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Transdermal Drug Delivery of an ACE Inhibitor (Fosinopril) by the Solution-Casting Technique: A Comprehensive Review of Formulation, Skin Permeation and Evaluation

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Abstract- ***Hypertension is among the foremost causes of cardiovascular morbidity and mortality worldwide, and angiotensin-converting enzyme (ACE) inhibitors are a mainstay of its long-term management. Conventional oral ACE-inhibitor therapy is nonetheless limited by hepatic first-pass metabolism, fluctuating plasma concentrations, frequent dosing and consequent lapses in patient adherence. The transdermal route offers an attractive alternative, delivering drug across the skin in a controlled, sustained fashion while bypassing first-pass metabolism and improving compliance. This review examines the rational design of a transdermal drug delivery system (TDDS) for the newer phosphinic ACE inhibitor fosinopril, fabricated as a matrix-type patch by the simple and widely used solution-(solvent-)casting technique. The structure of the skin and the mechanisms of percutaneous absorption are reviewed to frame the central barrier role of the stratum corneum, followed by the pharmacology of fosinopril—a lipophilic prodrug hydrolysed to the active diacid fosinoprilat—and the rationale for its transdermal delivery. The principal TDDS designs, the film-forming polymers (HPMC, PVA, ethyl cellulose and Eudragit), plasticizers and chemical permeation enhancers (DMSO, oleic acid and menthol) are surveyed, and the solution-casting process is described step by step. The complete evaluation framework—thickness, weight uniformity, folding endurance, tensile strength, drug content, moisture studies, in-vitro release and its kinetics, and ex-vivo permeation through excised skin in a Franz diffusion cell with determination of steady-state flux and lag time—is set out, with illustrative analytical data and current market context presented graphically. Polymer ratio, plasticizer level and permeation enhancers emerge as the key levers governing patch performance, and the solution-cast fosinopril matrix patch is shown to be a scientifically rational platform for sustained antihypertensive therapy.***

Keywords: Transdermal Drug Delivery, Fosinopril, ACE Inhibitor, Solution Casting, Matrix Patch; Permeation Enhancer, Franz Diffusion Cell; Stratum Corneum, Hypertension.

I. INTRODUCTION

The delivery of drugs across intact skin for systemic effect—transdermal drug delivery—has become one of the most actively developed areas of pharmaceutics since the introduction of the first transdermal scopolamine patch for motion sickness by the Alza Corporation, approved by the United States Food and Drug Administration in 1979. A transdermal drug delivery system (TDDS) is a discrete, self-contained dosage form that, when applied to the surface of healthy skin, delivers its drug through the skin and into the systemic circulation at a controlled rate. By providing a continuous input of drug over an extended period, a TDDS can maintain steady plasma concentrations, reduce dosing frequency, avoid the peaks and troughs associated with intermittent oral dosing, and—because absorption occurs across the skin rather than from the gastrointestinal tract—bypass hepatic first-pass metabolism altogether [72, 75].

These attributes are particularly valuable in the management of chronic conditions that demand long-

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term, reliable medication, of which hypertension is among the most important. Raised blood pressure is a leading cause of cardiovascular death and disability worldwide; in India alone it is estimated that more than two hundred million people are affected, and hypertension contributes substantially to deaths from coronary heart disease and stroke. Effective control depends on sustained, uninterrupted therapy, yet adherence to daily oral antihypertensive regimens is frequently poor. A transdermal system that delivers an antihypertensive agent steadily for twenty-four hours or more, while improving convenience and compliance, therefore addresses a genuine clinical need [105, 107].

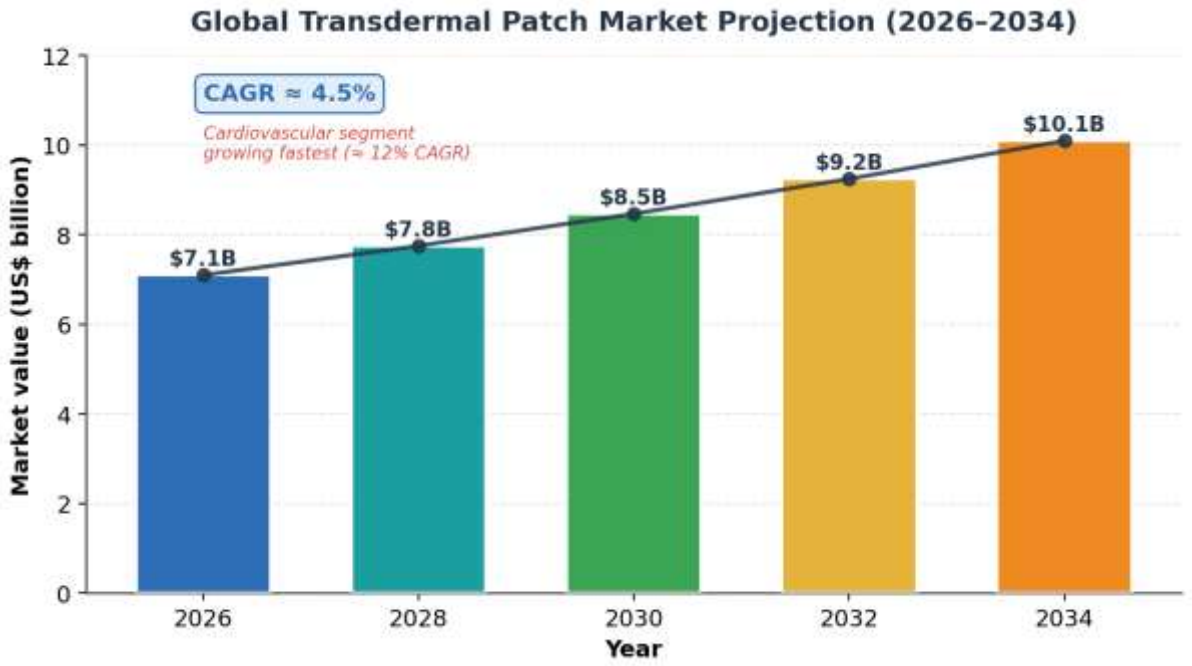

Figure 1. Projected growth of the global transdermal patch market, 2026–2034. While pain management currently dominates, the cardiovascular segment—including antihypertensive patches—is among the fastest-growing applications.

The commercial significance of transdermal delivery reflects this clinical demand. The global transdermal patch market was valued at roughly US$7.1 billion in 2026 and is projected to approach US$10 billion by 2034, expanding at a compound annual growth rate of about 4.5%; although pain management is currently the largest application segment, the cardiovascular segment—which includes antihypertensive systems such as clonidine and, prospectively, ACE-inhibitor patches—is among the fastest-growing, reflecting the strong fit between transdermal delivery and chronic cardiovascular therapy (Figure 1) [99, 100].

The scale of the underlying disease burden gives this fit particular weight. Hypertension is frequently asymptomatic yet, untreated, drives heart failure, stroke, myocardial infarction and chronic kidney disease, and its global prevalence continues to rise with ageing populations and changing lifestyles. ACE inhibitors are recommended first-line agents in many guidelines, but their benefit depends entirely on sustained, uninterrupted use over years or decades—a requirement poorly served by daily oral dosing, where forgetfulness, the asymptomatic nature of the disease and dosing-related plasma fluctuations all erode adherence. By replacing many tablets with a single patch worn for a day or longer and delivering drug at a steady rate, a transdermal antihypertensive system directly targets the principal practical failing of current therapy, which is why the cardiovascular application is regarded as one of the most promising frontiers for transdermal development.

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Among ACE inhibitors, fosinopril is an apt candidate for transdermal development. It is a newer, phosphinic-acid-containing prodrug whose conventional oral formulation, like that of other ACE inhibitors, is subject to first-pass metabolism and the compliance limitations of daily dosing. This review brings together the science underpinning the rational design of a fosinopril TDDS prepared by the solution-(solvent-)casting technique—the structure and barrier function of skin, the mechanisms of percutaneous absorption, the pharmacology of fosinopril, the principal patch designs and their components, the casting process itself, and the comprehensive battery of physicochemical and permeation tests by which such patches are evaluated—with illustrative analytical data presented throughout.

II. SKIN STRUCTURE AND PERCUTANEOUS ABSORPTION

Rational transdermal design begins with an understanding of the skin as both a target and a formidable barrier. The skin is the largest organ of the body and is organised into three principal layers: the epidermis, capped by the thin but highly impermeable stratum corneum; the viable epidermis beneath it; and the vascularised dermis, below which lies the subcutaneous tissue. The stratum corneum, composed of flattened, keratin-filled corneocytes embedded in a matrix of structured intercellular lipid bilayers in a "brick-and-mortar" arrangement, is the rate-limiting barrier to drug permeation and the principal obstacle that any transdermal system must overcome (Figure 2) [73, 77].

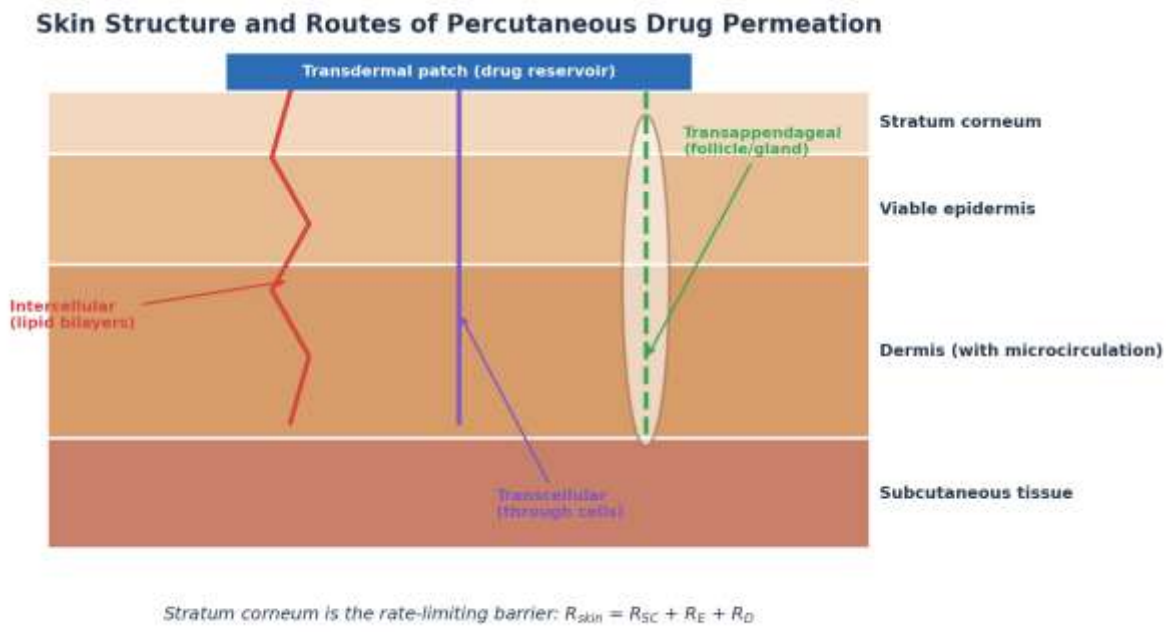

Figure 2. Skin structure and the three routes of percutaneous permeation—intercellular (between corneocytes, through the lipid bilayers), transcellular (through the cells) and transappendageal (via follicles and glands). The stratum corneum is the rate-limiting barrier.

Percutaneous absorption is a stepwise process comprising penetration of the drug into the stratum corneum, partitioning into and diffusion through the viable epidermis, and finally permeation into the dermal microcirculation for systemic distribution. Three routes are available: the intercellular route, in which molecules wind through the continuous lipid bilayers between corneocytes and which predominates for most small, lipophilic drugs; the transcellular route, directly through the corneocytes and intervening lipids; and the transappendageal route, via hair follicles and sweat glands, which offers a rapid but limited-area shunt pathway. The overall diffusional resistance of the skin, as defined by Chien, is the sum

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of the resistances of the stratum corneum, the viable epidermis and the dermis ($R_{skin} = R_sc + R_e + R_D$), of which the stratum corneum contributes by far the greatest share [77].

The rate and extent of permeation are governed by the physicochemical properties of the drug—its molecular weight, lipophilicity (partition coefficient), degree of ionisation and aqueous solubility—together with the properties of the vehicle and the condition of the skin, which varies with anatomical site, age, hydration and temperature. As a general guide, drugs best suited to passive transdermal delivery are potent (effective at low daily dose), of moderate molecular weight (broadly under 500 daltons) and of balanced lipophilicity. Because human skin is scarce, ex-vivo permeation studies commonly employ excised rodent skin, which is typically three to five times more permeable than human skin—a difference that must be borne in mind when interpreting results [75].

The combination of properties that makes a drug a good transdermal candidate is summarised in Table 1; fosinopril, being potent, lipophilic in its prodrug form and effective at low daily dose, satisfies most of these criteria.

Table 1. Ideal physicochemical properties of a candidate drug for passive transdermal delivery.

Property	Preferred value / character
Daily dose	Low (potent drug, ideally < 10–20 mg/day)
Molecular weight	Low to moderate (broadly < 500 Da)
Lipophilicity (log P)	Balanced (≈ 1–3); both lipid- and water-soluble
Melting point	Relatively low
Skin irritation / sensitisation	Absent or minimal
Half-life	Short-to-moderate oral half-life benefits most

III. FOSINOPRIL: PHARMACOLOGY AND RATIONALE FOR TRANSDERMAL DELIVERY

A. Drug Profile and Mechanism

Fosinopril is an angiotensin-converting enzyme (ACE) inhibitor that has been in clinical use for around three decades, marketed under trade names including Monopril and Staril; it was patented in 1980 and approved for medical use in 1991. It is distinguished from earlier ACE inhibitors such as captopril and enalapril by three features: it is the only phosphinic-acid (phosphonate)-containing ACE inhibitor in use, it has a comparatively long duration of action, and it possesses a balanced dual route of elimination. Fosinopril is administered as a lipophilic ester prodrug and is rapidly hydrolysed by esterases in the liver and intestinal wall to its active diacid metabolite, fosinoprilat (Figure 3) [81, 89].

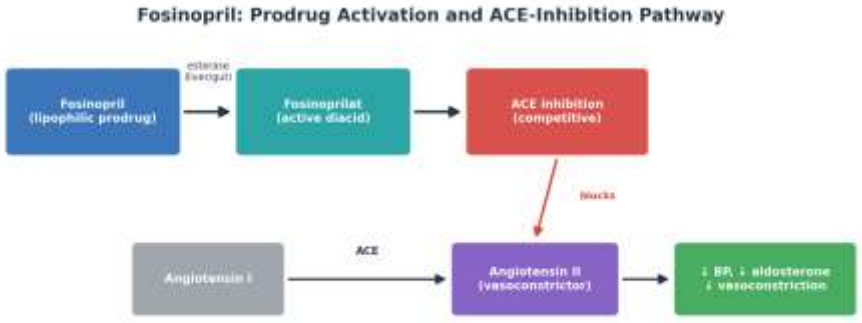

Figure 3. Fosinopril is a lipophilic prodrug hydrolysed by esterases to the active diacid fosinoprilat, which competitively inhibits ACE, blocking the conversion of angiotensin I to the vasoconstrictor angiotensin II and thereby lowering blood pressure.

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Fosinoprilat acts as a competitive inhibitor of ACE (kininase II), preventing the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. The resulting fall in angiotensin II reduces systemic vasoconstriction and aldosterone secretion, lowering blood pressure and, in heart failure, protecting the myocardium from the remodelling effects of angiotensin II. By interrupting the renin–angiotensin–aldosterone system, fosinopril is effective in hypertension, congestive heart failure and post-myocardial-infarction management, and is used off-label in diabetic and other nephropathies [85].

B. Pharmacokinetics and Rationale for a Patch

After oral administration the prodrug is converted to fosinoprilat, which reaches peak plasma concentrations within about three hours and has an effective accumulation half-life of approximately 11.5 to 12 hours. A distinctive and clinically useful feature is its balanced dual elimination: roughly half of the dose is cleared hepatobiliary and half renally, so that impairment of one route is partly compensated by the other, and dose adjustment is generally unnecessary in renal insufficiency. The hypotensive effect begins within about an hour of an oral dose and persists for twenty-four hours [83, 84].

Several of these properties make fosinopril a logical candidate for transdermal delivery. Like other ACE inhibitors it undergoes presystemic metabolism, and a transdermal route that bypasses first-pass conversion could improve the consistency of systemic exposure to the active species. Its lipophilic prodrug character favours partitioning into and permeation across the lipid-rich stratum corneum, and its long intrinsic half-life is well matched to the sustained, once-daily (or longer) delivery that a patch provides. A transdermal system would also smooth the plasma-concentration profile and remove the need for daily tablet-taking, directly addressing the adherence problem that undermines long-term antihypertensive therapy. These considerations underpin the formulation of a fosinopril matrix patch by solution casting, the subject of the remainder of this review.

IV. TRANSDERMAL SYSTEMS: DESIGNS AND COMPONENTS

A. Principal Patch Designs

Transdermal systems are conventionally classified by their architecture into several principal designs (Figure 4). In the single-layer drug-in-adhesive system, the drug is dissolved or dispersed directly within the skin-contacting adhesive, which serves simultaneously as the drug matrix and the means of adhesion; release is governed by diffusion through the adhesive and skin. The multi-layer drug-in-adhesive system is similar but incorporates two or more drug-containing adhesive layers, sometimes separated by a membrane, allowing an initial and a sustained release phase. In the reservoir system the drug is held as a solution or suspension in a discrete reservoir separated from the skin by a rate-controlling membrane that governs the delivery rate. In the matrix (monolithic) system—the design most relevant to the present review—the drug is uniformly dispersed within a semisolid polymeric matrix, with an adhesive applied around the periphery; release is controlled by diffusion from, and the properties of, the polymer matrix [100, 103].

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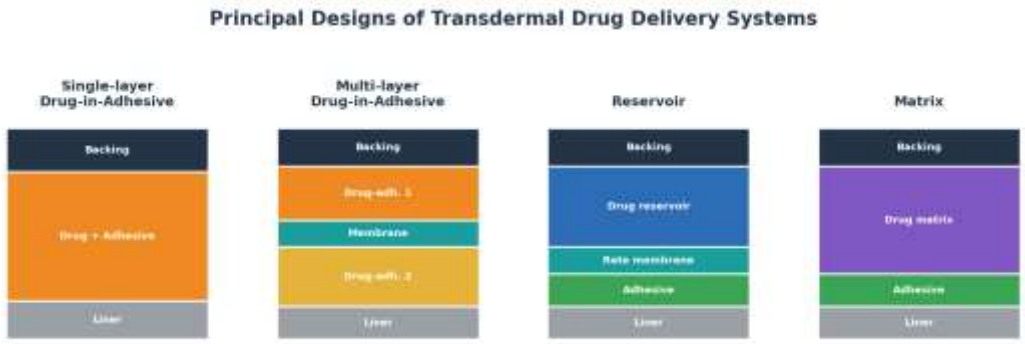

Figure 4. The principal designs of transdermal drug delivery systems: single- and multi-layer drug-in-adhesive, reservoir and matrix. The matrix design, in which drug is dispersed in a polymer film, is typical of solution-cast patches.

Every patch, whatever its design, shares a common set of components: a backing layer that provides occlusion and mechanical and environmental protection; the drug-containing polymer matrix or reservoir; in many designs a rate-controlling membrane; an adhesive to secure the patch to the skin; and a release liner that protects the patch until use and is removed before application. The polymer is the heart of the system, since its molecular weight, glass-transition temperature and chemical functionality determine whether the drug is released and diffuses at the intended rate.

B. Polymers, Plasticizers and Permeation Enhancers

The film-forming polymers used in matrix patches are chosen, often in combination, to balance release rate against mechanical strength. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) hydrate readily and promote faster release, whereas hydrophobic polymers such as ethyl cellulose (EC) and the Eudragit (polymethacrylate) series retard release and confer sustained delivery; blending the two allows the release profile to be tuned, and HPMC–EC matrices are a common and effective choice [91]. Plasticizers—glycerin, propylene glycol and polyethylene glycol (PEG 400)—are incorporated at modest levels to lower the glass-transition temperature of the polymer film and impart the flexibility needed to prevent cracking and to maintain conformability and folding endurance.

Because the stratum corneum so strongly limits permeation, chemical permeation enhancers are frequently included to increase flux. These agents act by reversibly disrupting or fluidising the ordered intercellular lipids of the stratum corneum, by increasing its hydration, or by enhancing the partitioning of drug into the barrier. Commonly used enhancers include dimethyl sulfoxide (DMSO), the unsaturated fatty acid oleic acid, and the terpene menthol, each at low concentration; the choice and level of enhancer are optimised against the need to avoid skin irritation. Suitable volatile solvents—ethanol, methanol or hydroalcoholic mixtures—are used to dissolve the polymers and drug for casting, and additional excipients such as antioxidants or preservatives may be included as required [76].

The principal components of a matrix-type fosinopril patch and their functions are summarised in Table 2.

Table 2. Principal components of a matrix-type transdermal patch and their functions.

Component	Examples	Function
Drug (API)	Fosinopril	Therapeutic agent delivered across skin
Film-forming polymers	HPMC, PVA, ethyl cellulose, Eudragit	Form matrix; control release rate
Plasticizers	Glycerin, propylene glycol, PEG 400	Impart flexibility; prevent cracking

Component	Examples	Function
Permeation enhancers	DMSO, oleic acid, menthol	Increase skin permeation / flux
Solvents	Ethanol, methanol, water mix	Dissolve polymers and drug for casting
Backing / liner	Aluminium foil, polyethylene	Protection; removed before use

V. THE SOLUTION-CASTING TECHNIQUE

The solution-casting (solvent-casting or solvent-evaporation) technique is the simplest, most economical and most widely used laboratory method for fabricating matrix-type transdermal patches, and it is the method specified for the present fosinopril system. The process is hydrous or hydroalcoholic and is well suited to a range of drugs and polymers, offering good control over film thickness, drug content and uniformity.

In a representative procedure, the selected film-forming polymer or polymer blend is dissolved in a suitable solvent under continuous stirring until a clear, homogeneous solution is obtained, and the plasticizer is incorporated to confer flexibility. The drug—fosinopril—is accurately weighed, dissolved in a minimal volume of solvent, and added slowly to the polymer solution under constant stirring to ensure uniform distribution; the chosen permeation enhancer is then incorporated. The resulting drug–polymer solution is de-aerated to remove entrapped air bubbles and poured into a mould or onto an inert casting surface such as a glass petri dish or a mercury substrate, and spread to a uniform thickness. The cast solution is dried—at room temperature or in a hot-air oven at a controlled temperature, typically 40 to 50 °C—until the solvent has evaporated and a coherent film has formed. The dried patch is carefully peeled from the mould, cut to the required area, backed and packaged, and stored in airtight conditions to prevent moisture uptake. By varying the polymer composition, plasticizer level and enhancer, a family of formulations can be prepared and screened to identify the optimum [90, 91]. The simplicity, reproducibility and low cost of solution casting account for its dominance in transdermal research.

Although solution casting predominates in laboratory development, it is worth situating it among the alternative fabrication routes. Hot-melt extrusion is a solvent-free, continuous process in which drug and polymer are melted and shaped, attractive for thermostable drugs and scalable manufacture but unsuitable for thermolabile actives. Other approaches include the asymmetric-membrane and reservoir-membrane techniques used for reservoir patches, hot-melt and pressure-sensitive-adhesive coating for drug-in-adhesive systems, and emerging printing-based methods that promise on-demand, personalised dosing. Against these, solution casting offers unrivalled simplicity and minimal equipment, excellent control over thickness and drug loading at small scale, and gentle, ambient or mildly heated processing that protects sensitive drugs and permeation enhancers—advantages that make it the natural choice for the early-stage development of a fosinopril matrix patch, even though a transition to a continuous, solvent-managed process would be required for commercial manufacture.

VI. EVALUATION OF TRANSDERMAL PATCHES

A comprehensive set of physicochemical, mechanical and biopharmaceutical tests is applied to characterise transdermal patches and to confirm that they meet the required quality and performance specifications.

A. Physical and Mechanical Properties

Thickness is measured at several points across each patch with a micrometer or digital calliper to confirm uniformity, since it bears directly on dose accuracy. Weight uniformity is assessed by individually weighing a sample of patches of defined area. Folding endurance, determined by repeatedly folding a strip at the same point until it breaks (or to a defined maximum), indexes the flexibility and handling robustness conferred by the plasticizer. Tensile strength and percentage elongation at break, measured with a tensiometer or texture analyser, quantify the mechanical strength and extensibility of the film. Moisture content and moisture uptake are determined to predict physical stability and to guide packaging, and surface pH is checked to ensure skin compatibility. As Figure 5 illustrates, increasing the plasticizer concentration generally raises folding

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endurance and elongation while reducing tensile strength, giving the formulator a direct means of balancing flexibility against rigidity [92, 96, 98].

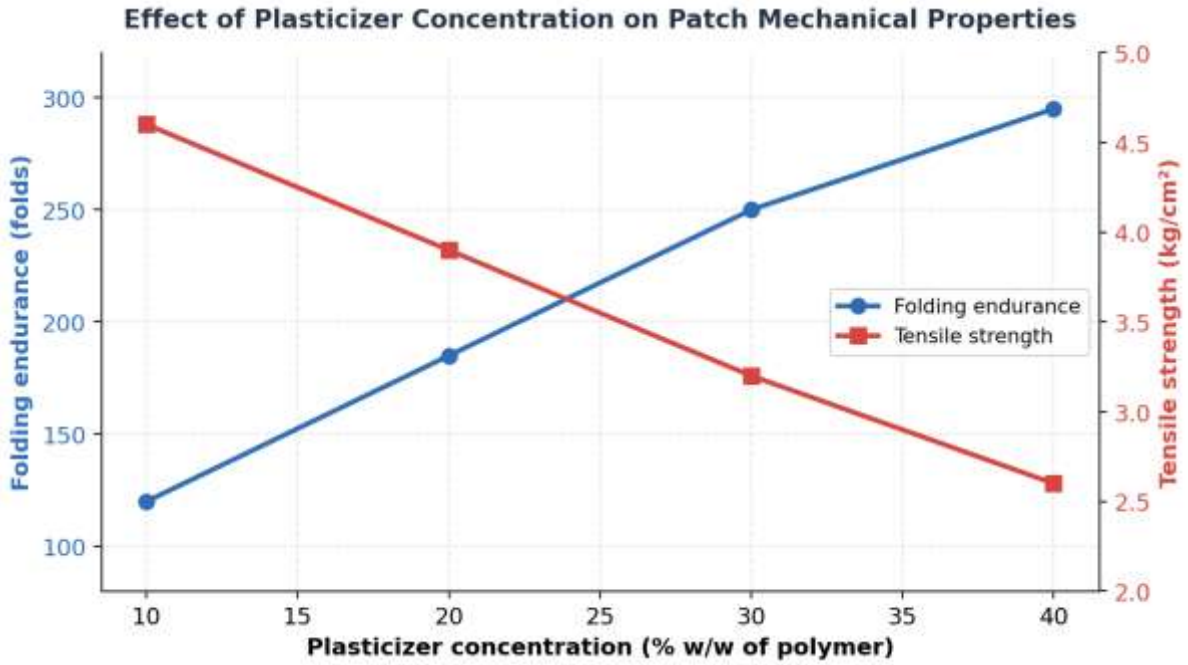

Figure 5. Illustrative effect of plasticizer concentration on patch mechanical properties: folding endurance rises while tensile strength falls as plasticizer content increases, reflecting the softening of the polymer film.

Two further physical tests merit mention. The water-vapour-transmission rate, measured by sealing the patch over a desiccant- or water-filled cell and recording mass change over time, characterises the occlusivity of the film and its likely effect on skin hydration, which in turn influences permeation. Percentage moisture uptake and moisture loss, determined by equilibrating weighed patches at defined humidities, indicate the hygroscopicity of the matrix: a small, controlled uptake keeps the film flexible and resists microbial growth, whereas excessive uptake risks bulkiness and instability and too little may leave the film brittle. Together with thickness, weight and folding endurance, these parameters define the physical quality of the patch and are reported for every formulation in a development series so that the influence of polymer and plasticizer can be tracked systematically [21, 27].

B. Drug Content and In-Vitro Release

Drug content uniformity is verified by dissolving a patch of known area and assaying the drug by validated ultraviolet spectrophotometry or high-performance liquid chromatography, confirming that each unit contains the intended dose within acceptable limits. In-vitro drug release is then studied, commonly using a Franz diffusion cell or a paddle-over-disc apparatus with a synthetic membrane, in phosphate-buffered saline at pH 7.4 and 37 °C, with samples withdrawn at intervals and assayed. The release profile is strongly governed by the polymer composition: hydrophilic-polymer-rich matrices release rapidly, whereas hydrophobic-polymer-rich matrices give slow, sustained release, and an intermediate blend can be tuned to deliver drug steadily over twenty-four hours (Figure 6) [91, 96].

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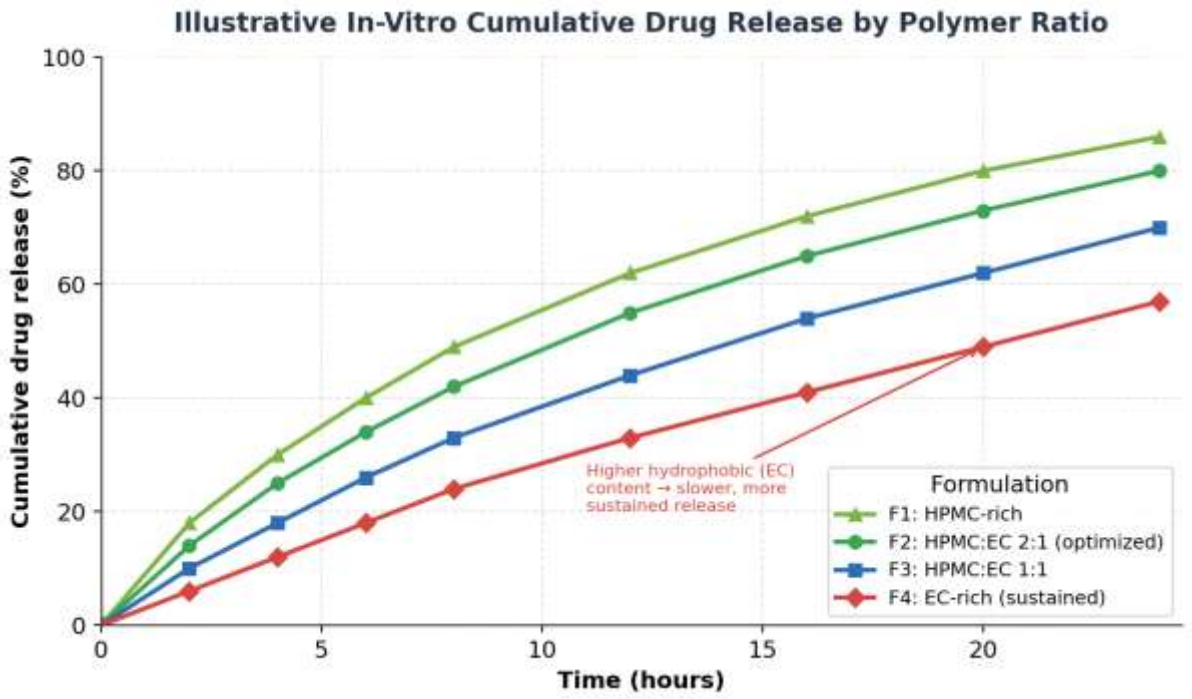

Figure 6. Illustrative in-vitro cumulative release profiles for matrix patches of differing HPMC:ethyl-cellulose ratio. Higher hydrophobic (ethyl cellulose) content slows release and extends it toward a sustained 24-hour profile.

The release data are routinely fitted to kinetic models—zero-order, first-order, the Higuchi diffusion model and the Korsmeyer–Peppas power-law model—to elucidate the release mechanism. Matrix transdermal films very commonly follow Higuchi (diffusion-controlled) kinetics, and the Korsmeyer–Peppas release exponent distinguishes Fickian diffusion from anomalous (non-Fickian) transport, providing a rigorous, comparative description of how formulation variables reshape the release profile.

C. Ex-Vivo Permeation, Flux and Lag Time

The most biopharmaceutically informative evaluation is the ex-vivo skin permeation study, conducted in a Franz diffusion cell using excised skin (commonly rat abdominal skin) mounted between the donor and receptor compartments (Figure 7). The receptor compartment, holding several millilitres of phosphate buffer at 37 °C, is continuously stirred, and the cumulative amount of drug permeating per unit area is measured against time. From the linear, steady-state portion of this plot two key parameters are derived: the steady-state flux (J_{ss}), the slope, expressing the rate of permeation per unit area; and the lag time, the intercept on the time axis, reflecting the time taken to saturate the skin barrier and establish steady-state diffusion. The permeability coefficient is obtained by normalising the flux to the donor drug concentration [90, 94].

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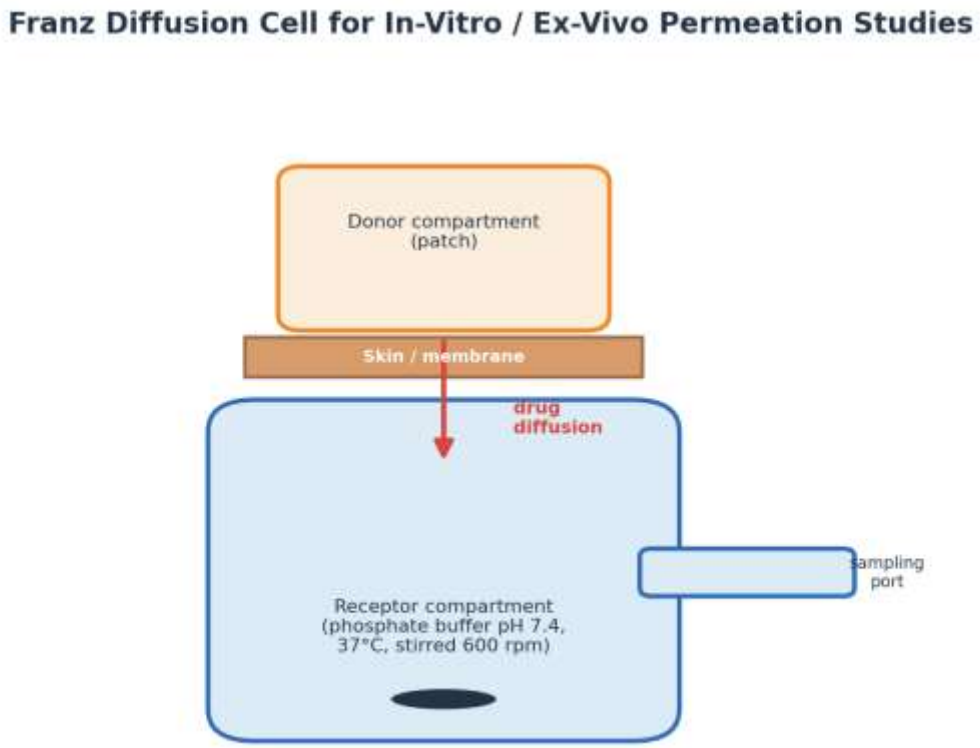

Figure 7. The Franz diffusion cell used for in-vitro and ex-vivo permeation studies. Drug permeates from the patch in the donor compartment, across the skin or membrane, into the stirred, thermostated receptor compartment, from which samples are withdrawn through the sampling port.

These permeation studies are the principal means of demonstrating the value of a permeation enhancer. By comparing flux with and without enhancer, the enhancement ratio can be quantified; incorporation of agents such as oleic acid, DMSO or menthol typically increases the steady-state flux of an ACE inhibitor severalfold by fluidising the stratum-corneum lipids, with the effect generally increasing with enhancer concentration up to a practical limit set by skin tolerability (Figure 8) [76, 92]. Optimising the enhancer is therefore central to achieving a therapeutically adequate flux from a fosinopril patch.

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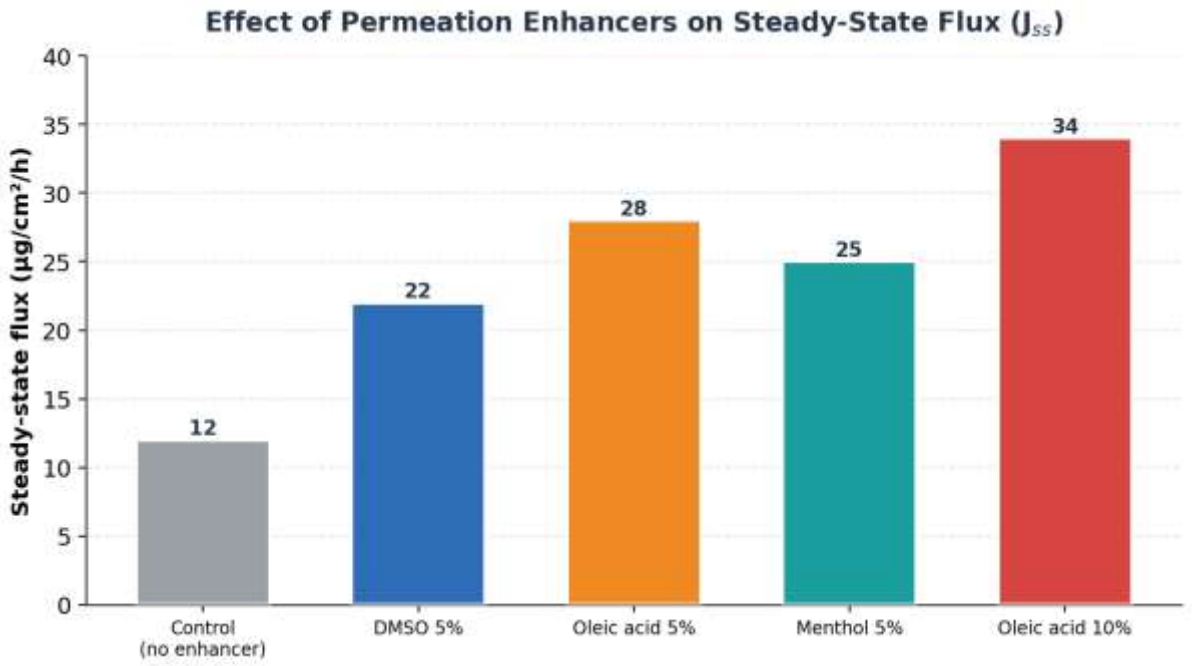

Figure 8. Illustrative effect of permeation enhancers on the steady-state flux of an ACE inhibitor across excised skin. Enhancers such as oleic acid, DMSO and menthol increase flux relative to the unenhanced control, the effect rising with concentration.

D. Stability Studies

Finally, the optimised patch is subjected to stability testing under International Council for Harmonisation (ICH) conditions—typically 40 ± 2 °C and 75 ± 5% relative humidity over a defined period—with periodic assessment of appearance, drug content, mechanical properties and release behaviour to establish the chemical stability of the drug in the formulation and the shelf life of the product. Such studies are an essential prerequisite to any subsequent in-vivo or clinical evaluation.

VII. RECENT ADVANCES IN TRANSDERMAL DELIVERY OF ACE INHIBITORS

A substantial body of work has established the feasibility of delivering ACE inhibitors transdermally by solution casting, providing valuable precedent for a fosinopril system. Several authors have prepared captopril films by solvent casting using HPMC E15 with Eudragit RS100 and plasticizers, incorporating enhancers such as DMSO, dimethylformamide and oleic acid, and have reported uniform films with satisfactory mechanical strength and sustained release for up to twenty-four hours; statistical optimisation of polymer ratios has been used to control the time for ninety percent release and the cumulative release [1, 6]. Enalapril maleate has been formulated with HPMC and ethyl cellulose, individually and in combination, the optimised batch showing excellent uniformity and sustained release with minimal burst, and separately with natural rosin and PVP, where Higuchi diffusion was the predominant release mechanism [2, 10].

Other ACE inhibitors have been delivered similarly. Ramipril matrix patches prepared with HPMC and ethyl cellulose, or with Eudragit RL and RS blends, have given controlled release over twenty-four hours with release best fitting the Higuchi model, demonstrating the value of polymeric blends in tailoring the rate [4, 5]. Trandolapril, which suffers from poor oral bioavailability owing to extensive first-pass metabolism, has been delivered both as solvent-cast Eudragit/HPMC matrix patches and, more recently, by embedding nanostructured lipid carriers within cast films to enhance solubility and sustain release [3, 9]. Perindopril, another low-bioavailability ACE inhibitor, has likewise been formulated into extended-release transdermal films [7]. A comprehensive review by Helal and colleagues drew

these threads together, emphasising solvent casting as the dominant fabrication route for matrix films of captopril, enalapril, lisinopril, perindopril and trandolapril, while highlighting the persistent challenges of poor skin permeation and variability and the need for clinical evaluation [8]. Representative studies are summarised in Table 3.

Table 3. Representative studies on solvent-cast transdermal patches of ACE inhibitors.

ACE inhibitor	Polymers / approach	Key outcome
Captopril	HPMC E15 + Eudragit RS100	Sustained release ≈ 24 h; DoE-optimised
Enalapril maleate	HPMC + ethyl cellulose; rosin + PVP	Uniform films; Higuchi diffusion release
Ramipril	HPMC + EC; Eudragit RL/RS	Controlled 24 h release; Higuchi model
Trandolapril	Eudragit/HPMC; NLC-loaded films	Sustained release; improved solubility
Perindopril	Polymeric matrix films	Extended release; low-bioavailability drug

This precedent strongly supports the rationale for a fosinopril patch: the drug shares the low oral bioavailability and chronic-use profile of these ACE inhibitors, and the solvent-casting matrix approach—with an optimised HPMC–ethyl-cellulose blend, a suitable plasticizer and a permeation enhancer—has been repeatedly validated for the class. Fosinopril's lipophilic prodrug character and long half-life may, if anything, make it a more favourable transdermal candidate than several of its predecessors.

VIII. ADVANTAGES, LIMITATIONS AND COMPARATIVE PERSPECTIVE

The transdermal route offers a distinctive constellation of advantages over conventional oral therapy, summarised comparatively in Figure 9. It provides a consistent, sustained input of drug that maintains steady plasma concentrations and prolongs the duration of action; it avoids hepatic first-pass metabolism, potentially improving the bioavailability of the active species; it reduces dosing frequency and so enhances patient adherence, an advantage of particular weight in chronic conditions such as hypertension; it permits easy termination of therapy simply by removing the patch; and it is non-invasive and amenable to self-administration. These benefits are especially pertinent to long-term antihypertensive treatment with a drug such as fosinopril [72, 75].

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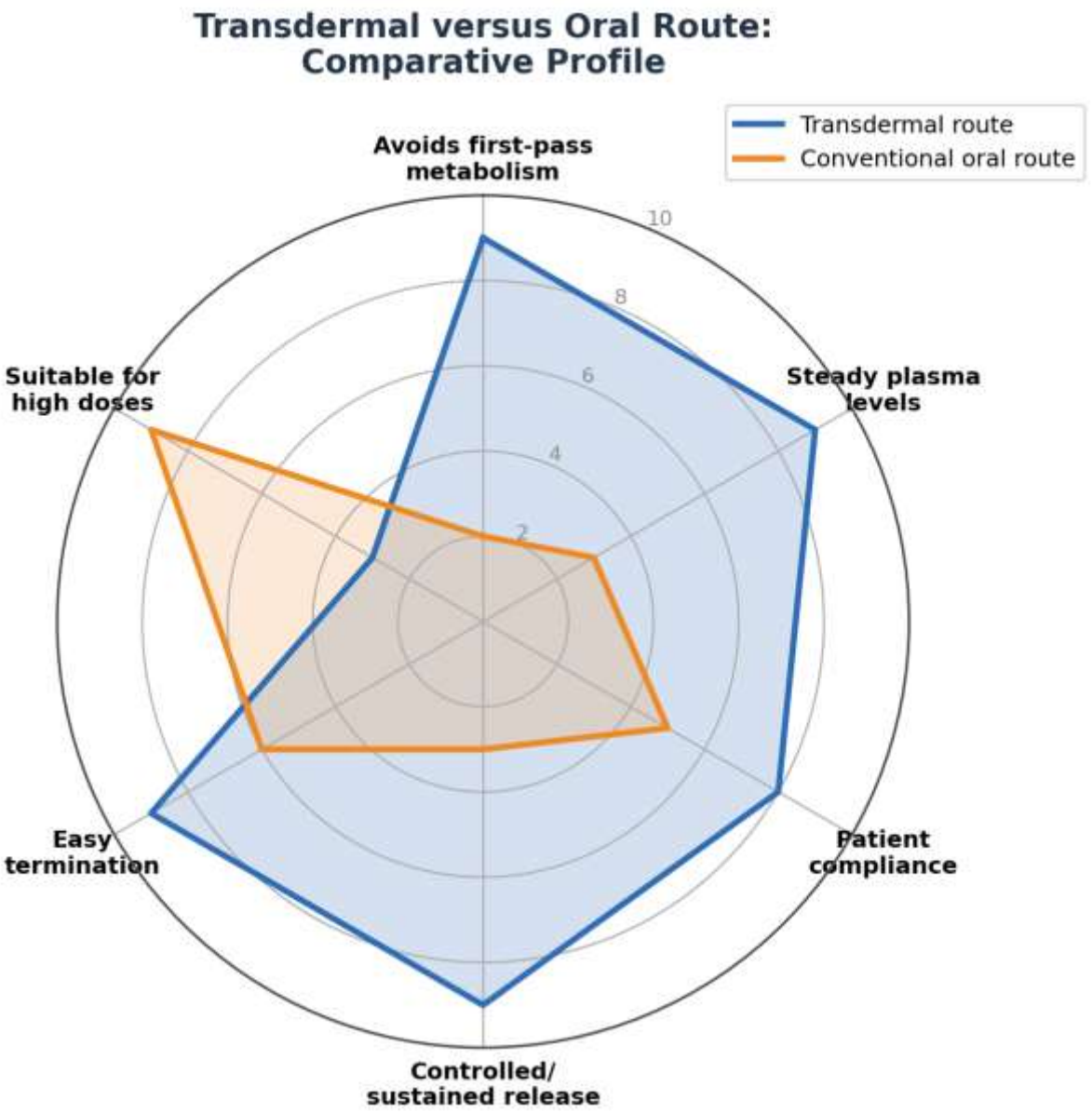

Figure 9. Comparative profile of the transdermal and conventional oral routes. The transdermal route excels in avoiding first-pass metabolism, maintaining steady plasma levels and supporting compliance, but is unsuited to high-dose drugs.

These advantages are balanced by real limitations. Transdermal delivery is feasible only for relatively potent drugs effective at low daily dose, because the skin restricts the total mass that can be delivered; high-dose drugs are therefore unsuitable. The drug must possess appropriate physicochemical properties—adequate lipophilicity, moderate molecular weight and sufficient potency—and the stratum corneum imposes wide inter-individual and site-to-site variability in permeation. Drugs, enhancers and adhesives may provoke skin irritation or sensitisation in some patients, and extensive in-vitro, ex-vivo and ultimately clinical evaluation is required before a product can be marketed. The barrier function of skin also varies with age and anatomical site. A clear appreciation of this benefit–limitation balance is essential to the rational selection of both the drug and the formulation [73].

IX. CHALLENGES AND FUTURE PERSPECTIVES

Several challenges shape ongoing research on transdermal ACE-inhibitor delivery. The foremost is the barrier function of the stratum corneum, which limits the flux achievable for many drugs; while chemical permeation enhancers and polymer-blend optimisation can substantially improve permeation, achieving a therapeutically adequate and reproducible flux remains demanding. The wide variability of skin permeability between individuals and body sites complicates dose prediction, and the reliance on animal skin models, which over-estimate human permeability, limits the direct translation of ex-vivo results. Maintaining the chemical stability of a prodrug such as fosinopril within a thin, high-surface-area film, and ensuring uniform drug distribution and reproducible casting at scale, are further practical hurdles.

The trajectory of the field is nonetheless encouraging. Physical enhancement technologies—microneedles, iontophoresis, sonophoresis and related approaches—are extending transdermal delivery to drugs and doses previously considered unsuitable, and microneedle systems in particular are among the fastest-growing segments of the market. The incorporation of nanocarriers such as nanostructured lipid carriers and vesicular systems into cast films offers a route to improved solubilisation and controlled release, as demonstrated for related ACE inhibitors. Design-of-experiments methodologies and Quality-by-Design principles are bringing rigour to the optimisation of polymer ratio, plasticizer and enhancer levels, while "smart" patches with integrated monitoring point toward more personalised therapy. For a fosinopril patch specifically, the logical next steps are systematic optimisation of the polymer–enhancer combination to maximise flux, confirmation of stability, and progression from the in-vitro and ex-vivo evidence reviewed here to in-vivo pharmacokinetic and clinical studies [76].

It is also worth emphasising the regulatory and translational dimension. A transdermal product is regulated as a drug–device combination, and its development must address not only flux and stability but also adhesion over the wear period, skin tolerability and the absence of dose dumping, supported by a robust in-vitro–in-vivo correlation. The gap between the high permeability of the rodent skin used in early screening and the lower permeability of human skin means that promising ex-vivo flux values must be confirmed in human studies before therapeutic adequacy can be claimed. For an antihypertensive intended for lifelong use, demonstrating consistent day-to-day delivery and reliable adhesion is as important as the average flux, since erratic delivery could destabilise blood-pressure control. These considerations do not diminish the promise of a solution-cast fosinopril patch, but they define the evidence that must be assembled to carry it from the laboratory bench toward the clinic.

X. CONCLUSION

Transdermal drug delivery offers a compelling, patient-centred alternative to oral therapy for the long-term management of hypertension, providing sustained and controlled drug input, steady plasma concentrations, avoidance of first-pass metabolism and markedly improved compliance. Fosinopril, a newer phosphinic ACE-inhibitor prodrug with a long half-life, balanced dual elimination and lipophilic character well suited to skin permeation, is a rational candidate for such delivery. Fabricated as a matrix-type patch by the simple, economical and widely used solution-casting technique, a fosinopril transdermal system can be engineered through the judicious selection of film-forming polymers—balancing hydrophilic HPMC or PVA against hydrophobic ethyl cellulose or Eudragit—together with appropriate plasticizers and chemical permeation enhancers such as oleic acid, DMSO or menthol to overcome the formidable barrier of the stratum corneum. The comprehensive evaluation framework reviewed here—encompassing thickness, weight uniformity, folding endurance, tensile strength, drug content, moisture studies, in-vitro release and its kinetics, and ex-vivo permeation in a Franz diffusion cell with determination of steady-state flux and lag time—enables rational optimisation and provides the preliminary evidence of performance. Drawing together the structure and barrier function of skin, the pharmacology of fosinopril, the principles of patch design and the solution-casting process, this review establishes the solution-cast fosinopril matrix patch as

a scientifically sound platform for sustained antihypertensive therapy and a firm foundation for the in-vivo and clinical studies that should follow.

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