Kathmandu University
Journal of Science, Engineering and Technology

Formulation and evaluation of clonidine hydrochloride transdermal patch

Barsha Sitaula, Achyut Bikram Thapa, and Uttam Budhathoki*

Department of Pharmacy Kathmandu University, Dhulikhel, Kavre, P.O. Box: 6250, Kathmandu, Nepal.

Abstract

Clonidine, an antihypertensive agent, undergoes extensive first-pass metabolism via the oral route. Transdermal delivery overcomes this limitation, providing steady plasma levels, improved patient compliance, and reduced side effects. Its favorable physicochemical properties, including low molecular weight (230.09 g/mol), moderate lipophilicity (Log P ≈ 2), and low daily dose requirement, facilitate permeation through the stratum corneum, with a reported transdermal flux of 0.0710 $\mu g/mm^2/hr$. The objective of this study was to formulate and evaluate a sustained-release transdermal patch of clonidine hydrochloride using the solvent casting method. Formulation development was carried out in three stages guided by Central Composite Design. 13 dummy patches with varying HPMC and PEG 4000 concentrations optimized folding endurance, followed by 8 API-containing patches with different enhancer combinations (DMSO, Tween 80, SLS, BZC) to identify the best formulation. The optimized formulation exhibited uniform weight (0.4887 ± 0.0086 g), consistent thickness (0.52 ± 0.04 mm), adequate moisture content (13.94 ± 0.77%), high folding endurance (403.6 ± 10.7), and a smooth, transparent surface. Drug assay and content uniformity were within acceptable limits (100.94% and 92.39 ± 2.78%, respectively). In vitro permeation studies across goat skin revealed higher flux (0.105 $\mu g/mm^2/hr$) and cumulative drug permeation (2.391%) compared to the control (0.036 $\mu g/mm^2/hr$, 0.761%). The release followed zero-order kinetics ($R^2 = 0.8187$), confirming controlled and sustained drug delivery from the optimized patch. The optimized transdermal patch shows superior drug release and permeation compared to the control.

Keywords: Transdermal drug delivery system; Clonidine hydrochloride; Optimization; Drug permeation; Franz cell diffusion cell.

1. Introduction

Transdermal Drug Delivery Systems (TDDS) provide a sustained mode of drug administration with several advantages such as bypassing first-pass metabolism, maintaining steady-state plasma levels, reducing gastrointestinal side effects, lowering dosing frequency, and improving patient compliance [1]. TDDS are designed for application to intact, healthy skin with adequate blood flow, allowing the drug to diffuse across the skin from a region of high to low concentration and maintain constant plasma levels over an extended period [2]. Despite these advantages, the primary challenge of TDDS lies in overcoming the skin barrier [3].

Clonidine, an antiadrenergic agent used for the management of hypertension, acts by decreasing heart rate and dilating blood vessels to enhance blood flow. Approved by the U.S. Food and Drug Administration (FDA) for transdermal use since 1984, clonidine offers benefits over oral therapy, such as reduced adverse effects like dry mouth and drowsiness. Transdermal clonidine has diverse therapeutic applications, including the management of depression, mood disorders, smoking cessation, menopausal hot flashes, and alcohol withdrawal syndromes. Although limitations such as dermatitis and higher cost exist, its ability to maintain constant plasma levels and improve compliance makes clonidine an ideal candidate for transdermal delivery [4].

Effective drug delivery through the transdermal route is dependent on the physicochemical properties of the drug and its ability to traverse the stratum corneum. Only a limited number of drugs can penetrate this barrier; hence, properties such as molecular weight, lipophilicity (log P), concentration, and solubility play critical roles in determining permeability [5].

The stratum corneum, approximately 10 μm thick, acts as the major barrier to drug absorption. Drug permeation across the skin occurs through intercellular, transcellular, and transappendageal routes, which involve traversal through both hydrophilic and lipophilic domains. Therefore, the use of chemical penetration enhancers (CPEs) in optimized concentrations is crucial to improve permeation [6].

CPEs such as dimethyl sulfoxide (DMSO), sodium lauryl sulfate (SLS), benzalkonium chloride (BC), and Tween 80 are commonly used to enhance skin permeability. An ideal enhancer should be inert, non-toxic, chemically stable, non-irritating, and compatible with formulation components; however, no single enhancer possesses all these qualities. DMSO, an aprotic solvent, modifies the stratum corneum by converting α-keratin into β-sheet structures and altering lipid composition. Tween 80, a nonionic surfactant, increases lipid fluidity by solubilizing intercellular lipids. SLS, an anionic surfactant, interacts with keratin and lipids to enhance permeability, while BC, a cationic surfactant, interacts with negatively charged sites in the stratum corneum to improve drug diffusion [7].

A typical TDDS formulation consists of a polymer matrix, drug, permeation enhancer, adhesive, backing membrane, and release liner. Polymers control drug release and may be natural (gelatin, cellulose derivatives, natural rubber) or synthetic (polyvinyl alcohol, polyethylene, polypropylene). Adhesives ensure proper contact with the skin without irritation or residue, while backing membranes such as polyester film or ethylene-vinyl alcohol copolymer (EVA) provide flexibility and protect the patch [8]. Drug candi-

*Corresponding author. Email: uttam@ku.edu.np

Table 1: Experimental design using CCD.

Std Order	Run Order	PtType	Blocks	HPMC (g)
6	1	-1	1	2.207107
3	2	1	1	1
10	3	0	1	1.5
11	4	0	1	1.5
2	5	1	1	2
7	6	-1	1	1.5
13	7	0	1	1.5
1	8	1	1	1
8	9	-1	1	1.5
4	10	1	1	2
5	11	-1	1	0.792893
12	12	0	1	1.5
9	13	0	1	1.5

dates suitable for transdermal systems usually have a molecular weight below 1000 Da, low melting point, amphiphilic nature, high potency, and low dose requirements [8].

Transdermal systems can be classified into single-layer drug-in-adhesive, multi-layer drug-in-adhesive, drug reservoir-in-adhesive, and drug matrix-in-adhesive types. Each type differs in structure, release kinetics, and drug loading capacity [9].

TDDS patches can be prepared using various methods, including the asymmetric TPX membrane method, circular Teflon mold method, mercury substrate method, IPM membrane method, EVAC membrane method, aluminum-backed adhesive film method, and proliposome technique [10, 11].

2. Materials and methods

2.1. Chemicals and reagents

Clonidine hydrochloride was gifted by Magnus Pharma Pvt. Ltd., Nepal. Hydroxypropyl Methylcellulose (HPMC), Dimethyl Sulfoxide (DMSO), Benzalkonium Chloride (BC), and Tween 80 were purchased from HiMedian Laboratory Pvt. Ltd. Polyethylene Glycol 4000 (PEG 4000) was procured from SRL Chem, India. Sodium Lauryl Sulfate (SLS) and methanol were purchased from Thermo Fisher Scientific India Pvt. Ltd., while ethanol was obtained from RCP Distilleries, India. Laboratory-grade water was used throughout the study. All chemicals and reagents were used as supplied without further purification.

2.2. Design of experiment (DoE)

A two factors two level (22) Central composite design (CCD) was done using Minitab 17 (Table 1). Hydroxypropyl methylcellulose (HPMC, lab grade) and Polyethylene glycol (PEG 4000) were taken as independent variables and thickness and folding endurance were dependent variables for optimization.Optimized amount of independent variables were determined using contor plot (Fig. 7).

DoE is done to optimize penetration enhancers (Dimethyl sulphooxide, DMSO; Sodium Lauryl sulphate, SLS; Tween 80 and Benzalkonium chloride,BZC separately using Minitab 17 for which 8 formulations were given (Table 3).The penetration enhancers were optimized (Table 4).

2.3. Fabrication of patches

Solvent casting method was used to prepare the drug loaded as well as placebo patches. Optimized concentrations of Hydroxypropyl Methylcellulose (HPMC) and Polyethylene Glycol 4000 (PEG 4000) (Table 2) were dispersed in a mixture of water and ethanol (1:1) and homogenized to ensure complete hydration. Chemical penetration enhancers and clonidine hydrochloride were then added, and the mixture was homogenized to achieve uniform dispersion. The resulting solution was carefully poured into pre-cleaned glass molds and allowed to dry at room temperature for 48 hours. After drying, patches of defined size (~530.93 mm²) were cut, individually wrapped in aluminum foil, and stored in a desiccator until further use.

Table 2: Optimized quantity of independent variables for dummy patch formulation.

HPMC (g)	PEG 4000(g)
1.7928	1

2.4. Drug permeation and flux study

The in-vitro drug release study was done using a Franz Diffusion Cell. Goat skin, with a thickness between 1.6 and 1.75 mm, was used as the membrane. The fat layer from the skin was removed with a surgical blade. The skin was then washed with distilled water, packed, and kept in the refrigerator until it was needed. During the test, the patch was placed on the top side of the skin (stratum corneum), and the skin was fixed between the donor and receptor compartments. Phosphate buffer with pH 7.4 was used in the receptor compartment. The temperature was kept at 37 ± 2°C, and the solution was stirred at 100 RPM using a Teflon-coated magnetic bead. At specific time intervals, 2 ml of liquid were taken out (at 0.5, 1, 1.5, 2 and 2.5 hour) and replaced with the same amount of fresh buffer. The drug release was measured by checking the absorbance of the samples at 224 nm using a UV spectrophotometer

2.5. Drug release

The in-vitro drug release study was carried out using a Franz Diffusion Cell. The patch was placed between the donor and receptor compartments. The temperature was maintained throughout the experiment. At specific time intervals, 2ml liquid were withdrawn and replaced with the same amount of fresh buffer. The amount of drug released was measured by checking the absorbance of the samples at 224 nm using a UV spectrophotometer.

2.6. Data treatment

Power law was used to describe the mechanism of drug release from the patch [12]:

$M\alpha/Mt = kt^n$

or, $logM\alpha/M_t = logk + nlogt$

Where M_t and $M\alpha$ are cumulative amount of drug released at time t and infinite time respectively, k represents constant incorporating structural and geometric characteristics of the device, n is the release exponent, indicative of the mechanism of drug release. Order of reaction was determined by graphical method. The equation for zero order of reaction is as follows:

Order of reaction was determined by graphical method. The equation for zero order of

reaction is as follows:

$A_0 - A_t = k_0 t$

Where $A_0 - A_t$ is the amount of drug released at time t, k_0 represents rate constant, t is

time.

Mean of $A_0 - A_t$ (n = 3) was calculated and a graph of $A_0 - A_t$ versus t was plotted for each batch. A trendline passing through the origin was drawn to see whether it followed zero order of release or not was confirmed by the value of degree of correlation (r^2).

Table 3: DoE of penetration enhancers optimization.

Std Order	Run Order	Center Pt	Blocks	DMSO (g)	Tween (g)	SLS (g)	BZC (g)
6	1	1	1	1	0.25	1	0.25
7	2	1	1	0.25	1	1	0.25
3	3	1	1	0.25	1	0.25	1
2	4	1	1	1	0.25	0.25	1
5	5	1	1	0.25	0.25	1	1
8	6	1	1	1	1	1	1
4	7	1	1	1	1	0.25	0.25
1	8	1	1	0.25	0.25	0.25	0.25

Table 4: Optimized chemical penetration enhancers.

DMSO (g)	Tween80 (g)	SLS (g)	BZC (g)
0.25	0.25	0.25	0.25

Drug release in first order reaction was dependent on the concentration of drug and thus its equation is stated as follows:

$LogC/C_0 = 2.303kt$

Where $C_0$is initial concentration of drug, C represents concentration remained at time t and k denotes rate constant.

Mean of $LogC/C_0$ (n = 3) was calculated and a graph of $LogC/C_0$ versus t was plotted for each batch. A trendline with y-intercept was drawn and the obtained degree of correlation (r^2 value) was used to confirm whether it followed first order release or not.

As the patch was of homogenous matrix type, the observed release values were also fitted in the Higuchi equation:

$Q = [D(2A\text{-}C_s)C_s t]^{1/2}$ Where Q represents amount of drug released at time t per unit area of exposure, C_s is the solubility of the drug in polymeric matrix, D denotes diffusion coefficient of drug in the matrix and A is the amount of drug per unit volume.

Mean of Q value (n=3) was calculated and a graph of Q versus $t^{1/2}$ was plotted. A trendline passing through the origin was drawn to see whether it followed Higuchi equation or not was determined by observing the r^2 value of the graph and trendline.

The order of reaction followed by the particular formulation was determined on the basis of the highest r^2 value among the graphs obtained by fitting the data in 1st order, zero order and Higuchi equations.

3. Results and discussions

3.1. Drug permeation and flux study

The in-vitro drug permeation study was carried out in triplicate, and the results showed standard deviations below 2%, indicating excellent reproducibility and experimental precision.

Among the tested formulations, the optimized patch (Patch 2) exhibited the highest cumulative drug permeation of 2.391% after 2.5 hours, with a mean flux of 0.105 $\mu g/mm^2 \cdot hr$ (Table 5). The other formulations, Patch 1 and Patch 3, showed slightly lower cumulative permeation values of 1.896% and 2.324%, respectively, confirming that variations in formulation composition influenced drug diffusion rates through the skin (Table 5).

In contrast, the control formulation (Fcontrol), which lacked the penetration enhancer system, demonstrated significantly lower permeation, with a maximum cumulative drug release of 0.761% and a flux of 0.036 $\mu g/mm^2 \cdot hr$ (Table 6). This marked difference highlights the essential role of the enhancer system in improving the drug's skin permeability and overall transdermal flux.

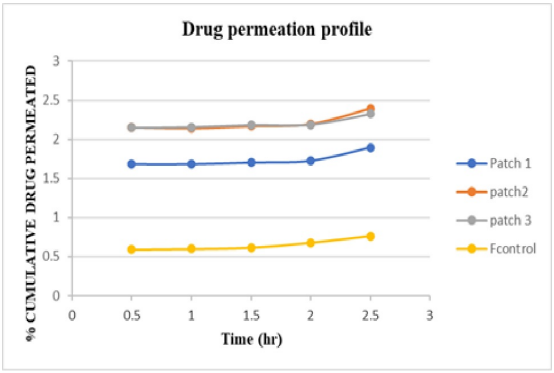

Figure 1: Drug permeation profile optimized formulation and Fcontrol.

The comparative permeation profile (Fig. 1) illustrates that the optimized patch maintained a consistently higher permeation rate across all sampling intervals, suggesting a well-balanced polymer–drug–enhancer interaction that facilitated controlled diffusion through the stratum corneum.

3.2. Drug release

The in-vitro drug release study of the optimized transdermal formulation was conducted to evaluate the release kinetics and mechanism of drug diffusion through the polymeric matrix. The optimized formulation demonstrated a cumulative drug release of 23.194% at 2.5 hours (Table 7), while the control formulation (F-control) without enhancer exhibited a significantly lower cumulative release of 8.418% at the same time point (Table 8). This result confirms that incorporation of penetration enhancers and optimized polymer composition effectively modulated the drug release rate, favoring a prolonged and controlled delivery pattern.

To elucidate the release mechanism, the data were fitted to various kinetic models including zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas equations. The optimized formulation showed the best fit to the zero-order model (R^2 = 0.8187), suggesting that the release rate was nearly independent of drug concentration and followed a sustained release behavior (Table 9). This indicates a uniform drug release over time, which is desirable for maintaining steady therapeutic levels during transdermal administration.

Moderate correlations were observed with the Hixson–Crowell (R^2 = 0.8106) and first-order (R^2 = 0.8065) models, suggesting that minor surface erosion and concentration-dependent diffusion also contributed to the release process (Table 9) .The lower correlation coefficients for the Higuchi (R^2 = 0.7366) and Korsmeyer–Peppas (R^2 = 0.7196) models indicate that while diffusion and polymer relaxation were involved, they were not the dominant mechanisms (Table 9).

In contrast, the control formulation exhibited much higher cor-

Table 5: Drug Permeation study, Foptimized.

Formulation	% Cumulative drug permeation					Flux ($\mu g/mm^2 * hr$)
	Time (hour)					
	0.5	1	1.5	2	2.5	
Patch 1	1.682	1.682	1.703	1.725	1.896	0.090
Patch 2	2.152	2.141	2.168	2.195	2.391	0.114
Patch 3	2.1471	2.155	2.187	2.187	2.324	0.110
Average of 3 patch	1.9938	1.992	2.0180	2.036	2.204	0.105
SD of 3 patch	0.2699	0.2691	0.272	0.269	0.268	0.013

Table 6: Drug Permeation study, Fcontrol.

Formulation	% Cumulative drug permeation					Flux ($\mu g/mm^2 * hr$)
	Time (hour)					
	0.5	1	1.5	2	2.5	
Fcontrol (n=3)	0.591	0.599	0.616	0.677	0.761	0.036

Table 7: Drug release study, Foptimized.

Formulation	% Cumulative drug release				
	Time (hour)				
	0.5	1	1.5	2	2.5
Patch 1	8.378	8.410	11.1	11.785	16.264
Patch 2	10.623	10.66	14.14	14.789	23.194
Patch 3	10.637	10.645	12.62	15.223	24.871
Average of 3 patch	9.879	9.906	12.62	13.932	21.443
SD	1.30	1.295	1.522	1.872	4.562

Table 8: Drug release study, Fcontrol.

Formulation	% Cumulative drug release				
	Time (hour)				
	0.5	1	1.5	2	2.5
Fcontrol (n=3)	6.618	6.935	7.449	8.127	8.418

relation coefficients across all models (R^2 > 0.96), demonstrating a rapid and nearly linear release typical of immediate-release systems (Table 9). The comparison between the optimized and control formulations clearly indicates that the designed polymer–enhancer matrix successfully slowed down the drug diffusion, converting a fast release into a controlled zero-order release profile. The overall drug release trend followed the order: Patch 2 > Patch 3 > Patch 1 > F-control, as represented in the release profile (Fig. 2 to Fig. 6).

Table 9: Kinetic modeling of drug release data for optimized formulation and F-control.

Model	R^2 (Formulation)	R^2(F-Control)
Zero order	0.8187	0.9834
First order	0.8065	0.9834
Higuchi	0.7366	0.9617
Hixson-Crowell	0.8106	0.9833
Korsmeyer-peppas	0.7196	0.925

4. Conclusion

The optimized transdermal patch shows superior drug release and permeation compared to the control. A cumulative drug release of 23.19% and a flux of 0.105 $\mu g/mm^2 \cdot hr$ confirmed the effectiveness of the selected polymer–enhancer combination in sustaining drug diffusion through the skin. The release followed zero-order kinetics ($R^2 = 0.8187$), indicating a controlled, concentration-independent mechanism, while the control patch showed faster, immediate-release behavior ($R^2 > 0.96$). Overall, the optimized formulation provided enhanced permeability and sustained release, supporting its potential for effective transdermal drug delivery.

Acknowledgments

The author sincerely thanks the supervisors for their valuable guidance, encouragement, and continuous support throughout the research work. Gratitude is also extended to all faculty members, laboratory staff of Kathmandu University for their assistance and cooperation. The author further acknowledges the Little Buddha College of Health Science, Purbanchal University, for providing laboratory facilities, and expresses heartfelt thanks to family, friends and colleagues for their constant motivation and support.

References

[1] Jaiswal P, Jangra A, Dahiya L, Sangwan Y & Saroha R, A review on transdermal patches, *The Pharma Research*, 3 (2010) 139. ISSN 0975-8216.

[2] Rastogi V & Yadav P, Transdermal drug delivery system: An overview, *Asian Journal of Pharmaceutics*, 6(3) (2012) 161. ISSN 0973-8398.

[3] Marapur S C, Wali D S, Hunasagi B S, Chetankumar M & Patil R G, Formulation and evaluation of transdermal drug delivery system of verapamil hydrochloride, *Journal of Drug Delivery and Therapeutics*, 8 (2018) 70. URL https://jddtonline.info/index.php/jddt/article/view/2081.

[4] Wrzosek A, Woron J, Dobrogowski J, Jakowicka-Wordliczek J & Wordliczek J, Topical clonidine for neuropathic pain, *Cochrane Database of Systematic Reviews*, 2017(4). ISSN 1465-1858. https://doi.org/10.1002/14651858.cd010967.pub2.

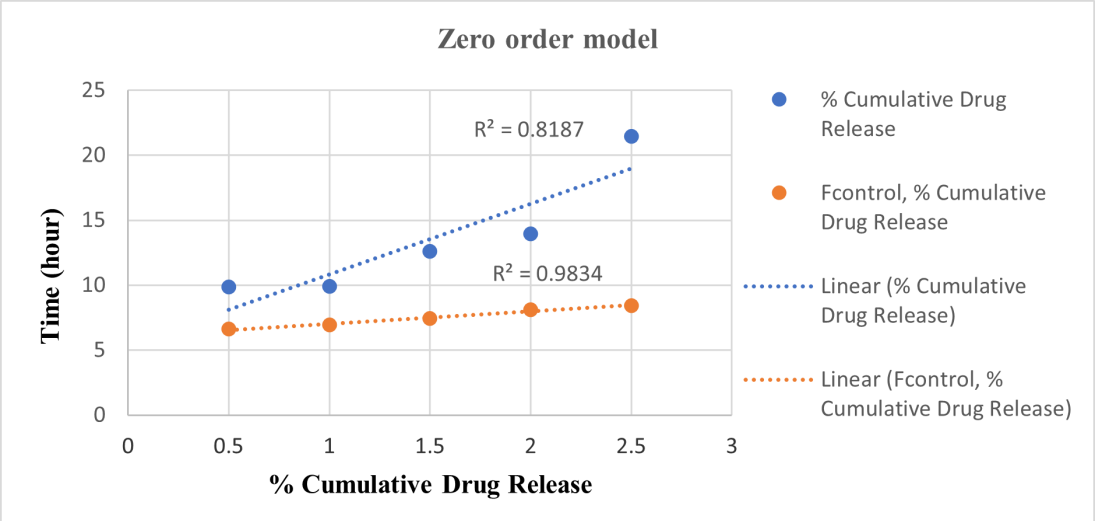

Figure 2: Zero-order kinetic model for cumulative drug release.

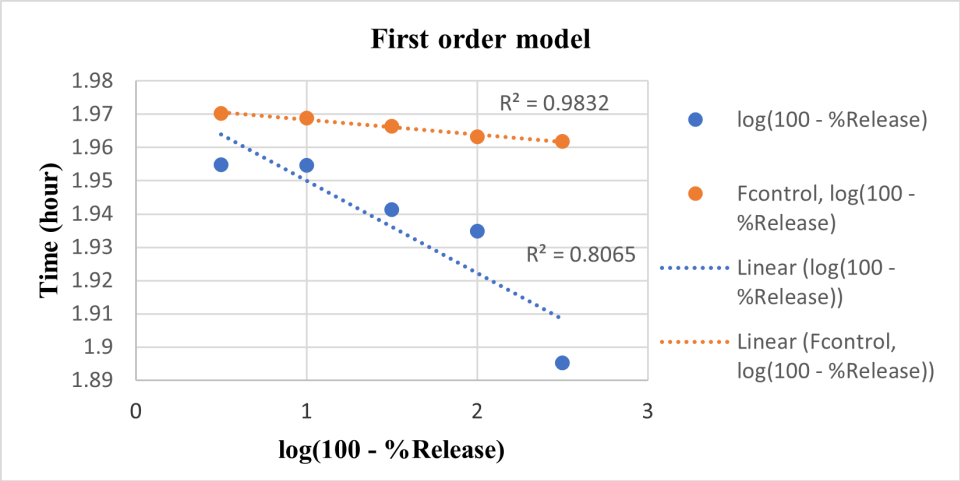

Figure 3: First-order kinetic model for cumulative drug release.

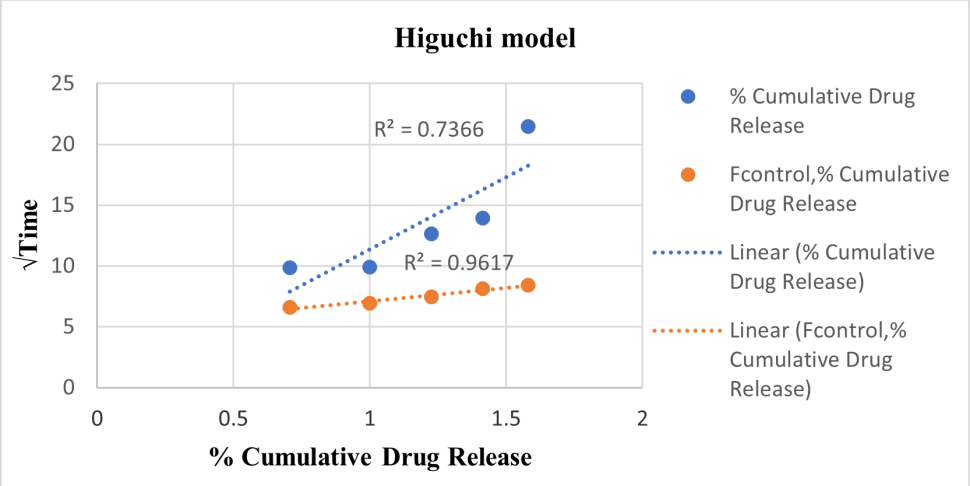

Figure 4: Higuchi model for cumulative drug release.

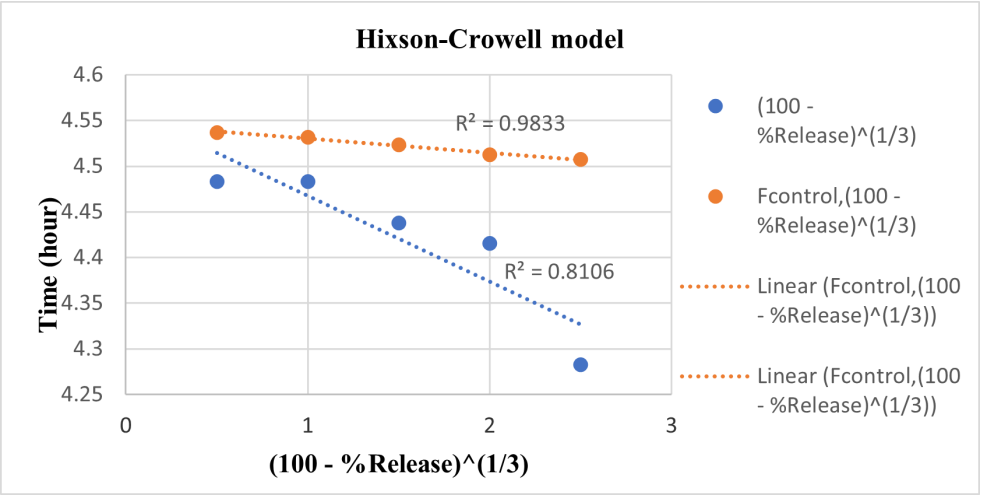

Figure 5: Hixon-Crowell model for cumulative drug release.

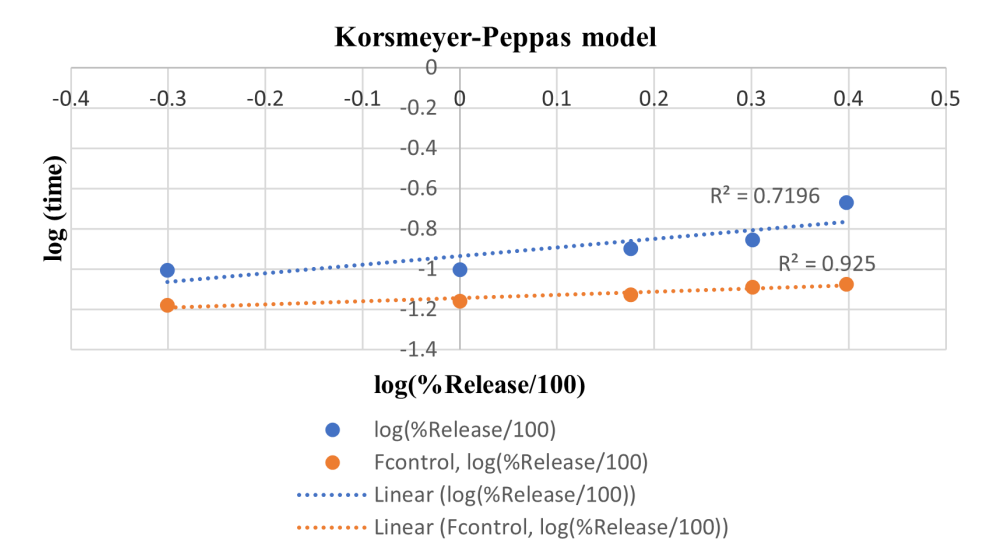

Figure 6: Korsmeyer-peppas model for cumulative drug release.

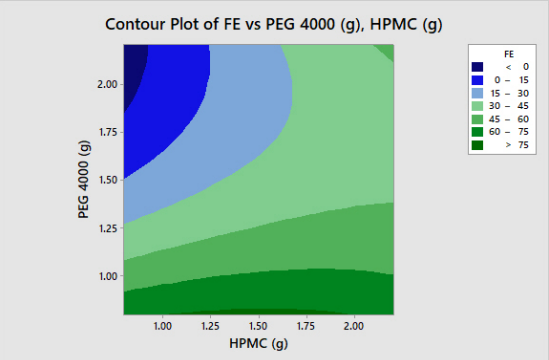

Figure 7: Contor plot used for optimization of HPMC and PEG (4000).

[5] Alkilani A, McCrudden M T & Donnelly R, Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum, *Pharmaceutics*, 7(4) (2015) 438–470. ISSN 1999-4923. https://doi.org/10.3390/pharmaceutics7040438.

[6] Marren K, Dimethyl sulfoxide: An effective penetration enhancer for topical administration of NSAIDs, *The Physician and Sportsmedicine*, 39(3) (2011) 75–82. ISSN 2326-3660. https://doi.org/10.3810/psm.2011.09.1923.

[7] Kapoor A, Mishra S K, Verma D K & Pandey P, Chemical penetration enhancers for transdermal drug delivery system, *Journal of Drug Delivery and Therapeutics*, 8(5-s) (2018) 62–66. ISSN 2250-1177. https://doi.org/10.22270/jddt.v8i5-s.1952.

[8] Pal R, Thakur S, Chanana A, Singh R & Pandey P, Transdermal drug delivery system (TDDS) as a novel tool for drug delivery, *World Journal of Pharmaceutical Research*, 12 (2023) 688–711. URL https://www.researchgate.net/publication/367204329_TRANSDERMAL_DRUG_DELIVERY_SYSTEM_TDDS_AS_A_NOVEL_TOOL_FOR_DRUG_DELIVERY.

[9] Sheth N S & Mistry R B, Formulation and evaluation of transdermal patches and study of permeation enhancement effect of eugenol, *Journal of Applied Pharmaceutical Science*, 1 (2011) 96–101.

[10] Hafeez A, Jain U, Singh J, Maurya A & Rana L, Recent advances in transdermal drug delivery system (TDDS): An overview, *International Journal of Pharmaceutical Sciences and Research*, 4 (2013) 733–744. URL https://www.researchgate.net/publication/341121046_Recent_Advances_in_Transdermal_Drug_Delivery_System_TDDS_An_Overview.

[11] Kajal, Sharma D R, Pandit V & Ashawat M S, Recent advancement in transdermal drug delivery system (TDDS), *Journal of Positive School Psychology*, 6(8) (2022) 12. ISSN 6260-6271. URL https://journalppw.com/index.php/jpsp/article/view/10922/7051.

[12] Siepmann J & Peppas N A, Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC), *Advanced Drug Delivery Reviews*, 48(2–3) (2001) 139–157. ISSN 0169-409X. https://doi.org/10.1016/s0169-409x(01)00112-0.