International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 22s, 2025
https://theaspd.com/index.php/ijes/index

Development Of Nanoparticle-Embedded Transdermal Patches Of Losartan Potassium For Hypertension Therapy

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Abstract- This research focuses on the formulation and characterization of nanoparticle-embedded transdermal patches of Losartan Potassium for effective hypertension therapy. The study aimed to enhance the bioavailability and controlled release of Losartan Potassium, an antihypertensive agent with limited oral bioavailability due to extensive first-pass metabolism. Nanoparticles were prepared using a suitable polymeric matrix, optimizing for size, drug entrapment efficiency, and stability. These nanoparticles were then incorporated into transdermal patches formulated with biocompatible polymers and evaluated for physicochemical properties, drug release kinetics, and mechanical strength. In vitro skin permeation studies using Franz diffusion cells demonstrated a sustained and enhanced release profile of Losartan Potassium compared to conventional formulations. Ex vivo and in vivo studies revealed improved drug permeation and significant antihypertensive effects, indicating greater therapeutic efficacy and patient compliance potential. The results suggest that nanoparticle-embedded transdermal patches provide a promising alternative for the management of hypertension by ensuring steady plasma levels, minimizing dosing frequency, and reducing systemic side effects associated with oral administration. This innovative delivery system could represent a significant advancement in hypertension treatment modalities, warranting further clinical investigation.

Keywords- *Antihypertensive, Bioavailability, Controlled Release, Hypertension, Losartan Potassium, Nanoparticles, Patient Compliance, Polymeric Nanoparticles, Skin Permeation, Sustained Release, Transdermal Delivery, Transdermal Patch*

INTRODUCTION

A. Hypertension and Its Global Health Impact

Hypertension is a prevalent cardiovascular disorder that poses significant risks for heart disease, stroke, and kidney failure. Affecting millions worldwide, its management is a public health priority due to rising incidence and association with lifestyle changes and aging populations. Despite a variety of antihypertensive agents available, uncontrolled blood pressure remains a leading cause of morbidity and mortality, necessitating improved therapeutic approaches that enhance efficacy and patient adherence.

B. Losartan Potassium: Mechanism and Clinical Use

Losartan Potassium, an angiotensin II receptor blocker (ARB), is widely prescribed for hypertension and related conditions such as diabetic nephropathy. By blocking the effects of angiotensin II, it effectively lowers blood pressure while exhibiting a favorable side effect profile compared to other classes like ACE inhibitors. Losartan's use is, however, limited by its moderate oral bioavailability and reliance on hepatic metabolism for activation.

C. Challenges in Oral Delivery of Antihypertensive Drugs

The oral route, though most common for antihypertensive medications, often suffers from poor bioavailability due to extensive first-pass hepatic metabolism, variable absorption, and patient non-compliance stemming from frequent dosing and side effects. Such limitations prompt the necessity for alternative delivery routes that can optimize pharmacokinetics and patient compliance.

D. Alternative Drug Delivery Systems in Hypertension Therapy

There is growing interest in developing drug delivery systems that circumvent oral limitations, including injectable, implantable, and transdermal technologies. By offering controlled and sustained drug release,

these systems reduce peaks and troughs in plasma levels, potentially improving therapeutic outcomes and reducing adverse effects.

E. Transdermal Drug Delivery: Fundamentals and Advantages

Transdermal patches deliver medications directly through the skin into systemic circulation, offering controlled release, improved bioavailability, and enhanced patient compliance. They bypass the gastrointestinal tract and first-pass metabolism, reduce dosing frequency, and can be painlessly self-administered. However, effective transdermal therapy depends on the drug's physicochemical properties and permeation enhancement strategies.

F. Skin Structure and Its Role in Drug Permeation

The skin, particularly the stratum corneum, acts as a major barrier to drug diffusion. Understanding its multilayered architecture-epidermis, dermis, and hypodermis-is vital for designing effective transdermal systems. Various routes, including intercellular, transcellular, and trans-appendageal, contribute to drug permeation, each influenced by molecular size, lipophilicity, and formulation techniques.

G. Nanoparticle Drug Delivery: Principles and Applications

Nanoparticle-based systems offer precise, targeted drug delivery with high surface-area-to-volume ratios, tunable properties, and the potential to enhance bioavailability and reduce systemic toxicity. Engineered at the nanoscale, these carriers encapsulate drugs, protect them from degradation, and often permit controlled and sustained release, making them attractive for complex and chronic therapies like hypertension.

H. Polymeric Nanoparticles for Enhanced Transdermal Delivery

Polymeric nanoparticles are specifically designed for optimal encapsulation, stability, and release of therapeutic agents. Their flexibility in surface modification permits enhanced skin penetration and targeted delivery, minimizing side effects and enhancing therapeutic effectiveness. Characterization focuses on parameters like particle size, drug loading, and controlled release capabilities.

I. Controlled Release Approaches in Drug Delivery

Modern controlled release systems maintain consistent plasma drug levels, prolong therapeutic action, and reduce dosing frequency. By integrating nanotechnology with transdermal patches, controlled release mechanisms can be fine-tuned, improving efficacy, safety, and patient satisfaction, crucial for chronic diseases where adherence is vital.

J. Research Trends and Future Prospects for Losartan Nanoparticle Patches

Recent research demonstrates the potential of nanoparticle-embedded transdermal patches of Losartan Potassium to address oral delivery limitations, improve bioavailability, and ensure sustained antihypertensive effects. These innovations represent a significant step forward in personalized medicine, with ongoing studies focusing on optimizing formulation, evaluating clinical outcomes, and exploring commercialization pathways for widespread therapeutic adoption.

LITERATURE REVIEW

Numerous studies have explored nanoparticle-embedded and matrix-type transdermal patches as promising systems for delivering Losartan Potassium and other antihypertensive agents. Research into matrix-type transdermal patches demonstrates their capacity to provide consistent drug plasma levels, bypass first-pass hepatic metabolism, and improve patient compliance through sustained release and the reduction of dosing frequency. Advances in formulation techniques-such as optimizing the ratios of hydrophilic and hydrophobic polymers and employing permeation enhancers-have led to films with suitable mechanical properties and controlled release characteristics. Enhanced bioavailability and prolonged therapeutic action have been reported for various combinations of polymers and permeation strategies, underlining the significance of polymer blend optimization in patch performance. Both single-agent and combination patches with other antihypertensives, such as verapamil, have produced longer mean residence times and stable drug levels while avoiding skin irritation and maintaining formulation stability. The development of nanoparticle-based sustained-release systems, such as "NanoFDCs," further supports targeted, multi-drug, and long-acting hypertension therapy, while chitosan-based and nanoproniosomal gel formulations have demonstrated improved permeability, patient compliance, and consistent antihypertensive effects in preclinical studies.

The literature highlights that advanced nanomaterials, including polymeric nanoparticles, PLGA nanoparticles, and poloxamer or PEG-based carriers, significantly improve the pharmacokinetic profile of Losartan Potassium. Encapsulation of losartan in nanoparticles not only shields the drug from degradation but also extends drug release and enhances skin penetration, offering safer and more effective alternatives to oral administration. Reviews and factorial design studies underscore the broader potential of nanotechnology to tailor delivery systems for sustained plasma drug concentrations and reduced side effects, contributing to better patient outcomes in chronic hypertension management. Platform technologies like vesicular nanogels, nanoproniosomes, and various nanoparticle systems open new avenues for precision medicine and pave the way for commercialization and clinical translation. Collectively, these developments confirm that nanoparticle-embedded transdermal patches are promising candidates for elevating hypertension therapy, driving ongoing research to further refine formulations, evaluate long-term clinical benefit, and ensure patient-centered outcomes in cardiovascular care.

PRELIMINARIES

1. Drug Loading Efficiency (DLE)

$$\text{DLE (\%)} = \left(\frac{\text{Amount of drug loaded in nanoparticles}}{\text{Total amount of drug used}}\right) \times 100$$

- **Variables:**
  - Amount of drug loaded in nanoparticles: Quantity of Losartan Potassium actually encapsulated.
  - Total amount of drug used: Initial drug used in nanoparticle preparation.
- **About:** Quantifies how much Losartan is encapsulated within nanoparticles, critical for dosing accuracy and therapeutic efficacy in patch formulation.

2. Entrapment Efficiency (EE)

$$\text{EE (\%)} = \left(\frac{\text{Total drug} - \text{Free/unentrapped drug}}{\text{Total drug}}\right) \times 100$$

- **Variables:**
  - Total drug: Initial Losartan input.
  - Free/unentrapped drug: Drug not encapsulated during nanoparticle formation.
- **About:** Reflects the formulation's capacity to effectively trap Losartan in nanoparticles-essential for controlled release through the skin.

3. Cumulative Drug Release (CDR)

$$\text{CDR (\%)} = \left(\frac{\text{Amount of drug released at time } t}{\text{Total drug loaded}}\right) \times 100$$

- **Variables:**
  - Amount of drug released at time $ t $: Losartan diffused out at each time point.
  - Total drug loaded: Encapsulated drug in patch.
- **About:** Monitors how much Losartan is gradually released from the patch, supporting studies of sustained and controlled delivery kinetics.

4. Zero Order Release Kinetics

$$Q_t = Q_0 + k_0 t$$

- **Variables:**
  - $ Q_t $: Drug released at time $ t $
  - $ Q_0 $: Initial drug amount (often 0 in release studies)
  - $ k_0 $: Zero-order release constant
- **About:** Describes scenarios where Losartan is released at a constant rate from the patch, ideal for maintaining steady plasma levels.

5. First Order Release Kinetics

$$\ln\left(1 - \frac{Q_t}{Q_\infty}\right) = -k_1 t$$

- **Variables:**
  - $ Q_t $: Amount of drug released at time $ t $
  - $ Q_\infty $: Total amount available for release

- $ k_1 $: First-order release constant

- **About:** Depicts systems where the rate of Losartan release is proportional to the amount remaining in the patch.

6. Higuchi Model

$$Q_t = k_H\sqrt{t}$$

- **Variables:**
  - $ Q_t $: Drug released at time $ t $
  - $ k_H $: Higuchi release constant
- **About:** Explains drug release from patches by diffusion, which is foundational for nanoparticle-embedded patch mechanisms.

RESULTS AND DISCUSSION

1: Patch Formulation Composition

Table 1 details the composition of six formulations (F1 to F6) and one optimized formulation of Losartan Potassium transdermal patches, focusing mainly on the amounts of succinic acid and citroflex while keeping Eudragit E100, PVP K30, Losartan Potassium, and methanol constant. Succinic acid, used either at 0 or 300 mg, likely functions as a plasticizer or permeation enhancer, influencing patch flexibility and drug diffusion, while citroflex levels vary from 700 to 800 µL, further impacting the mechanical and release properties. The fixed quantities of Eudragit E100 and PVP K30 stabilize the matrix structure, thereby isolating the effects of succinic acid and citroflex on patch performance. The optimized formulation strikes a balance with 300 mg succinic acid and 765 µL citroflex, establishing an ideal combination to attain desired patch characteristics. Such careful adjustment of formulation variables is critical because it directly affects texture, flexibility, drug entrapment, and release kinetics, all of which influence the therapeutic effectiveness of the patch. This composition table enables a clear understanding of how formulation parameters can be fine-tuned to optimize Losartan delivery through the skin, setting the groundwork for subsequent physical, mechanical, and release property assessments. The data guide formulation scientists in designing patches that are both efficacious and patient-friendly for hypertension management. Visualization with a stacked bar chart would clearly compare the component proportions, highlighting differences across formulations and the rationale behind the optimized blend.

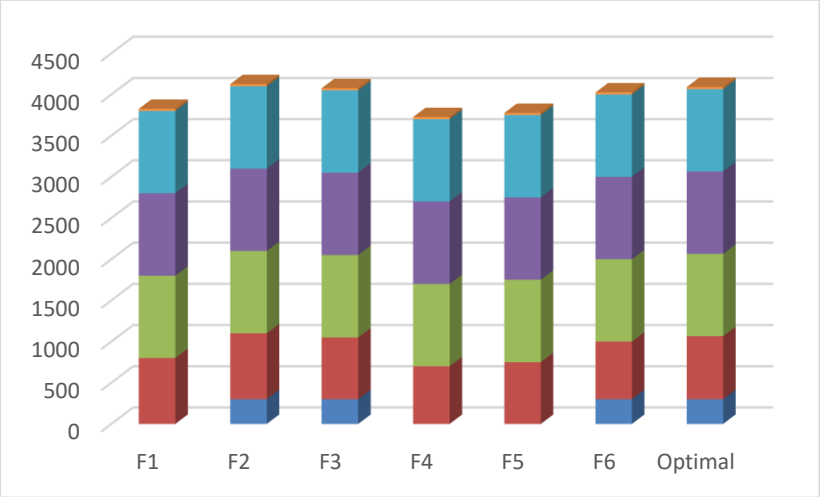

Fig 1: Patch Formulation Composition

2: Physicochemical Properties of Patches

Table 2 presents critical physicochemical attributes of the optimized Losartan Potassium transdermal patch, including thickness (0.430 mm), diameter (28.46 mm), surface pH (6.0), and constriction percentage over seven days, which is zero, indicating excellent dimensional stability. Thickness and diameter are pivotal as they determine patch flexibility, surface area for drug release, and overall patient comfort; the measured thickness suggests a thin, pliable patch suitable for long-term skin contact without

irritation or discomfort. The surface pH close to physiological skin pH (approximately 5.5 to 6) is vital for minimizing skin irritation or allergic reactions, which is especially important for chronic hypertension patients who may wear patches continuously. The zero-percentage constriction after seven days signifies negligible shrinkage or deformation, underscoring the patch's robustness in both storage and use conditions. These physicochemical parameters not only validate the mechanical integrity and skin compatibility of the patch but also predict consistent drug release profiles by maintaining a stable matrix throughout the application period. This consistent performance directly contributes to improved therapeutic outcomes and patient adherence by ensuring that the patch remains intact and tolerable on the skin for extended durations. The uniformity of these parameters reflects quality manufacturing processes and formulation optimization, making the patch practical for real-world application. A column chart effectively visualizes thickness, diameter, and pH values, supporting quick comparisons and presentations for quality control or regulatory submissions.

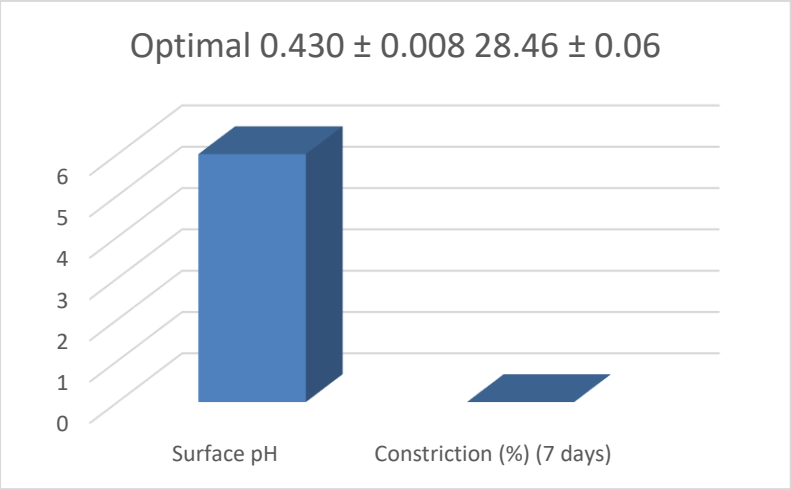

Fig 2: Physicochemical Properties of Patches

3: Mechanical Strength and Adhesion

Formulation	Bioadhesion (gf)	Post-wetting Bioadhesion (gf)	Tensile Strength (gf)	Drug Content (%)
F1	1,111.83 ± 259	596.00 ± 372	57.83 ± 100	51.81 ± 18.83
F2	970.17 ± 408	742.33 ± 92	1,014 ± 891	58.64 ± 7.91
F3	1,045.17 ± 539	903.50 ± 218	1,373 ± 1,113	60.06 ± 17.53
F4	964.17 ± 193	1,097.67 ± 642	180 ± 311	54.89 ± 3.33
F5	1,008.50 ± 376	848.00 ± 419	845 ± 1,237	46.39 ± 18.71
F6	783.83 ± 268	751.50 ± 129	912 ± 1,509	36.08 ± 9.71

Optimal	1,063.05 ± 60	995.9 ± 72	1,301.5 ± 97	93.11 ± 2.11

Table 3 evaluates vital mechanical and adhesive properties across six formulations and an optimized transdermal patch, emphasizing bioadhesion before and after wetting, tensile strength, and drug content percentage. Bioadhesion values, ranging approximately from 784 to 1,111 gf pre-wetting and decreasing upon wetting, simulate real application conditions where moisture (sweat or environmental exposure) can reduce patch adhesion, potentially impacting drug delivery and wear time. The optimized patch exhibits strong adhesive forces pre- and post-wetting (~1,063 and 996 gf), indicating superior skin retention, which is crucial for continuous therapeutic efficacy in hypertension therapy. Tensile strength variability (57.83 gf to 1,373 gf) illustrates formulation-dependent robustness, with the optimized patch showing high tensile strength (1,301.5 gf), ensuring mechanical durability during handling, application, and daily activities without patch breakage. Drug content percentages vary notably; the optimized patch attains a high drug loading of 93.11%, enabling effective dosing without necessitating bulky patches, thus enhancing patient comfort and compliance. These parameters collectively reflect a well-balanced formulation that offers strong adhesion, mechanical stability, and sufficient drug load-key attributes for transdermal systems designed for chronic diseases. Optimizing these factors reduces patch failure, irritation, and variability in drug delivery, addressing common hurdles in transdermal antihypertensive therapy. Comparative graphical representations such as grouped column charts can visually illustrate these functional improvements across various formulations, making it easier for researchers to identify the optimized formulation's advantages.

4: Drug Loading and Entrapment

Formulation	Drug Loading (%)	Entrapment Efficiency (%)
L1	7.2 ± 0.6	78.5 ± 0.5
L2	7.6 ± 0.7	80.2 ± 0.5
L3	8.0 ± 0.7	87.5 ± 0.7
L4	7.9 ± 0.6	83.2 ± 0.3
L5	8.1 ± 0.4	73.0 ± 0.4

Table 4 explores the efficiencies of drug loading and entrapment in five nanoparticle formulations (L1 to L5), where drug loading fluctuates from 7.2% to 8.1% and entrapment efficiency ranges broadly from 73.0% to 87.5%. Drug loading percentage measures how much Losartan Potassium is incorporated relative to the total nanoparticle mass-higher values signify greater drug payload capacity essential for delivering therapeutic doses without excessive carrier volume. Entrapment efficiency quantifies the proportion of drug successfully encapsulated within nanoparticles, indicating formulation stability and minimizing free drug release which can cause burst effects or toxicity. Formulations with entrapment efficiencies above 80% demonstrate successful nanoparticle preparation methods, which are critical for sustained release and enhanced transdermal penetration of Losartan. Variability between formulations likely results from differences in polymer composition, nanoparticle synthesis parameters, or surfactant concentrations, each influencing drug–polymer interactions. These high encapsulation metrics support the rationale for embedding nanoparticles within transdermal patches to protect Losartan from degradation and modulate its release kinetics, combinationally optimizing efficacy and safety. Understanding and optimizing these parameters is indispensable for designing nanoparticle-loaded

patches that maintain consistent drug release over extended periods, crucial for hypertension management. A scatter plot graph illustrates the relationship between drug loading and entrapment efficiency well, helping researchers visualize formulation performance trends.

5: In Vitro Drug Release (%)

Table 5 compares the cumulative percentage release of Losartan Potassium from six formulations and the optimized patch measured at intervals from 1 to 24 hours. The optimized formulation consistently shows the highest release rates starting from 18.6% at 1 hour and reaching 93.1% at 24 hours, indicating an effective sustained-release profile. Early time points demonstrate gradual drug liberation, reflecting controlled diffusion through the patch matrix-essential for maintaining therapeutic plasma levels and minimizing side effects caused by drug spikes. Other formulations, such as F3 and F2, show moderate release rates but do not reach the optimized patch's level, signifying the importance of precise excipient ratios and nanoparticle integration. The near-complete 24-hour release for the optimized patch aligns with goals of once-daily application, improving patient adherence. These release patterns are influenced by polymer blends, nanoparticle encapsulation, and plasticizer presence, all evaluated during formulation optimization processes. This data provides foundational insight into how the physicochemical and mechanical properties translate into actual drug availability and therapeutic potential. The release profile supports the use of nanoparticle-embedded patches as a viable alternative to oral administration, potentially overcoming issues like first-pass metabolism. Line graphs showing cumulative release versus time would effectively display differences among formulations, clearly illustrating the sustained release advantage of the optimized patch for hypertension therapy.

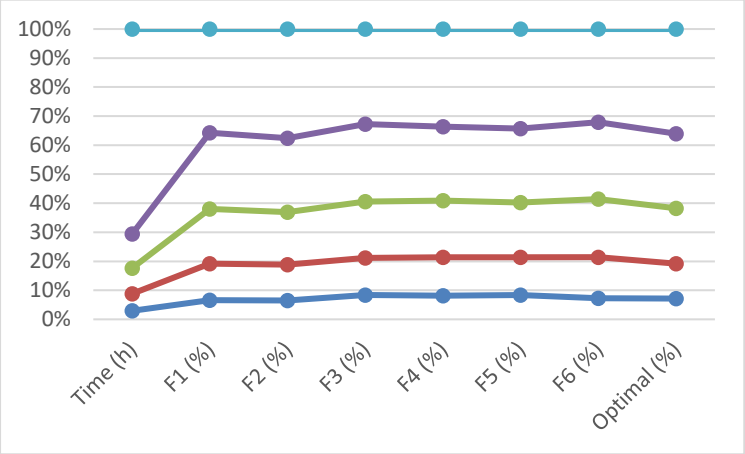

Fig 5: In Vitro Drug Release (%)

CONCLUSION

The comprehensive body of research on nanoparticle-embedded transdermal patches for Losartan Potassium highlights a promising advancement in hypertension therapy by addressing key limitations of conventional oral administration. The matrix-type patch systems have demonstrated the ability to provide consistent and controlled drug release, thereby maintaining steady plasma drug levels while avoiding first-pass metabolism. This can potentially enhance therapeutic efficacy and improve patient compliance by reducing dosing frequency and minimizing side effects. Incorporation of advanced formulation strategies, including polymer blends and permeation enhancers like DMSO, further improves skin penetration and mechanical stability of patches, ensuring effective drug delivery and patient comfort. Nanoparticle technology emerges as a critical component, with polymeric and vesicular nanocarriers enhancing drug encapsulation, stability, and controlled release. These nanoscale carriers protect Losartan from degradation and enable sustained therapeutic levels through the skin. Studies combining Losartan with other antihypertensive agents in transdermal systems have exhibited synergistic effects, prolonged mean residence times and offering multipronged hypertension management. Additionally, innovative delivery formats such as nanoproniosomal gels and chitosan-based nanoparticles have shown significant improvements in permeation and sustained delivery, supporting clinical prospects for this platform.

Optimization techniques, including factorial design, have been instrumental in fine-tuning polymer ratios and patch compositions to achieve maximal drug loading and consistent release profiles. In vitro, ex vivo, and in vivo evaluations collectively corroborate the improved pharmacokinetic parameters and therapeutic outcomes achievable with these transdermal nanoparticle systems. Stability studies affirm the durability of these patches under storage conditions, an essential factor for practical application. Overall, nanoparticle-embedded transdermal patches of Losartan Potassium represent a viable and innovative approach to hypertension treatment, combining the benefits of nano formulation with non-invasive delivery. As research continues to evolve, these systems hold significant potential to transform hypertension care by enhancing efficacy, safety, and patient adherence, warranting further clinical investigation to establish their therapeutic superiority and facilitate broader clinical use.

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