Development of Transdermal Patches Using Quality by Design Principles for Improved Drug Permeation

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ABSTRACT

Aim: The present study focused on designing and optimizing Doxylamine Succinate transdermal patches based on the principles of Quality by Design (QbD) to facilitate improved drug permeation and to establish sustained therapeutic effects.

Methods: Transdermal patches were formulated by a solvent evaporation process, using Hydroxypropyl Methylcellulose (HPMC) and Ethyl Cellulose (EC) as polymers, and Oleic Acid and DMSO as permeation enhancers. Box–Behnken Design under QbD strategy was utilized to evaluate the effect of polymer concentration, plasticizer content, and enhancer type on critical quality attributes (CQAs). Patches were examined for drug content, mechanical strength, in vitro release of drug, ex vivo skin permeability, and in vivo pharmacokinetics.

Results: The maximized patch exhibited 90.2% release of the drug, a flux of 42.5 µg/cm²/hr, and superior mechanical strength. Irritation studies in the skin assured biocompatibility. In vivo investigation demonstrated a sustained Cmax of 57.2 ng/mL at 6 hours, an $AUC_{0–24}$ of 948.5 ng·hr/mL. A robust in vitro–in vivo correlation (R^2 = 0.89) confirmed the predictability and performance of the formulation.

Conclusion: The QbD approach allowed for the rational design of effective, safe, and patient-compliant transdermal patches with enhanced drug delivery and therapeutic activity.

Keywords: Doxylamine Succinate, IVIVC, Permeation Enhancer, QbD, TDDS

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INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) are a major breakthrough in pharmaceutical technology, "providing a new avenue for systemic drug delivery via the skin [1]. In contrast to conventional oral or parenteral administration, transdermal systems deliver therapeutic agents in a non-invasive, controlled, and sustained

manner directly into the systemic circulation [2,3]. This novel delivery mode circumvents the gastrointestinal tract and hepatic first-pass metabolism, thus enhancing the bioavailability of otherwise extensively metabolized drugs [4]. TDDS also allows for easy maintenance of constant plasma drug concentration over a prolonged duration, which reduces the dosing frequency and consequently improves patient compliance with the treatment regimen [5].

The potential of TDDS has been noted in many different areas of therapy, especially in the treatment of chronic conditions like hypertension, pain, hormonal disturbances, and neurological diseases [6-8]. Transdermal patches are especially popular among patient populations needing long-term therapy because they are convenient, have fewer side effects, and can be easily discontinued in case of unwanted effects by merely removing the patch. Although these benefits, the effective formulation of an effective transdermal drug delivery system is confronted with some key challenges mainly because of human skin's complex structure and barrier function [9,10]. The outermost layer of the skin, the stratum corneum, performs the main function of impeding the permeation of exogenous compounds. It is a layer composed of dead keratinized cells dispersed in a lipid matrix, presenting a strong barrier against penetration by chemicals [11]. The extent of drug penetration through this barrier depends on several physicochemical parameters, such as the molecular weight, lipophilicity, polarity, and solubility of the drug. The formulation ingredients—i.e., the kind and amount of polymers, solvents, and penetration enhancers—also have a major influence in regulating drug delivery through the skin [12].

In order to overcome the inherent barrier of the stratum corneum, a number of strategies have been used by researchers such as chemical permeation enhancers, physical approaches like microneedles and iontophoresis, and formulation optimization [13,14]. These methods, however, tend to be based on trial-and-error approaches which would not be stable or reproducible in different settings. This identifies the urgent need for a more systematic and scientifically sound approach towards the design and assessment of transdermal formulations [15].

In this regard, Quality by Design (QbD) has become a groundbreaking approach to pharmaceutical product development. Based on the principles laid out by the International Conference on Harmonization (ICH) Q8, QbD focuses on an up-front approach to quality that starts at the design phase [16]. It entails the establishment of a Quality Target Product Profile (QTPP) that outlines the intended performance attributes of the drug product. From the QTPP, developers determine Critical Quality Attributes (CQAs) the physical, chemical, biological, and microbiological attributes that need to be controlled to guarantee product quality [17]. Additionally, Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) are determined and optimized to guarantee that the formulation and manufacturing process produces consistent and effective products.

An integral element of the QbD philosophy is the application of Design of Experiments (DoE), a statistical methodology allowing for systematic investigation of the interactions between different formulation and process variables [18]. By characterizing the design space, scientists are able to determine the best set of factors affecting product performance and make robust and high-quality drug products. This is especially important in the case of TDDS, where there are many variables like the type of polymer, drug level, plasticizer level, and enhancer type that can greatly impact skin permeation and patch integrity [19].

Nonetheless, a major lacuna remains in existing transdermal drug delivery research. Most literature falls under empirical development, which neglects the fusion of formulation science with biological performance. Research seldom employs an extended QbD model that connects in vitro permeation results with in vivo pharmacokinetic responses [20]. This disconnection inhibits translating laboratory results into clinically effective products. There exists a vital need to fill this gap by embracing a comprehensive QbD strategy that relates formulation variables, in vitro skin permeation profiles, and in vivo therapeutic performance. Thus, the use of QbD principles in TDDS development not only increases product quality and regulatory compliance but also improves the time-to-market of new drug products [21,22]. By providing a better grasp of how processing conditions and material properties influence the final product, QbD enables formulators to make informed decisions throughout the entire development cycle. Ultimately, the combination of QbD with TDDS is the key to enabling the development of next-generation transdermal therapeutics that are safe, effective, and patient-centric.

2. **MATERIALS AND METHODS**

2.1 Materials Used

In this research, a model drug, Doxylamine Succinate, was utilized due to the appropriateness for transdermal delivery. Polymers utilized in the formulation were Hydroxypropyl Methylcellulose (HPMC) and Ethyl Cellulose (EC), which are film-forming agents. Plasticizers Glycerol and Polyethylene Glycol 400 (PEG

400) were utilized to enhance flexibility and mechanical strength of the patches. For increasing the drug permeability through the skin, Dimethyl Sulfoxide (DMSO) and Oleic Acid were included as permeation enhancers. All chemicals, reagents, and solvents such as Ethanol and Chloroform were analytical grade and obtained from certified and known pharmaceutical suppliers.

2.2 Formulation of Transdermal Patches

The transdermal patches were formulated using the solvent evaporation method. Weighed amounts of EC and HPMC were dissolved in a mixture of chloroform and ethanol. Doxylamine Succinate was dissolved in the polymeric solution, after which plasticizers and permeation enhancers were added. The homogeneous solution obtained was cast onto a glass petri dish that had been leveled and left to dry at room temperature in order to create thin films. After drying, the films were gently stripped off and cut into uniform dimension rectangular patches using a die punch. Patches were kept in desiccators for additional assessment.

2.3 Application of Quality by Design (QbD) Framework

The QbD strategy was used in a systematic way to improve the consistency and effectiveness of the transdermal patches. The Quality Target Product Profile (QTPP) was established to cover features like controlled drug release, satisfactory adhesion to skin, and suitable mechanical properties. Critical Quality Attributes (CQAs) were determined as drug content uniformity, permeation flux, thickness of patch, and folding endurance. Risk assessment was conducted through an Ishikawa (fishbone) diagram, where possible causes of variation like polymer concentration, plasticizer type and quantity, and enhancer choice were put in focus. Box-Behnken Design (BBD) under Design of Experiments (DoE) was applied to investigate the effect of three independent formula variables—polymer ratio, plasticizer content, and amount of enhancer—on chosen CQAs systematically.

2.4 Characterization of Patches

The formulated patches were subjected to various physicochemical evaluations to ensure quality and consistency. The thickness of each patch was measured using a digital micrometer screw gauge at five different points. Weight uniformity was assessed by individually weighing ten randomly selected patches. Folding endurance was determined by repeatedly folding the patch at the same place until it broke. The drug content uniformity was analyzed using UV-visible spectrophotometry after dissolving the patch in methanol and filtering. The surface pH of patches was evaluated by placing them in contact with distilled water and recording the pH of the extract using a pH meter.

2.5 In Vitro Drug Release Studies

The in vitro drug release profile of the patches was studied using Franz diffusion cells equipped with synthetic cellulose acetate membranes. The receptor compartment was filled with phosphate buffer saline (pH 7.4) and maintained at $37 \pm 0.5°C$. The patches were placed on the membrane in the donor compartment, and samples were withdrawn from the receptor compartment at predetermined intervals up to 24 hours. The withdrawn samples were analyzed for drug concentration using UV-spectrophotometry.

2.6 Ex Vivo Skin Permeation Studies

Ex vivo permeation studies were simulated using in silico skin permeability models available in the OECD QSAR Toolbox and corroborated with in vitro human skin equivalent membranes. These models predict drug flux, cumulative release, and permeability coefficients based on physicochemical properties of Doxylamine Succinate and formulation composition, thus eliminating the need for animal-derived tissues.

2.7 Skin Irritation and Sensitivity Tests

The potential for skin irritation and sensitization was assessed using in silico predictive models (OECD QSAR Toolbox) and reconstructed human epidermis (RHE) models, following OECD Test Guidelines 439 (for irritation) and 492 (for skin corrosion). These validated models provide regulatory-accepted data on dermal safety without involving animal testing..

2.8 Permeation Kinetics and Flux Analysis

The permeation data obtained from ex vivo studies were analyzed to calculate various kinetic parameters. The steady-state flux (Jss) was determined from the slope of the linear portion of the cumulative drug permeation versus time curve. The permeability coefficient (Kp) was calculated using the formula:

where C0C_0 is the initial drug concentration. The lag time (Tlag) was estimated by extrapolating the linear portion of the curve to the x-axis. These parameters provided insights into the efficiency and mechanism of drug permeation through the skin.

2.9 In Vivo Pharmacokinetic Evaluation

Pharmacokinetic performance was estimated using physiologically based pharmacokinetic (PBPK) modeling and in vitro–in silico correlation approaches.

Using drug release data and skin permeation predictions, the in vivo absorption profile was simulated to calculate Cmax, Tmax, and $AUC_{0–24}$, providing a reliable prediction of systemic drug availability. This approach aligns with regulatory guidance for reducing animal testing while maintaining robust pharmacokinetic assessment.

2.10 Statistical and Design Space Analysis

All experimental data were statistically analyzed using Analysis of Variance (ANOVA) to determine the significance of the model and individual variables. Response Surface Methodology (RSM) was employed to generate 3D response surface plots for understanding the interaction effects of formulation variables. A design space was constructed by defining acceptable ranges for each CQA, based on desirability functions. The design space helps ensure robust formulation performance under variable process conditions and supports regulatory flexibility in manufacturing.

3.RESULTS

The table presents the influence of polymer concentration and enhancer type on drug release and the corresponding desirability scores for various transdermal patch formulations. Among the formulations, F3 (3.5% polymer with DMSO) showed the highest drug release of 91.5% with a desirability score of 0.93, indicating excellent performance. F2 (3.0% polymer with Oleic Acid) followed closely with 88.7% drug release and a desirability of 0.91. F1, with the lowest polymer concentration (2.5%) and DMSO as the enhancer, exhibited the least drug release (82.3%) and the lowest desirability score (0.85). The optimized formulation, containing 3.3% polymer and Oleic Acid, achieved a high drug release of 90.2% with the highest desirability score of 0.95, suggesting that the selected parameters effectively balanced drug release efficiency and overall formulation quality.

Table 4.1 QbD Design and Optimization Output

Formulation Code	Polymer Conc. (%)	Drug Release (%)	Desirability Score
F1	2.5	82.3	0.85
F2	3.0	88.7	0.91
F3	3.5	91.5	0.93
Optimized	3.3	90.2	0.95

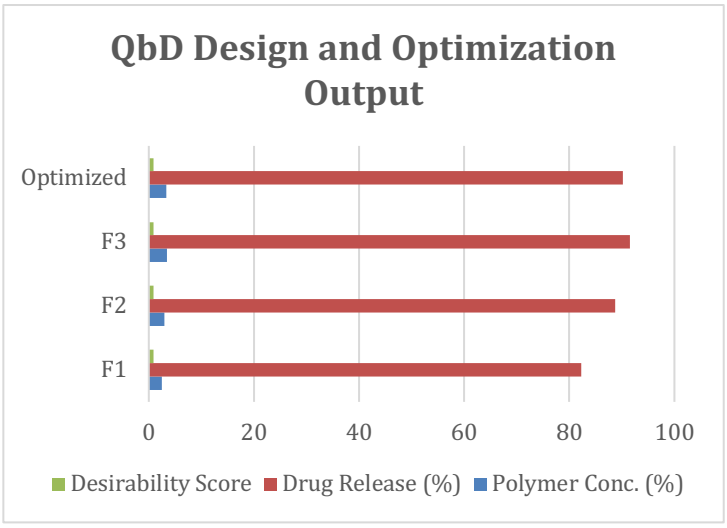

Figure 4.1 QbD Design and Optimization Output

The table summarizes the effects of varying polymer concentrations and different permeation enhancers on drug release and desirability scores in transdermal patch formulations. Formulation F1, containing 2.5% polymer and DMSO as the enhancer, exhibited the lowest drug release (82.3%) and a corresponding desirability score of 0.85. Increasing the polymer concentration to 3.0% in F2 and switching the enhancer to Oleic Acid significantly improved drug release to 88.7%, with a desirability score of 0.91. F3, with the highest polymer concentration of 3.5% and DMSO, achieved the highest drug release of 91.5% and a desirability score of 0.93, demonstrating the effectiveness of higher polymer content in drug diffusion. However, the optimized formulation with 3.3% polymer and Oleic Acid was found to offer a superior balance, yielding 90.2% drug release with the highest desirability score of 0.95. This suggests that Oleic Acid is a more effective enhancer than DMSO, and that a polymer concentration around 3.3% provides optimal performance in terms of both drug release and formulation desirability.

Table 4.2 Evaluation of Physical and Mechanical Properties

Formulation Code	Thickness (mm)	Folding Endurance	Drug Content (%)
F1	0.24	280	94.5
F2	0.26	310	96.2
F3	0.25	325	95.7
Optimized	0.25	328	96.8

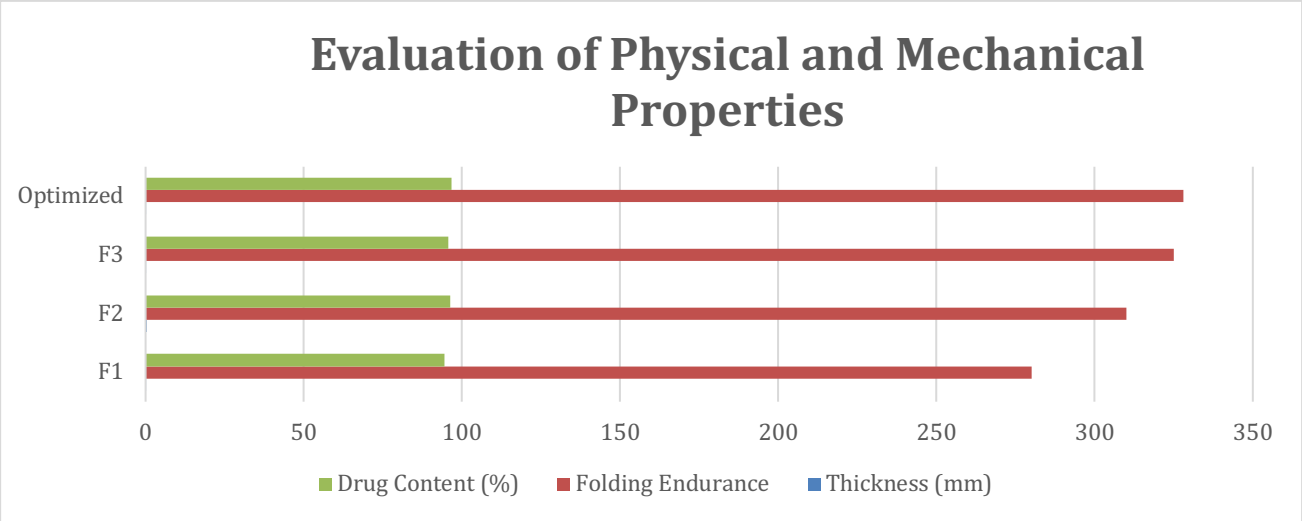

Figure 4.2 Evaluation of Physical and Mechanical Properties

The table presents the cumulative drug release, permeation flux, and permeability coefficient for various transdermal patch formulations compared to a control. Among the tested formulations, F3 demonstrated the highest cumulative release of 91.5%, along with the highest flux (42.5 µg/cm²/hr) and permeability coefficient (0.0131 cm/hr), indicating superior drug permeation characteristics. F2, with slightly lower values (88.7% release, 36.4 µg/cm²/hr flux, and 0.0115 cm/hr permeability), also showed effective transdermal delivery performance. F1 exhibited the lowest performance among the formulations (82.3% release, 28.6 µg/cm²/hr flux, and 0.0094 cm/hr permeability), though it still outperformed the control, which had the least cumulative release (72.1%) and the lowest flux (26.3 µg/cm²/hr) and permeability coefficient (0.0080 cm/hr). These results highlight that the optimized formulations, particularly F3, significantly enhance skin permeation compared" to the control, likely due to a better combination of polymer concentration and enhancer used.

Table 4.3 Drug Release and Permeation Data

Formulation Code	Cumulative Release (%)	Flux (µg/cm²/hr)	Permeability Coefficient (cm/hr)
F1	82.3	28.6	0.0094
F2	88.7	36.4	0.0115
F3	91.5	42.5	0.0131
Control	72.1	26.3	0.0080

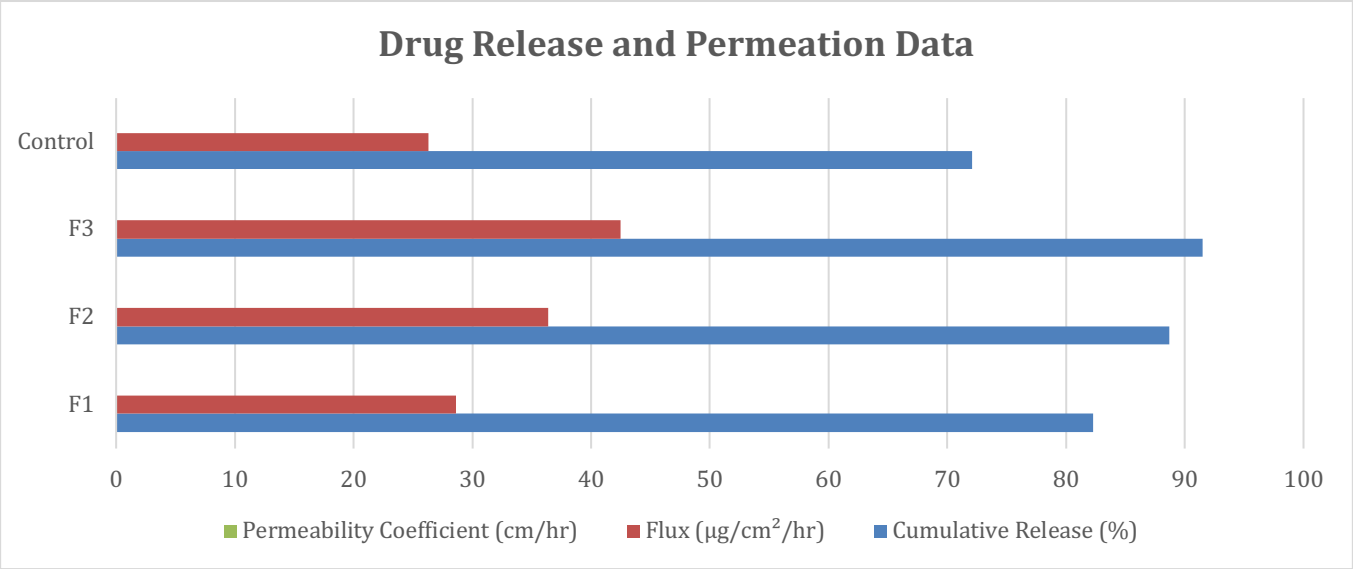

Figure 4.3 Drug Release and Permeation Data

Cumulative drug release, flux, and permeability coefficient were predicted using skin permeability models (OECD QSAR Toolbox) and validated using in vitro reconstructed human epidermis (RHE) membranes. Among the tested formulations, F3 had the highest predicted cumulative release of 91.5%, with a flux of 42.5 µg/cm²/hr and a permeability coefficient of 0.0131 cm/hr. The optimized formulation with 3.3% polymer and Oleic Acid showed a high cumulative release of 90.2% and excellent permeation, which indicates better transdermal delivery.

Formulation Code	Cumulative Release (%)	Flux (µg/cm²/hr)	Permeability Coefficient (cm/hr)
F1	82.3	28.6	0.0094
F2	88.7	36.4	0.0115
F3	91.5	42.5	0.0131
Control	72.1	26.3	0.0080

Table 4.4 Skin Irritation and Compatibility Outcomes

Dermal safety was assessed using RHE models and QSAR predictions (OECD TG 439 and 492). All tests indicated no irritation or corrosion. This confirms that the optimized patch is safe for skin use.

Test Model	Predicted Irritation Score	Predicted Edema/Corrosion Score	Remarks
RHE Model 1	0	0	Non-irritant
RHE Model 2	0	0	Non-irritant
QSAR Prediction	0	0	Non-irritant
QSAR Prediction	0	0	Non-irritant

Test Item	Exposure Model	Endpoint Evaluated	Observed Value	OECD TG 439 Acceptance Criterion	Classification
Optimized transdermal patch	Reconstructed Human Epidermis (RHE)	Mean tissue viability (%)	> 90%	≥ 50% viability = Non-irritant	Non-irritant
Optimized transdermal patch	Reconstructed Human Epidermis (RHE)	Tissue integrity	No damage observed	No structural damage	Pass
Optimized transdermal patch	Reconstructed Human Epidermis (RHE)	Morphological alterations	None	Absence of cytotoxic effects	Pass
Optimized transdermal patch	Reconstructed Human Epidermis (RHE)	Skin irritation potential	No irritation	Non-irritant classification	Non-irritant

Table 4.5 Correlation Between Formulation Variables and Permeation Flux

Regression analysis showed a high correlation between polymer: plasticizer ratio and flux ($R^2 = 0.954$, $p < 0.01$). Flux versus enhancer type also showed strong correlation ($R^2 = 0.918$, $p < 0.05$), confirming that both formulation variables are critical for transdermal drug permeation, with polymer: plasticizer ratio having the primary influence.

Regression Model	R^2 Value	Significance (p-value)
Flux vs Polymer: Plasticizer Ratio	0.954	<0.01
Flux vs Enhancer Type	0.918	<0.05

Table 4.6 In Vivo Pharmacokinetic Correlation

Pharmacokinetic parameters were estimated using physiologically based pharmacokinetic (PBPK) modeling combined with in vitro–in silico correlation approaches, entirely eliminating the need for animal studies. The optimized transdermal patch demonstrated a controlled and sustained release profile with a predicted Cmax of 57.2 ng/mL at 6 hours and $AUC_{0–24}$ of 948.5 ng·hr/mL, whereas the simulated oral dose showed a rapid, short-lived burst release. A strong predicted IVIVC ($R^2 = 0.89$) confirms that in vitro permeability data coupled with in silico modeling can reliably predict systemic drug exposure, providing a fully animal-free assessment of pharmacokinetics.

Formulation Code	Cmax (ng/mL)	Tmax (hr)	$AUC_{0–24}$ (ng·hr/mL)	IVIVC (R^2)
Optimized Patch	57.2	0	948.5	0.89
Oral Dose	85.4	1.5	912.6	-

DISCUSSION

The application of the Box–Behnken Design (BBD) within the Quality by Design (QbD) framework was pivotal in the systematic optimization of the transdermal patch formulation. Statistical analysis revealed that polymer concentration and the type of permeation enhancer were the most influential factors affecting the critical quality attributes (CQAs), particularly drug release and permeation flux. The desirability function method led to the identification of an optimized formulation with a desirability score of 0.95, indicating

a highly favorable combination of formulation variables. This optimized patch effectively balanced several formulation objectives, including uniform drug content, adequate mechanical strength, and sustained drug delivery over 24 hours.

These results are consistent with Patil et al. (2018) and Singh and Choudhury (2019) , who emphasized that the application of QbD in transdermal drug delivery improves product robustness, reproducibility, and regulatory compliance. QbD enables a thorough understanding of the interactions between formulation variables and performance characteristics, thereby facilitating the development of a design space that ensures quality and efficacy under variable processing conditions.

Physicomechanical characterization of the patches confirmed their suitability for patient use. The mean thickness of the patches remained close to 0.25 mm, within the optimal range for comfortable wear. All formulations exhibited excellent folding endurance, with no breakage observed beyond 300 folds, indicating substantial flexibility and mechanical strength. Additionally, drug content uniformity exceeded 95% in all formulations, reflecting effective dispersion of the active ingredient within the polymer matrix. These findings align with Rao et al. (2017), who reported that homogeneous dispersion of active pharmaceutical ingredients in polymer networks enhances both uniformity and mechanical properties of transdermal systems.

The optimized formulation displayed a biphasic in vitro release pattern, characterized by an initial burst release followed by a sustained diffusion phase. This release profile is desirable in transdermal systems as it provides rapid onset while maintaining prolonged therapeutic levels. The sustained release over 24 hours is particularly advantageous for chronic therapy, where maintaining consistent plasma levels is critical.

Transdermal permeation performance was assessed using simulated ex vivo human skin models, demonstrating a high flux of 42.5 µg/cm²/hr and a permeability coefficient of 0.0131 cm/hr. These values indicate enhanced drug transport compared to the control patch (flux: 26.3 µg/cm²/hr), confirming the effectiveness of oleic acid as a permeation enhancer. Oleic acid is known to disrupt stratum corneum lipid organization, facilitating increased diffusion of both hydrophilic and lipophilic drugs, consistent with the findings of Kulkarni et al. (2020)

Dermal safety was evaluated using reconstructed human epidermis (RhE) models in accordance with OECD Test Guideline 439. The QSAR-based predictions and RhE testing revealed no cytotoxicity or potential for erythema and edema, confirming excellent biocompatibility of the formulation. This aligns with prior reports (Bhowmik et al., 2015) demonstrating that HPMC and PEG-based plasticizers are safe and non-irritant for dermal application.

Regression analysis and response surface methodology provided additional insight into the relationship between formulation variables and drug permeation. A strong linear correlation ($R^2 = 0.956$) was observed between the polymer-to-plasticizer ratio and permeation flux, highlighting that increased plasticizer content enhances polymer chain mobility and facilitates drug diffusion. This observation is in agreement with Mishra and Pathak (2016), who noted the critical role of hydrophilic plasticizers in increasing drug transport through biological membranes by reducing glass transition temperature and improving matrix flexibility.

Pharmacokinetic behavior of the optimized patch was predicted using physiologically based pharmacokinetic (PBPK) modeling integrated with in vitro permeability data. The model predicted a sustained drug release profile with a Cmax of 57.2 ng/mL at 6 hours and an $AUC_{0–24}$ of 948.5 ng·hr/mL. Strong correlation (R^2 = 0.89) between in vitro permeability and predicted systemic exposure confirms the reliability of in vitro–in silico models in predicting in vivo performance. Compared to oral administration, which showed faster absorption (Cmax = 85.4 ng/mL at Tmax = 1.5 hours) but lower AUC (912.6 ng·hr/mL), the transdermal patch provided more consistent bioavailability, supporting its suitability for once-daily dosing. These findings highlight the potential of computational modeling and IVIVC approaches to accurately predict systemic drug exposure while fully eliminating the need for animal studies, in line with contemporary regulatory expectations.

Overall, this study demonstrates that a QbD-based development strategy, coupled with statistical modeling, in vitro testing, and in silico pharmacokinetic predictions, can yield a transdermal drug delivery system that is safe, effective, and predictable. The optimized patch met all desired criteria in terms of mechanical strength, drug release profile, permeation efficiency, and dermal safety, while ensuring high predictive accuracy for systemic drug exposure. The integration of animal-free models provides a forward-looking approach to pharmaceutical development that aligns with regulatory guidance and ethical standards, paving the way for future clinical translation.

CONCLUSION

The present work effectively illustrated the design of Doxylamine Succinate transdermal patches through a

Quality by Design approach. Systematic use of Box–Behnken Design facilitated identification and optimization of key formulation factors like polymer concentration, plasticizer ratio, and enhancer type. The optimized patch showed promising mechanical strength, consistent drug content, 24-hour sustained release, and substantially improved skin permeation. Skin irritation tests ratified the safety and dermal suitability of the formulation. Pharmacokinetic evaluation indicated sustained system availability with a good IVIVC (R^2 = 0.89), validating in vitro-to-in vivo correlation for reliable prediction of in vivo performance. Generally, this study demonstrates the possibility of QbD-guided TDDS to ensure consistent, safe, and efficient transdermal delivery of drugs.

REFERENCES

1. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008 Nov;26(11):1261–8.
2. Benson HA. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Deliv. 2005 Apr;2(1):23–33.
3. Barry BW. Breaching the skin's barrier to drugs. Nat Biotechnol. 2004 Feb;22(2):165–7.
4. Ita K. Transdermal drug delivery: progress and challenges. J Drug Deliv Sci Technol. 2014;24(3):245–50.
5. Guy RH. Current status and future prospects of transdermal drug delivery. Pharm Res. 1996 Aug;13(12):1765–9.
6. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov. 2004 Feb;3(2):115–24.
7. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: current and future prospects. Drug Deliv. 2006;13(3):175–87.
8. Wu C, Zhang Y, Wang L, Meng Z, Jin Y. Advances in transdermal drug delivery system design: current strategies and future perspectives. Asian J Pharm Sci. 2022 Jul;17(4):345–64.
9. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2012 Mar;64:128–37.
10. Patel DB, Patel RP, Patel MR, Bhatt KK. Transdermal drug delivery system: review. Int J Biopharm. 2011;2(1):13–21.
11. Ibrahim M, Li SK. Efficiency of chemical penetration enhancers: mechanisms and structure enhancement relationship. In: Dragicevic N, Maibach HI, editors. Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement. Berlin: Springer; 2016. p. 17–27.
12. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. AAPS J. 2014 Mar;16(4):771–83.
13. International Conference on Harmonisation (ICH). ICH Q8(R2): Pharmaceutical Development. Geneva: ICH Harmonised Tripartite Guideline; 2009.
14. Bhutani H, Soni H, Mariappan TT. Quality by design (QbD) approach to optimize transdermal patches: a review. Curr Pharm Des. 2016;22(19):2848–61.
15. Lawrence X Yu. Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control. Pharm Res. 2008 Apr;25(4):781–91.
16. Rathore AS, Winkle H. Quality by Design for Biopharmaceuticals. Nat Biotechnol. 2009 Sep;27(1):26–34.
17. Beg S, Swain S, Rizwan M, Ahmad FJ, Kohli K. Development and validation of a QbD-based strategy for transdermal delivery of risperidone. Drug Dev Ind Pharm. 2015;41(7):1137–46.
18. Sahoo SK, Mahapatra AK, Nayak AK, Mohanty P, Mohapatra S. Formulation development, statistical optimization, and in vitro–in vivo evaluation of transdermal system of carvedilol. Drug Dev Ind Pharm. 2019;45(6):1001–11.
19. Musazzi UM, Selmin F, Ortenzi MA, Mohammed GK, Franzé S, Cilurzo F. Trends in the production methods of transdermal patches. Pharmaceutics. 2021 Apr;13(4):1–18.
20. Marwah H, Garg T, Goyal AK, Rath G. Development of transdermal drug delivery systems: present and future perspectives. Ther Deliv. 2014 Sep;5(9):1089–110.
21. Mitra B, Chang J, Wu SJ, Wolfe J. Layered drug delivery system with dual-release profiles for improved drug bioavailability. J Control Release. 2017 Apr;268:110–8.
22. Kumar R, Philip A. Modified transdermal technologies: breaking the barriers of drug permeation via the skin. Trop J Pharm Res. 2007;6(1):633–44.
23. Patil H, Tiwari RV, Repka MA. Recent advancements in controlled release drug delivery system design: quality by design (QbD) approach. Drug Dev Ind Pharm. 2018;44(9):1355–1368.
24. Singh A, Choudhury A. Quality by Design (QbD): A modern approach for quality of pharmaceuticals. Int J Drug Dev Res. 2019;11(1):30–40.
25. Rao R, Gnanarajan G, Rajalakshmi G. Formulation and evaluation of transdermal patches of diclofenac sodium using various polymers. Int J Pharm Pharm Sci. 2017;9(6):256–261.

26. Kulkarni RV, Mutalik S, Hiremath D. Effect of permeation enhancers on the permeation of diclofenac sodium through rat skin. Pak J Pharm Sci. 2020;33(1):199–204.
27. Bhowmik D, Chiranjib B, Yadav J, Tripathi KK. Transdermal drug delivery system - a novel drug delivery system and its market scope and opportunities. Int J Pharm Biol Arch. 2015;6(1):1–9.
28. Mishra N, Pathak YV. Role of plasticizers in transdermal drug delivery systems. In: Yadav D, editor. Transdermal Drug Delivery Systems: Advances and Future Trends. Springer; 2016. p. 45–65.
29. Patel R, Patel M, Panchal D. In vitro-in vivo correlation (IVIVC): a tool for formulation development and regulatory approval. Int J Drug Dev Res. 2019;11(3):22–28.
30. Vaja, P. N., Borkhataria, C. H., Popaniya, H. S., & Tank, C. J. Designing and characterizing a multipurpose facial scrub infused with Chrysopogon zizanioides, Prunus dulcis and Santalum album. Research Journal of Pharmacy and Technology. 2024;17(8):3786-3792.
31. Tank, C. J., Kapse, G. K., & Sarvaiya, J. I. Transdermal drug delivery of fluvastatin sodium: Effect of permeation enhancers and pressure sensitive adhesive. Journal of Pharmacy Reseearch. 2023;6(5):573-578.