EJPMR, 2026, 13(4), 27-31 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

FORMULATION AND EVALUATION OF ATENOLOL TRANSDERMAL PATCHES- A REVIEW

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DOI: https://doi.org/10.5281/zenodo.19309137

How to cite this Article: *Sangram Bhogam, Miss. Rutuja Shah, Mr. Akshy Mane, Mr. Ritesh Bhosale, Mr. Prashant Dhokare, Mr. Atharv Chougale (2026). Formulation And Evaluation Of Atenolol Transdermal Patches- A Review. European Journal of Pharmaceutical and Medical Research, 13(4), 27–31.

Article Received on 19/02/2026 **Article Revised on 11/03/2026** **Article Published on 01/04/2026**

ABSTRACT

Atenolol is a widely prescribed β_1-selective adrenergic blocker used in the management of hypertension and angina, but its oral therapy is limited by first-pass metabolism, variable plasma levels, and patient non-compliance. Transdermal drug delivery systems offer a promising alternative by providing sustained drug release, improved bioavailability, and enhanced patient adherence while minimizing gastrointestinal side effects. This review outlines the fundamental principles of transdermal drug delivery, skin structure and permeation barriers, and key formulation strategies for atenolol transdermal patches. It highlights polymer selection, excipients, preparation methods, evaluation techniques, and the role of chemical and physical enhancement technologies. Overall, transdermal delivery represents a viable approach for improving long-term antihypertensive therapy.

KEYWORDS: Overall, transdermal delivery represents a viable approach for improving long-term antihypertensive therapy.

INTRODUCTION

Transdermal drug delivery systems (TDDS) provide controlled, non-invasive delivery of systemic drugs through the skin. Compared with oral dosing, TDDS can avoid first-pass hepatic metabolism, reduce dosing frequency, and improve compliance. Atenolol is a hydrophilic, low-lipophilicity drug (log P ≈ 0.16–0.5 depending on source) with a molecular weight (~266 Da) within the commonly accepted range for transdermal delivery. However, its limited partitioning into stratum corneum and relatively low skin permeability require formulation strategies that improve flux without causing unacceptable irritation. The following sections examine formulation approaches and evaluation parameters used to develop atenolol transdermal patches.

Hypertension is recognized as one of the leading global risk factors for cardiovascular morbidity and mortality. Epidemiological data indicate a high prevalence of hypertension in both urban and rural populations, particularly in developing countries such as India since hypertension is a lifelong condition, sustained and controlled drug delivery is essential to maintain therapeutic efficacy and reduce adverse effects.

Oral administration of antihypertensive drugs is associated with several drawbacks, including hepatic first-pass metabolism, frequent dosing, variable absorption, and poor compliance. Transdermal drug delivery systems overcome many of these limitations by delivering drugs directly into systemic circulation through the skin, thereby maintaining steady plasma drug concentrations and reducing dosing frequency.[1]

1. Concept of Transdermal Drug Delivery System

Transdermal drug delivery refers to the administration of therapeutic agents across the skin to achieve systemic effects. Transdermal patches are self-contained dosage forms designed to release drugs at a predetermined rate over an extended period of time this route bypasses the gastrointestinal tract and hepatic metabolism, making it suitable for drugs with short half-lives or extensive first-pass metabolism.

2. Components of Transdermal Patches

A typical transdermal patch consists of:

1. Drug reservoir or polymer matrix
2. Active pharmaceutical ingredient
3. Permeation enhancers

4. Pressure-sensitive adhesive
5. Backing laminate
6. Release liner
7. Plasticizers and solvents

3. Patch design types & choice of polymers

Transdermal systems for atenolol are generally designed as either matrix (drug dispersed in polymer matrix) or reservoir systems (drug solution in a compartment with rate-controlling membrane). Matrix systems are favoured for simplicity, safety, and ease of manufacture.

Common polymer classes and roles.

- **Hydrophilic polymers** (HPMC, PVA, PVP): Promote drug dispersion and sustained release for water-soluble drugs like atenolol. Often used when high moisture uptake is acceptable.
- **Hydrophobic polymers** (ethyl cellulose, Eudragit): Slow drug release and can be used to modify release kinetics when blended with hydrophilic polymers.
- **Plasticizers** (propylene glycol, PEG): Improve film flexibility and can act as penetration enhancers (PG is both plasticizer and solubilizer).

4. Factors Affecting Transdermal Drug Permeation

Drug permeation across the skin is influenced by.

- Physicochemical properties of the drug (molecular weight, lipophilicity, solubility)
- Formulation factors (polymer type, drug concentration, permeation enhancers)
- Physiological factors (skin hydration, age, blood flow, site of application)

5. Types of Transdermal Patches

Transdermal patches are classified into.

- Drug-in-adhesive systems
- Reservoir systems
- Matrix systems
- Micro-reservoir systems.[2]

MANUFACTURING METHODS[3]

1) Solvent Casting Method

The solvent casting technique is one of the most commonly used laboratory methods for preparing transdermal patches, especially in academic research.

In this method, the selected polymer (such as HPMC, PVA, or Eudragit) is first dissolved in a suitable volatile solvent like ethanol, methanol, or a mixture of solvents. After complete dissolution, the drug (Atenolol) is added along with a plasticizer (e.g., PEG 400, propylene glycol) to improve film flexibility. If required, a permeation enhancer is also incorporated to improve skin penetration.

The resulting homogeneous solution is poured onto a flat surface such as a glass plate or a Teflon-coated mould. This process is called "casting." The solvent is then allowed to evaporate slowly at room temperature or in a controlled oven. After complete drying, a thin, uniform film is formed. The dried film is carefully peeled off and cut into patches of defined size.

Why It Is Popular in Research

1. Simple and economical
2. Requires minimal equipment
3. Suitable for small-scale laboratory formulation
4. Easy to modify polymer composition
5. Limitations
6. Residual solvent risk
7. Long drying time
8. Not ideal for large-scale production
9. This method is widely described in pharmaceutical formulation literature because of its simplicity and reproducibility.

2) Hot-Melt Extrusion (HME)

Hot-melt extrusion is a solvent-free manufacturing technique increasingly used in modern pharmaceutical industries. In this method, the drug and polymer are blended in solid form and fed into an extruder. The mixture is exposed to controlled heat and mechanical shear. As the temperature rises, the polymer softens or melts, allowing the drug to disperse uniformly within the polymer matrix. The molten mass is then forced through a die to form a thin film, which is cooled and cut into patches.

Since no organic solvents are used, this technique eliminates solvent-related toxicity and environmental concerns.

Advantages

i. No solvent residue
ii. Short processing time
iii. Suitable for industrial-scale production
iv. Better content uniformity

Limitations

i. Not suitable for heat-sensitive drugs
ii. Requires specialized equipment
iii. High initial setup cost
iv. For atenolol patches, this method is appropriate only if the drug and polymer are thermally stable during processing.

3) Coating Techniques (Adhesive-Based Systems / DIA Systems)

Coating methods are primarily used for Drug-in-Adhesive (DIA) type transdermal systems. In this approach, the drug is directly incorporated into a pressure-sensitive adhesive (PSA).

First, the drug is dissolved or dispersed uniformly in the adhesive solution. This mixture is then coated as a thin layer onto a backing membrane using precision coating equipment (such as knife-over-roll or slot-die coaters). The coated layer passes through a drying chamber where the solvent evaporates, forming a uniform adhesive film containing the drug.

Finally, a release liner is laminated over the adhesive layer to protect it until application.

Advantages

i. Produces very thin and flexible patches
ii. Uniform drug distribution
iii. Suitable for commercial-scale manufacturing
iv. Better control over thickness and dosing

Limitations

i. Requires advanced coating machiner
ii. Optimization of adhesive–drug compatibility is critical
iii. This method is commonly used in marketed transdermal systems because it ensures dose precision and consistent adhesive properties.

EVALUATION METHODS[4]

A robust evaluation covers physicochemical, mechanical, in-vitro, ex-vivo and in-vivo tests.

➢ **Physicochemical & mechanical tests**

- **Thickness and weight uniformity**: Micrometer and balance.
- **Folding endurance**: Evaluate flexibility by repeated folding until break.
- **Tensile strength & elongation**: Assess mechanical resilience.
- **Moisture uptake/loss and water vapor transmission rate (WVTR)**: Important for storage and adhesion.
- **Drug content and uniformity**: Typically, by validated UV spectrophotometry or HPLC after extraction.

➢ **Compatibility & characterization**

- **FTIR spectroscopy**: Check for drug-polymer interactions that may indicate incompatibility.
- **DSC (Differential Scanning Calorimetry)**: Assess drug crystallinity and thermal interactions.
- **XRD (X-ray Diffraction)**: Evaluate crystalline vs amorphous state.

➢ **In-vitro release & permeation**

- **Franz diffusion cell**: The standard for in-vitro skin permeation studies. Choice of membrane (synthetic vs excised animal/human skin) influences extrapolation to in-vivo.
- **Kinetics analysis**: Zero-order, first-order, Higuchi, and Korsmeyer-Peppas models identify release mechanisms.

➢ **Beta-Blockers as Transdermal Therapeutic Agents**

Beta-blockers are widely used in the management of hypertension but are limited by extensive first-pass metabolism and short half-lives when administered orally. Transdermal delivery of beta-blockers such as propranolol, atenolol, metoprolol, and carvedilol has been extensively studied to improve bioavailability and maintain steady plasma levels

➢ Propranolol: Shows enhanced bioavailability and sustained therapeutic effect via transdermal route.
➢ Atenolol: Suitable candidate due to low molecular weight and reduced CNS side effects.
➢ Carvedilol: Benefits from bypassing first-pass metabolism and prolonged action.

➢ **Role of Permeation Enhancement Techniques[5]**

Advanced techniques such as iontophoresis, electroporation, sonophoresis, and microneedles have been explored to enhance skin permeability, especially for hydrophilic antihypertensive drugs. These methods significantly improve drug flux without causing permanent skin damage.

ADVANTAGES[6]

1. Bypasses First-Pass Metabolism

When Atenolol is taken orally, part of the drug is metabolized before it reaches systemic circulation. Delivering it through the skin avoids this initial liver metabolism, which can improve the consistency of drug levels in the body.

2. Provides Sustained and Controlled Drug Release

A properly designed transdermal patch can release atenolol slowly over an extended period. This helps maintain relatively stable plasma concentrations and reduces fluctuations that are commonly seen with conventional oral tablets.

3. Improves Patient Compliance[7]

Since hypertension requires long-term therapy, reducing dosing frequency is beneficial. A once-daily or extended-release patch is often more convenient than taking multiple tablets per day, improving adherence.

4. Reduces Gastrointestinal Disturbances

Oral β-blockers may cause gastric discomfort in some patients. Transdermal delivery avoids direct contact with the gastrointestinal tract, thereby minimizing such issues.

5. Non-Invasive and Easily Reversible[8]

The patch is painless and easy to apply. If adverse effects occur, therapy can be stopped immediately simply by removing the patch.

6. Suitable for Drugs with Short Half-Life

Atenolol has a relatively short half-life (around 6–7 hours). A transdermal system can maintain prolonged therapeutic levels without repeated dosing.

7. Better Therapeutic Control in Chronic Conditions

Steady drug delivery may contribute to more consistent blood pressure control compared to fluctuating oral dosing.

DISADVANTAGES[9]

1. Limited Skin Permeability[10]

The outermost layer of the skin (stratum corneum) acts as a strong barrier. Since atenolol is hydrophilic, it does not easily penetrate the skin, which may necessitate the use of permeation enhancers.

2. Risk of Skin Irritation
Adhesives, polymers, or chemical enhancers used in patch formulation may cause redness, itching, or allergic reactions in some individuals.

3. Drug Physicochemical Limitations
Transdermal systems are best suited for drugs with specific molecular and lipophilic properties. Atenolol's hydrophilic nature can limit passive diffusion across the skin.

4. Variability in Drug Absorption
Drug absorption may vary depending on the site of application, skin thickness, age, hydration level, and individual patient differences.

5. Higher Manufacturing Cost
Compared to conventional tablets, transdermal patches require more complex formulation techniques and specialized materials, which increase production costs.

6. Adhesion Issues
Improper adhesion to the skin can affect drug delivery efficiency and therapeutic outcome.

DRUG PROFILE OF ATENOLOL

General Information
Generic Name: Atenolol
Category: β_1-selective adrenergic receptor blocker (cardioselective beta-blocker)
Therapeutic Class: Antihypertensive, Antianginal, Antiarrhythmic
Chemical Class: Aryloxypropanolamine derivative
Molecular Formula: $C_{14}H_{22}N_2O_3$
Molecular Weight: 266.34 g/mol
Solubility: Freely soluble in water; slightly soluble in alcohol
Half-life: Approximately 6–7 hours
Bioavailability: Around 40–50% (oral)
Protein Binding: Low (about 6–16%)
Atenolol is a selective β_1-adrenergic receptor antagonist mainly used in the management of hypertension, angina pectoris, myocardial infarction, and certain cardiac arrhythmias.

Mechanism of Action
Atenolol selectively blocks β_1-receptors located primarily in the heart. By inhibiting sympathetic stimulation:
Heart rate decreases
Cardiac output reduces
Blood pressure lowers
Myocardial oxygen demand decreases
Because it is β_1-selective, it has less effect on bronchial β_2-receptors compared to non-selective beta-blockers.

Pharmacokinetic Profile
Absorption: Incompletely absorbed from the gastrointestinal tract
Distribution: Limited penetration into the central nervous system
Metabolism: Minimal hepatic metabolism
Excretion: Mainly excreted unchanged in urine

CONCLUSION

Transdermal delivery of atenolol has shown considerable potential as an alternative approach for the long-term management of hypertension. Although the drug's hydrophilic nature and the barrier function of the stratum corneum present challenges, these limitations can be addressed through appropriate formulation strategies. The selection of suitable polymer combinations, optimized drug loading, and the use of permeation enhancers play a crucial role.

Overall, transdermal drug delivery systems offer clear advantages over conventional oral therapy, including avoidance of first-pass metabolism, maintenance of steady drug levels, and improved patient adherence. With ongoing advancements in formulation technology, physical enhancement methods, and carrier systems, transdermal patches are expected to broaden the therapeutic options for antihypertensive treatment. Continued research in this area may ultimately lead to clinically effective and patient friendly atenolol transdermal systems for blood pressure control.

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