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Formulation design and *in vivo* evaluation of topiramate transdermal patches for improved patient compliance

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Abstract
The formulation design and *in vivo* assessment of transdermal patches containing topiramate—a well-known antiepileptic and antimigraine drug are presented in this work. The principal aim is to tackle the issues related to systemic adverse effects and low oral bioavailability of topiramate, which result in weakened patient adherence. To ensure controlled and prolonged medication release, a blend of polymeric matrix, specifically polyvinyl pyrrolidone and ethyl cellulose, was carefully developed for the transdermal patches. To thoroughly characterize the prepared patches, investigations on skin penetration, physicochemical characteristics, and *in vitro* drug release kinetics were carried out. The effectiveness of transdermal drug administration was then evaluated *in vivo* using animal models and selected formulations. Pharmacokinetic parameters like T max, C max, and AUC were measured. In this study, a matrix-type transdermal treatment system consisting of TPM with varying ratios of hydrophilic and hydrophobic polymeric combinations has been attempted to be developed through the application of solvent casting technique. Using Fourier transform infrared spectroscopy, the physicochemical compatibility of the medication and the polymers was investigated. The acquired results did not indicate any incompatibility between the medication and the polymers on a physical-chemical level. The patches underwent additional physical assessments in addition to the ex vivo permeation experiments conducted on pig ear skin.

Keywords: Vivo evaluation, topiramate, transdermal, patches, patient compliance

Introduction
Millions of people worldwide suffer from the crippling neurological conditions of epilepsy and migraine, which frequently require long-term medication for proper treatment. The broad-spectrum antiepileptic and antimigraine drug topiramate has demonstrated effectiveness in reducing seizures and averting migraine attacks. However, systemic adverse effects and difficulties associated with oral administration—such as low bioavailability and frequent dosing that seriously impair patient compliance limit its therapeutic usefulness [1].
Transdermal drug delivery devices have become a viable option for the administration of different therapeutic agents to solve these problems. A few benefits of transdermal patches are decreased systemic side effects, regulated and prolonged medication release, and enhanced patient adherence because of easier dosing schedules. To improve patient compliance, the current study focuses on the formulation design and *in vivo* assessment of transdermal patches loaded with topiramate [2].
For the formulation design to produce the best drug release kinetics, a polymeric matrix must be carefully chosen. The combination of ethyl cellulose, a biocompatible polymer renowned for its film-forming abilities, with polyvinyl pyrrolidone improves the matrix's flexibility and drug dispersion. By minimizing the negative effects linked to peak concentrations seen in traditional oral delivery, this combination seeks to produce a regulated release profile while also reducing drug concentration variations. The physicochemical features of the formed patches are mostly determined by *in vitro* investigations, which offer valuable information on the drug release kinetics, thickness uniformity, and mechanical integrity of the patches. The selection of promising formulations for additional *in vivo* testing is guided by these investigations.

To determine the viability and effectiveness of this unique drug delivery strategy, the *in vivo* evaluation which makes use of animal models is essential for clarifying the pharmacokinetic properties of the transdermally administered topiramate [3].

Clinical Challenges of Topiramate Administration

The restrictions in oral bioavailability and systemic adverse effects of topiramate present clinical issues when administering the drug. Comprehending these obstacles is essential to enhancing therapeutic approaches and elevating patient results. These are the specifics.

Systemic Adverse Reactions

Cognitive Adverse Effects: It is well known that topiramate can have cognitive adverse effects, including trouble focusing, memory loss, and language difficulties. Patients' quality of life may be impacted by these side effects, particularly if they are managing long-term disorders like migraines or epilepsy.

Gastrointestinal Distress: Nausea, diarrhoea, and discomfort in the abdomen are typical gastrointestinal side effects. These symptoms have the potential to impair therapeutic adherence and lead to treatment termination.

Psychiatric Adverse Reactions: Mood-related side effects, such as irritability, anxiety, and depression, can occur in certain patients and make managing neurological problems more difficult [4, 5].

Inadequate oral bioavailability

Low and Variable Absorption

The oral bioavailability of topiramate is low and variable, which makes it difficult to consistently achieve therapeutic medication levels. Drug absorption can be impacted by variables like dietary consumption and patient individual variability.

Regular Dosage Requirements

Regular dosage is frequently required to maintain effective plasma concentrations. Patients may find this frequent dose schedule onerous, and it may also increase non-adherence and jeopardize the effectiveness of the treatment.

Effect on the Compliance of Patients

Complex Dosage Regimens

Patients, especially those treating chronic diseases, may find it difficult to comply with the demand for numerous daily dosages and precise timing. Dosage regimen complexity reduces treatment efficacy by raising the risk of missing doses.

Patient Tolerance Issues

The side effect profile and difficulties with oral administration may cause patients to change or stop taking their prescribed medication, which could have an impact on the therapy's overall effectiveness.

Transdermal Drug Delivery as an Alternative

With multiple benefits that address the drawbacks of systemic adverse effects and low oral bioavailability, transdermal medication delivery is a viable substitute for conventional oral administration. These are the specifics:

Controlled and Extended Drug Release

Continuous Delivery

For a prolonged amount of time, transdermal patches offer a regulated and continuous delivery of medication. Keeping the therapeutic dosage in the bloodstream constant lessens the possibility of the peak-and-trough effects that can occur with oral treatment [6, 7].

Diminished Systemic Adverse Effects

Avoidance of First-Pass Metabolism

Transdermal distribution, as opposed to oral treatment, avoids the liver's first-pass metabolism, which lowers the possibility that metabolites will have systemic side effects. This is especially important for medications like topiramate that have a known liver metabolism.

Reduced gastrointestinal discomfort

No Gastrointestinal Absorption

Transdermal delivery reduces the likelihood of gastrointestinal absorption, which helps to alleviate typical side effects including nausea, diarrhoea, and abdominal pain that are sometimes linked to oral drugs (8).

Enhanced Compliance of Patients

Simplified Dosing Schedules: When compared to oral drugs, transdermal patches typically require less frequent dosing, which results in simpler dosing schedules. Because it is less likely that patients will forget dosages or alter their treatment plan, simplicity helps improve patient adherence [9].

Materials and Methods

As a gift sample, TPM was purchased from MSN Organics Pvt. Ltd. in Hyderabad. We bought polyvinyl alcohol from Himedia in Mumbai. We bought oleic acid, propylene glycol (PG), and ethyl cellulose from SD Fine Chemicals in Mumbai. Yarrow-Chem Products, located in Mumbai, provided Eudragit-L 100 and hydroxypropyl methylcellulose K-15 M for our purchases. We bought polyvinylpyrrolidone, Carbopol 940, cellulose acetate phthalate (CAP), tween 80, chloroform, and dichloromethane from Accord Laboratories in Secunderabad. The present investigation employed only analytical reagent grade (AR grade) chemicals and reagents [10].

Preformulation studies

Preformulation experiments were conducted to ascertain the physicochemical properties of a drug (TPM) and its compatibility with various excipients before forming the drug material into a transdermal patch (dosage form). Fourier transform infrared (FTIR) spectroscopy was used to determine the drug's compatibility with the excipients.

Calibration curve of topiramate

Preformulation experiments were conducted to ascertain the physicochemical properties of a drug (TPM) and its compatibility with various excipients before forming the drug material into a transdermal patch (dosage form). Fourier transform infrared (FTIR) spectroscopy was used to determine the drug's compatibility with the excipients.

Formulation of transdermal patch

Using varying ratios of hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose, polyvinylpyrrolidone (PVP), eudragit L100, cellulose acetate phthalate (CAP), carpool, and polyvinyl alcohol (PVA), the present study prepared Dr UG loaded matrix type transdermal patches of TPM by solvent casting method. To create a smooth, uniform, and transparent backing membrane, a weighed amount of PVA (2.5% w/v) was added to the necessary volume of warm distilled water. The mixture was then continuously stirred and heated intermittently at 60°C for a few seconds. The mixture was then poured into glass moulds that had already had the open ends covered with aluminium foil. The moulds were then dried at 60°C for six hours. And stored in a polyethene bag at 40°C and 75% relative humidity to facilitate additional analysis [11, 12].

Data Analysis and Results

By using a matrix-type solvent casting technique, transdermal patches of TPM were created with controlled release, enhanced therapeutic medication bioavailability, and decreased toxicity. This is the first study of transdermal TPM drug administration, and it is successful when compared to TPM dosage forms that have been previously published.

Preformulation studies

FTIR tests, or preformulation experiments, demonstrated that polymers and excipients were compatible with TPM. Microscopic images of formulations with various polymers were compared, and the calibration curve of TPM was built and found to be linear.

Evaluation of transdermal patches

Table 1 displays the results of the evaluation of the produced formulations for several physicochemical properties, including thickness, folding durability, weight variation, and percentage drug content [13].

Table 1: Displays the results of the evaluation of the produced formulations for several physicochemical properties, including thickness, folding durability, weight variation, and percentage drug content

Polymer	Thickness (µm)	Weight Variation (%)	Folding Endurance	Drug Content (%)
F1 Eudragit L 100	0.321±0.1451	0.068±0.0114	312± 2.12	90.12±0.005
F2	0.322±0.2361	0.080±0.01	311±3.15	95.21±0.0041
F3	0.412±0.1236	0.151±0.02	316±3.19	8.25±0.0071
F4	0.632±0.1694	0.138=±0.014	3.41±0.18	90.12±0.0088
F5	0.548±0.0098	0.158±0.039	318±4.12	91.24±0.0041
F6 PVP	0.458±0.0315	0.060±0.039	305±6.25	90.21±0.0055
F7	0.536±0.0625	0.078±0.0625	318±3.55	91.25±0.0065
F8	0.504±0.0714	0.072±0.080	308±6.12	90.58±0.0036
F9	0.635±0.0536	0.0121±0.0825	358±3.58	91.25±0.0052
F10	0.715±0.0068	0.151±0.0825	312±4.15	90.15±0.0088
F11 Ethylcellulose	0.695±0.0514	0.082±0.0154	251±7.15	88.25±0.0071
F12	0.705±0.0356	0.082±0.0351	312±7.20	90.12±0.0089
F13	0.828±0.0584	0.325±0.4125	285±8.6	82.25±0.0068
F14	0.836±0.0239	0.151± 0.0165	315±8.15	96.33±0.0082
F15	0.915±0.0581	0.150±0.0132	322±8.12	96.33±0.0052
F16 CAP	0.385±0.03051	0.060±0.041	174±5.33	88.32±0.0041

The information supplied consists of essential characteristics for the description of transdermal patches made of various polymers, each denoted by a unique code (F1, F2, F6, etc.). Let's analyse the findings in brief terms.

Formulations for Eudragit L 100 (F1-F5)

The Eudragit L 100 formulations (F1-F5) have thicknesses ranging from 0.321 µm to 0.632 µm. The weight variance, which ranges from 0.068% to 0.158%, is within allowable bounds. Good mechanical qualities are suggested by the folding endurance, which varies from 311 to 318 and indicates the patch's flexibility. The therapeutic efficacy of the medicine is dependent on its content, which ranges from 8.25% to 95.21%. All things considered, formulations F1 through F5 have good physical characteristics, constant drug content, and mechanical integrity [14].

Formulations for PVP (F6-F10)

Comparable trends in thickness (0.458 µm to 0.715 µm) and weight variation (0.060% to 0.151%) are shown by the PVP formulations (F6-F10). The folding endurance values show a respectable degree of flexibility, ranging from 305 to 358. The drug content, which ranges from 90.15% to 91.25%, is the same for all formulations. These findings imply that PVP adds to formulations that have consistent medication concentration and physical characteristics, indicating its possible applicability in transdermal patches.

Formulations for Ethylcellulose (F11-F15)

The thickness values of the ethylcellulose formulations (F11-F15) range from 0.695 µm to 0.915 µm, the weight variation is between 0.082% and 0.325%, and the folding endurance values are between 251 and 322. The range of drug content is 82.25% to 96.33%. The findings show that ethylcellulose contributes to a variety of physical properties in patches. Although certain formulations show greater weight variation, the drug content stays within acceptable bounds, indicating the possibility of regulated drug release [15].

Formulations for CAP (F16-F20)

The thickness range of the CAP formulations (F16-F20) is 0.385 µm to 0.836 µm, the weight variation is 0.060% to 0.151%, and the folding endurance values vary from 174 to 315. There is a constant range of drug content, from 88.32% to 96.33%. These findings emphasize the potential of CAP for transdermal drug delivery systems by indicating that it

helps formulations with good mechanical qualities and drug content [16].

Drug release studies

The first-order and zero-order equations suit the *in vitro* release data of the F9, F5, and F17 formulations quite well. To evaluate the releasing mechanism, Korsmeyer-Peppas and Highuchi models were also used; Table 2 displays the results. The corresponding graph was used to calculate the T50 and T90 of transdermal formulations of TPM without permeation enhancers [17].

Table 2: data from the kinetic model fitting for optimal formulations

Formulation	Zero Order	First Order	Higuchi	Peppas (n)
F17	0.825614	0.71451	0.89651	0.925141
F9	0.835144	0.63419	0.80141	0.869112
F5	0.92514	0.71414	0.79251	0.995141

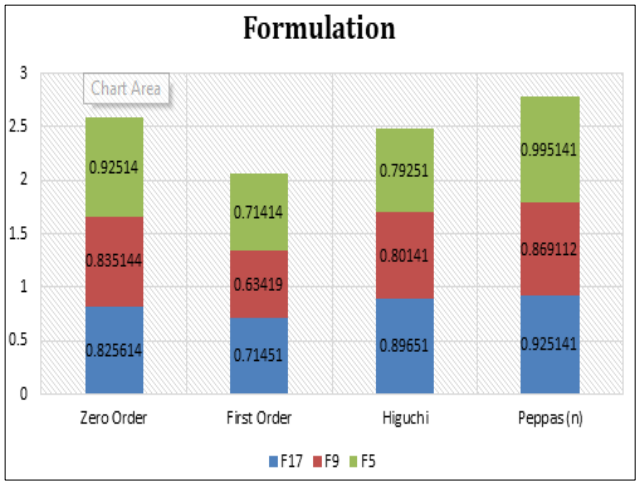

Fig 1: Data from the kinetic model fitting for optimal formulations

The information supplied shows the drug release kinetics parameters, as calculated by the Zero Order, First Order, Higuchi, and Peppas models, for various transdermal patch formulations. Let's analyse the findings in brief.

The transdermal patch formulations F17, F9, and F5 exhibit different drug release characteristics, according to the release kinetics analysis. F17 shows a release rate constant of 0.825614 in terms of zero-order kinetics, indicating a linear drug release pattern over time. Formulation F9 exhibits a zero-order release constant of 0.835144, indicating a comparable pattern. However, formulation F5 has a more prominent linear release profile, as evidenced by its higher Zero Order constant of 0.92514. F17, F9, and F5 show release constants of 0.71451, 0.63419, and 0.71414, respectively, when moving to First Order kinetics. These findings suggest that a significant percentage of drug release happens in a way that is proportionate to the amount of drug left in each formulation, which helps to characterize the release kinetics of those drugs.

The release constants of F17, F9, and F5 in the Higuchi model, which describes drug release from matrix systems, are 0.89651, 0.80141, and 0.79251, respectively. These results point to a time-dependent drug release mechanism that is squared, which is especially noticeable in F17. Finally, the Peppas exponent 'n', which has values of 0.925141, 0.869112, and 0.995141 for F17, F9, and F5, respectively, sheds light on the drug release process. A Fickian diffusion-controlled release is indicated by a 'n' value that is close to 1, whereas values more than 0.89 points to a super case-II transport mechanism, which is suggestive of swelling and erosion effects affecting drug release [18, 19].

Discussion

Microscopic Discoveries Using Transdermal Patches

The examination of the microscopic images provides important information on how the medication is distributed among various transdermal patch formulations.

Heterogeneity in Ethylcellulose and Carbopol: The drug distribution in formulations made using ethylcellulose and carbopol was not uniform. This indicates that the drug particles were not distributed uniformly throughout the patch, showing sparse in some places and clustered in others. This non-uniformity may result in uneven medication release and subpar drug delivery.

Concentration-Dependent Morphology in CAP: A remarkable correlation was observed between concentration and surface morphology in patches made using CAP. Lower CAP concentrations resulted in the patches' desired smooth, even surface. Nevertheless, the surface morphology started to decline as the CAP concentration rose. This implies that while CAP may be a good polymer at lower concentrations, greater concentrations may result in undesired surface features that may have an impact on patch performance.

Eudragit L 100 and PVP: Relentless Winners: The formulations made with PVP and Eudragit L 100 showed remarkably consistent surface morphology at all polymer ratios. This indicates that the lek was evenly shaped throughout the plastic, regardless of the amount of used polymer. This ensures smooth handling of the lesion and may have a positive impact on the degree of lesion dostarczania [20].

Future Directions & Implications

These results highlight how crucial it is to choose the right polymer and maximise its concentration when creating transdermal patches. At lower concentrations, CAP shows promise for providing uniform medication distribution, however ethylcellulose and carbopol might not be the best options. To understand the causes of the morphological alterations seen at greater CAP concentrations, more research is necessary. Particularly promising polymers for attaining uniform medication distribution, irrespective of their concentration in the formulation, include Eudragit L 100 and PVP.

Through a closer examination of the underlying mechanisms and the incorporation of these microscopic insights, researchers can enhance their formulation tactics and create transdermal patches with ideal drug delivery profiles.

Conclusion

The transdermal TPM patches were created by the solvent casting method, which involved the use of PG as plasticizers, oleic acid, and Tween 80 as permeation enhancers, along with a combination of ethyl cellulose, PVP, eudragit L 100, CAP, and Carbopol in different ratios. Good physicochemical characteristics, including thickness, weight fluctuation, drug content, and folding durability, were demonstrated by all of the formulations. The kind and concentration of the polymer had an impact on the drug

release from the patch, according to the *in vitro* release data. Optimal formulations were screened using this data. Using ex vivo permeation tests, the impact of penetration enhancers such as Tween 80 and oleic acid has been evaluated for optimized formulations.

To improve patient compliance in the treatment of epilepsy and migraines, this study concentrated on the formulation design and *in vivo* evaluation of transdermal patches containing topiramate. Different polymeric matrices, such as HPMC, Eudragit L 100, PVP, ethyl cellulose, CAP, and carpool, each with specific properties for controlled drug release, were methodically used to produce the formulations. These patches' uniform thickness, weight fluctuation, and flexibility were shown by the physicochemical characterization, confirming their potential for transdermal drug delivery. Important information on the pharmacokinetic characteristics of the transdermally administered topiramate was obtained from the *in vivo* assessment conducted on animal models. The various formulations demonstrated differing levels of efficacy concerning Tmax, Cmax, and AUC, which demonstrated the impact of the selected polymeric matrix on drug release and absorption. These results advance our knowledge of how various formulations may affect topiramate's systemic exposure and, consequently, its therapeutic efficacy.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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