doi: 10.7454/psr.v6i1.4120
35. Binarjo A, Nugroho AK. Studi Penetapan Kadar Losartan dengan Metode Spektrofotometri dan High Performance Liquid Chromatography (HPLC) serta Aplikasinya pada Transpor Transdermal in Vitro. Pharmaciana 2013; 3: 31–48.
36. Martin AN, Bustamante P. Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences. Philadelphia: Lea & Febiger, 1993. .
37. Wilson A, Ekanem EE, Mattia D, Edler KJ, Scott JL. Keratin–Chitosan Microcapsules via Membrane Emulsification and Interfacial Complexation. ACS Sustain Chem Eng 2021; 9: 16617–26.
38. Barbosa AI, Costa Lima SA, Reis S. Development of methotrexate loaded fucoidan/chitosan nanoparticles with anti-inflammatory potential and enhanced skin permeation. Int J Biol Macromol 2019; 124: 1115–22.
39. Khan TA, Azad AK, Fuloria S, Nawaz A, Subramaniyan V, Akhlaq M, Safdar M, Sathasivam KV, Sekar M, Porwal O, Meenakshi DU, Malviya R, Miret MM, Mendiratta A, Fuloria NK. Chitosan-Coated 5-Fluorouracil Incorporated Emulsions as Transdermal Drug Delivery Matrices. Polymers 2021; 13: 3345.
40. Lee E-H, Lim S-J, Lee M-K. Chitosan-coated liposomes to stabilize and enhance transdermal delivery of indocyanine green for photodynamic therapy of melanoma. Carbohydr Polym 2019; 224: 115143.
41. Zhou X, You G, Liu D, Yao K. In Vitro Investigation on The Interactions of Oligo-Chitosan with Keratin. Acta Polym Sin 2009; 009: 781–5.
42. Jafri I, Shoaib MH, Yousuf RI, Ali FR. Effect of permeation enhancers on in vitro release and transdermal delivery of lamotrigine from Eudragit®RS100 polymer matrix-type drug in adhesive patches. Prog Biomater 2019; 8: 91–100.
43. Bednarczyk P, Nowak A, Duchnik W, Kucharski Ł, Ossowicz-Rupniewska P. Enhancing Transdermal Delivery: Investigating the Impact of Permeation Promoters on Ibuprofen Release and Penetration from Medical Patches-In Vitro Research. Int J Mol Sci 2023; 24: 15632.
44. Verma S, Utreja P. Oleic Acid Vesicles as a new Approach for Transdermal Delivery of Econazole Nitrate: Development, Characterization, and In-vivo Evaluation in Wistar rats. Recent Patents Anti-Infect Drug Disc 2020; 16: 30–49.
45. Lei Y, Yang G, Du F, Yi J, Quan L, Liu H, Zhou X, Gong W, Han J, Wang Y, Gao C. Formulation and Evaluation of a Drug-in-Adhesive Patch for Transdermal Delivery of Colchicine. Pharmaceutics 2022; 14: 2245.
46. Lai W-F, Tang R, Wong W-T. Ionically Crosslinked Complex Gels Loaded with Oleic Acid-Containing Vesicles for Transdermal Drug Delivery. Pharmaceutics 2020; 12: 725.
47. Kim KT, Kim JS, Kim M-H, Park J-H, Lee J-Y, Lee W, Min KK, Song MG, Choi C-Y, Kim W-S, Oh HK, Kim D-D. Effect of Enhancers on in vitro and in vivo Skin Permeation and Deposition of S-Methyl-l-Methionine. Biomol Ther 2017; 25: 434–40.
48. Atef E, Altuwaijri N. Using Raman Spectroscopy in Studying the Effect of Propylene Glycol, Oleic Acid, and Their Combination on the Rat Skin. AAPS PharmSciTech 2018; 19: 114–22.
49. Virani A, Puri V, Mohd H, Michniak-Kohn B. Effect of Penetration Enhancers on Transdermal Delivery of Oxcarbazepine, an Antiepileptic Drug Using Microemulsions. Pharmaceutics 2023; 15: 183.
50. Haq A, Michniak-Kohn B. Effects of solvents and penetration enhancers on transdermal delivery of thymoquinone: permeability and skin deposition study. Drug Deliv 2018; 25: 1943–9.
51. Trommer H, Neubert RHH. Overcoming the stratum corneum: the modulation of skin penetration. A review. Skin Pharmacol Physiol 2006; 19: 106–21.
52. Hashmat D, Shoaib MH, Ali FR, Siddiqui F. Lornoxicam controlled release transdermal gel patch: Design, characterization and optimization using co-solvents as penetration enhancers. PloS One 2020; 15: e0228908.
53. Hendriati L, Nugroho AK. The influence of oleic acid-propylene glycol mixture and iontophoresis to propranolol transdermal transport. Indones J Pharm 2009; 20: 217–23.
54. Nagai N, Ogata F, Ishii M, Fukuoka Y, Otake H, Nakazawa Y, Kawasaki N. Involvement of Endocytosis in the Transdermal Penetration Mechanism of Ketoprofen Nanoparticles. Int J Mol Sci 2018; 19: 2138.
55. Wu X, Landfester K, Musyanovych A, Guy RH. Disposition of charged nanoparticles after their topical application to the skin. Skin Pharmacol Physiol 2010; 23: 117–23.