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Enhancing Transdermal Delivery of Ketorolac Tromethamine Using Dimethyl Sulfoxide: A Systematic Study

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Abstract: *Transdermal delivery systems which are directly applied on the skin serve as a substitute for oral drug delivery avoiding first-pass metabolism. The problem of drug penetration through the skin definitely remains one of the biggest issues. This study ascertains the likelihood of DMSO, a penetration enhancer to boost KT, one of the most powerful analgesics. Through DMSO amount variations on KT were prepared and then permeation was studied by means of a Franz Diffusion cell system on rat skin. It increased the permeability coefficient and flux with the increase of the DMSO level, and it reached the maximum when the DMSO concentration was 0. 1. Further understanding of mechanisms and optimal DMSO concentrations seem to be necessary for future development of this promising anticancer treatment approach. Briefly summarizing, DMSO does seem to meet the demands, according to the transdermal drug delivery efficacy standpoint, being safe and convenient for topical application.*

Key Words: Transdermal drug delivery, Dimethyl Sulfoxide, Ketorolac Tromethamine, Franz Diffusion Cell, Permeability

Introduction

Transdermal drug delivery systems pave the way to the approach of drug determination, which provides some benefits including bypassing the first-pass metabolism and lessening of the systemic side effects. Though skin drug delivery has some advantages, still the most critical thing is the drug delivery through the skin not influencing its barrier properties since the stratum corneum limits the permeation. (Ramadon et al., 2021). Intravenous injection of ketorolac tromethamine (KT), a fast pain reliever for post-operative pain, has to overcome its short half-life in the blood and the gastrointestinal side effects if administered orally. (Abdeltawab, 2021). Creating a transdermal rank of delivery for KT might be a way to overcome the shortcomings of conventional drug delivery systems and achieve better therapeutic outcomes. This research project is aimed at evaluating the efficiency of DMSO as the penetration enhancer used in KT when administering and delivering drugs through the skin. DMSO can be converted from the usual permeation barrier of the stratum corneum structure, enhance the skin moisturizing, and optimize the drug's physicochemical properties, resulting in increasing drug permeation. The current study aims to use Franz diffusion cells to investigate the impact of exploring the varied concentrations of the DMSO on the permeation of the KT through the rat skin. Resultantly, the possibility of the DMSO to improve the transdermal delivery of KT can be elucidated. This study will explore the following objectives such as the development of KT formulations consisting of

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different DMSO concentrations, carrying out skin permeation studies using Franz diffusion cells and rat skin as the permeable membrane, investigating the permeation kinetics of KT in the presence of various DMSO concentrations, measure permeation parameters like permeability coefficient and flux, and measure an enhancement ratio of biological(Usman Abid et al., 2023). Consequently, the investigation of these aims would be soon to argue the enhanced delivery of drugs via transdermal drug delivery systems, especially for KT. Establishing how DMSO helps to improve the permeability which is based on the calculated formulation and transdermal delivery is the core step that should be done to navigate the problems that are related to how pharmacologically active substances get through the skin (Akhlaq et al., 2024). The study's findings might have important consequences for pharmaceutical formulations aimed at improving medication delivery efficiency and patient compliance. To summarize, the research into DMSO as a penetration enhancer for KT transdermal administration marks a key milestone in developing transdermal drug delivery technology.(Pandey et al., 2022). This work intends to improve KT penetration by harnessing the unique features of DMSO, paving the path for the creation of more effective and patient-friendly drug delivery systems. (Abid et al., 2024).

Methodology

Chemicals and Reagents

Ketorolac tromethamine was obtained from Nimrall Laboratories, Islamabad, Pakistan, while DMSO was purchased from Sigma Laboratories, Germany. Methanol and normal saline were sourced locally, and rat skin was procured from the Pharmacology Laboratory of the Pharmacy Department at The Islamia University of Bahawalpur, Pakistan.

Instruments and Apparatus

Several instruments were utilized in the study, including an analytical weighing balance (Precisa BJ-210), water bath (HH. S214), refrigerator (Dawlance), UV-VIS spectrophotometer (Lambda 25, Perkin Elmer, USA), water distillation apparatus (Merit, Model W4000/EXP), Franz diffusion cell apparatus (Heidolph), diffusion pump (Heidolph pumpdrive 5001), dissection box, plastic bags, binocular microscope, and adjustable micropipette (Eppendorf).

Software

Data analysis and compilation were performed using Microsoft Word 2013, Microsoft Excel 2013, EndNote X7 version 17.2.1, and ChemDraw Ultra from Cambridge Soft Corporation (2004).

Analysis of Ketorolac Tromethamine

A certificate of analysis for Ketorolac Tromethamine was obtained from Symed Labs Limited (Unit-VI), India, detailing its physical and chemical properties, solubility, melting range, storage conditions, pH, and loss on drying.

Control and Test Solutions Preparation

A control solution comprising 10 mg of Ketorolac Tromethamine dissolved in 5 mL of methanol and made up to 100 mL with normal saline was prepared. Test solutions were prepared by dissolving 1 gram of KT in 5 mL of methanol and diluting to a final volume of 100 mL with normal saline containing varying concentrations (0.1%, 0.2%, 0.4%, and 0.6%) of DMSO.

Preparation of Skin

Healthy female albino rat skin, obtained from rats aged 3-4 months and weighing 150-200 grams, was used. The ventral side of the skin was depilated using a hair removal lotion, cleaned with water and cotton swabs, and carefully removed under anesthesia. Subcutaneous fat was removed, and the skin was cleaned, sealed in plastic bags, and stored at -20°C until use.

Skin Permeation Studies

Skin permeation studies were conducted using three vertical Franz diffusion cells with rat skin mounted on the receptor compartment. After temperature equilibration at 37 1°C for 10 minutes, formulations were applied to the skin surface, and samples were drawn at predetermined time intervals (0.5, 1.5, 2.5, 4.5, and 6 hours) for analysis.

UV Analysis

Samples collected from the receptor compartment were analyzed using a UV-VIS spectrophotometer at 323 nm after auto-zero with normal saline. Absorbance values were recorded and entered into an Excel spreadsheet for comparison with standards.

Calculation of Permeability Coefficient

Permeability parameters, including permeability coefficient (P) and flux (J), were calculated using mathematical equations based on drug concentration and time. Enhancement ratio (ER) was determined by comparing permeability coefficients with and without DMSO.

The cumulative drug concentration was calculated via the following equation:

$$Q_t = V_r C_r + \sum V_s C_i \quad \text{(i)}$$

In the above equation, Ct represents the drug concentration in the receiving compartment at sampling time, and Ci represents the initial drug concentration of the sample. Whereas Vs and Vr represent the volume of the receiving compartment and sample compartment respectively.

The flux constant J was calculated via linear regression interpolation of various drug concentration data given

$$\mathcal{Z} J_{ss} = \frac{\Delta Q_t}{\Delta t.S} \quad \text{(ii)}$$

The permeability coefficient was calculated using the equation given below

$$Kp = \frac{J_{ss}}{C_d} \quad \text{(iii)}$$

In this equation, Cd represents the concentration of the sample drug in the donor compartment.

The enhancement ratio of the Drug sample and Standard solution was calculated using the following equation:

$$ER = \frac{Kp\ with\ enhancer}{Kp\ without\ enhancer} \quad \text{(iv)}$$

Data Analysis and Interpretation

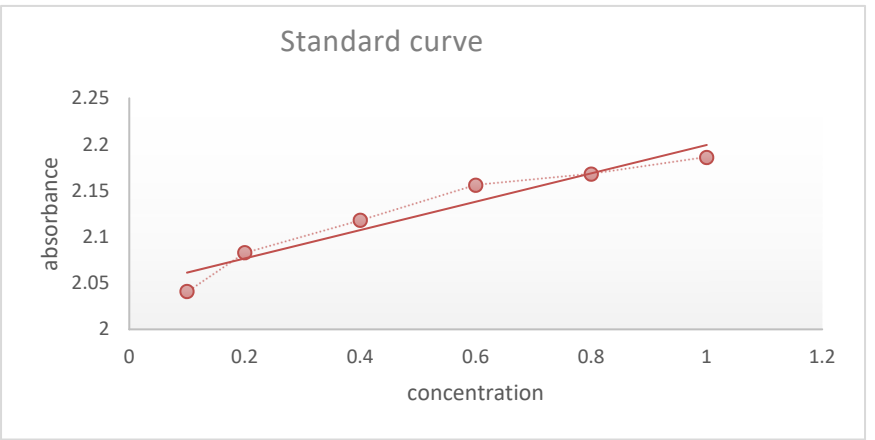
The obtained data were subjected to mathematical analysis to calculate permeation parameters and evaluate the effect of DMSO on KT permeation. Results were interpreted to draw conclusions regarding the efficacy of DMSO as a penetration enhancer for transdermal drug delivery.

Results and Discussion

The permeation data was analyzed using the mathematical method and the parameters like the permeability coefficient (P), the flux (j), and the Enhancer ratio (ER) were obtained by the equations that are already established. This research was done both in a regular control solution and at different concentrations of DMSO solutions. The following table gives the calculated values that are summarized. From the viewpoint of the interpretation, it was pointed out that both the permeability coefficient and flux were rising with the height of DMSO concentration.(Pandey et al., 2022). At a DMSO concentration of 1%, we noticed the highest flux value.

Figure 4.1

Standard curve



Several studies have proved the high connection between the skin permeability coefficient and various physical barriers when supplied as penetrates. The skin models are, thus, effective means for the identification of the skin-permeability of various pharmacological compounds, particularly those with hydrophilic and lipophilic properties. The stratum corneum refers to the skin's outer layer and functions as a perfect diffusion barrier. In our present study, we investigated the diffusion flux and permeability coefficients of different DMSO concentrations utilizing Ketorolac Tromethamine in a diffusion cell with Rat hairless Skin. The results yielded promising outcomes, indicating a significant increase in these parameters with escalating DMSO concentration(Naz, Akhtar, et al., 2024).DMSO exhibited a short lag time (ranging from 15 to 1.5 hours), signifying its potent enhancing effect compared to control solutions lacking DMSO. Previous studies utilizing radio-labeled DMSO solutions have demonstrated rapid penetration, with radioactive indicators appearing within 10 minutes in Rat skin and within 5 minutes in humans. These findings align with our current conclusions. Physiochemically, Ketorolac, being a low molecular weight NSAID existing in a non-ionized form at cutaneous pH, readily traverses the cutaneous barrier, unlike high molecular weight substances such as insulin(Devine, 2023). Past research indicates that a minimum DMSO concentration exceeding 90% is necessary for effective cutaneous absorption, even for non-ionized and low molecular weight drugs like Ketorolac(Naz, Khan, et al., 2024). However, the rationale behind the optimal 90% concentration of DMSO remains unclear. In another skin permeation study involving Guinea Pig Skin, the cutaneous penetration properties of Picrate ions in conjunction with DMSO conform to Fick's law of diffusion. Notably, the diffusion rate constant of DMSO surpasses that of Picrate ions by a factor of 100. In our study, DMSO permeability coefficients peaked at concentrations of 0.4% and 0.6%. Nonetheless, the precise mechanism responsible for DMSO's permeability-enhancing effects warrants further elucidation. In another study, the addition of DMSO to an antimicrobial spray containing oxytetracycline significantly boosted antibacterial activity. The spray, applied at concentrations of 0.25% and 0.5% with oxytetracycline concentrations of 62 ppm, yielded similar results to those obtained at 132 ppm oxytetracycline concentration. This underscores the significant impact of the DMSO solution on altering the therapeutic activity of antibiotics against bacterial pathogens, although the underlying mechanism remains elusive. Numerous studies have reported enhanced cutaneous absorption of drugs when DMSO is added to the drug solution. Another study assessed the transdermal absorption of 17 -Estradiol using Rat Skin, demonstrating a significant increase in uterine weight. Additionally, in a separate study, the percutaneous permeation of Testosterone and hydrocortisone exhibited a 3 to 4-fold rise in both drugs' permeation (Rungseevijitprapa et al., 2021).

Table 1

Penetration kinetics of Ketorolac Tromethamine in Standard and different concentrations of DSMO

Test Solution (%)	Permeation Coefficient (P) (cm.h1) 10 4	Flux (J) (g.cm-2.h-1) 10 3	Enhancement Ratio (E.R)
0.1%	3.06	3.88	2.83
0.2%	5.13	5.02	3.09
0.4%	4.78	13.4	4.46
0.6%	5.89	15.6	2.34

One study reported that the utilization of penetration enhancers facilitates the deep and rapid delivery of drugs into the corneal layer of the skin. This underscores the efficacy of NSAIDs and anti-inflammatory drugs in treating superficial dermatological infections like pyodermas. Moreover, research has indicated that DMSO facilitates the transportation of active drug ingredients into the deeper layers of the dermatome and stratum corneum(Yeh, 2020). This leads to the formation of reservoirs lasting up to 16 days and extends the contact time of active drugs on the skin. Even intact layers of the drug exhibit resistance to washing with soaps, water, and alcohol. Several other studies have highlighted the significant permeation and cutaneous absorption rates achieved with nonionic surfactants such as Tween and Spans. These surfactants play a crucial role in drug molecule permeation across the

stratum corneum due to their structural compatibility with the skin's hydrophilic and lipophilic nature. Two possible mechanisms have been proposed: firstly, by enhancing penetration into deeper dermal layers through solubilization of skin lipid layers, and secondly, by altering the fluidity of skin lipid components. Nonionic surfactants also disrupt keratinocytes by binding to the skin's keratin filaments(Shehata et al., 2021).

In another investigation, acetone and DMF were employed as permeation enhancers. The underlying mechanism for both enhancers involves solvating the polar groups of lipid layers in the stratum corneum of the skin. Recent studies have indicated that fatty acids exhibit significant skin permeation properties due to their lipophilic characteristics. Additionally, permeability-enhancing properties increase significantly when PGs are used as permeability enhancers. Given Ketorolac's hydrophobic nature and low solubility in water, adding DMSO to the drug solution significantly enhances its permeation across the stratum corneum. This is not only due to the higher concentration of DMSO but also because it modifies the lipid bilayer fluidity of the skin, thereby increasing skin permeability. Enhanced drug permeability is also attributed to increased drug retention within skin layers (Yu et al., 2021).

In a study conducted on human skin, the effect of DMSO on the permeation of Scopolamine across human skin was investigated. Results showed that the sorption properties of human skin remained largely unaffected even at high concentrations of DMSO. Conversely, skin permeation properties were observed to double in the presence of DMSO solution. Microscopic analysis of the same skin post-permeation studies revealed distortion, dilatation, and significant swelling of the stratum corneum under the influence of DMSO. The proposed mechanism behind this distortion and swelling is believed to be the osmotic pressure generated by water and DMSO within the stratum corneum as they penetrate the skin. Previous Studies evaluated the effect of DMSO on skin permeation and enhancing effects using various drugs on human skin models. Utilizing bladder perfusion techniques, drugs like heparin, insulin, and topical salicylic acid were solubilized in DMSO solution, resulting in significant improvement in absorption and permeation properties across the human skin model(Otterbach & Lamprecht, 2021). Another study assessed the permeation effect of acyclovir across a model skin using DMSO as a solvent. Acyclovir was formulated into a topical gel, and significant effects of 5% and 10% DMSO on permeation and flux properties were observed. Statistically significant effects ($P<0.05$) were noted regarding the lag time of permeation compared to the standard drug solution(Hussain et al., 2023). The permeability coefficient of acyclovir rose dramatically ($P<0.05$) with different DMSO concentrations. Measurement of retention time for both the control and test medication acyclovir revealed a statistically significant increase in retention time via rat skin application.

Conclusion

The study identifies Dimethyl Sulfoxide (DMSO) as a possible enhancer of Ketorolac Tromethamine (KT) in transdermal medication delivery. The work increases understanding of this subject by systematically measuring its effect on permeation metrics such as the permeability coefficient and flow. These findings provide important insights for improving treatment outcomes using transdermal drug delivery methods.

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