



Advancements in nanocarrier-based transdermal estrogen delivery with patents and clinical outcomes

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ABSTRACT

Hormone replacement therapy (HRT) remains the cornerstone for alleviating symptoms associated with menopause by replenishing declining estrogen levels. The primary goal of HRT is to restore estrogen levels, which naturally decline after menopause. The skin provides a convenient and noninvasive route for administering medications, making transdermal drug delivery an area of ongoing research and innovation. Recent advancements have focused on vesicular drug delivery systems such as liposomes, niosomes, and transferosomes, which enhance skin permeability and enable controlled estrogen release. These novel nanocarriers have shown promise in improving the transdermal delivery of drugs with enhancement in skin permeability, offering more accurate dosing and reduced side effects compared to conventional estrogen therapies. This review critically evaluates the transdermal estrogen therapy using nanocarriers, alongside recent patents and clinical trials, to highlight current progress and future directions.

1. INTRODUCTION

Hormone replacement therapy (HRT) is the administration of exogenous hormones to offset the hormonal deficiencies experienced during the menopausal transition [1]. Menopause, a natural physiological event generally occurring at an average age of 51, is defined clinically as the cessation of menstruation for 12 consecutive months [2,3]. This period is characterized by prominent fluctuations in the hormones, with several women experiencing symptoms such as vasomotor disturbances (night sweats and hot flashes), sleep disruptions, genitourinary changes, and mood swings [3]. Estrogen is hypothesized to play a pivotal role in modulating the thermoregulatory zone (TRZ) width within the hypothalamus. Estrogen deficiency may cause TRZ narrowing, making minor changes in the body temperature and eventually leading to vasomotor symptoms [3,4]. HRT is widely regarded as the gold standard for managing vaginal symptoms and menopausal

vasomotor symptoms [5]. The therapy typically includes estrogen, which improves these symptoms. For women with an intact uterus, a progestogen is added to the treatment regimen to protect the endometrium. The estrogen component of HRT can be delivered in various forms, including Estradiol 17 β , estrone, conjugated equine estrogen, or estradiol. Depending on the individual's needs, progestogen can be administered either in a cyclic (sequential) or a daily regimen [2]. HRT provides advantages for the treatment of menopausal symptoms, hypogonadism, and osteoporosis.

A recent study in 2023 developed estradiol-loaded solid lipid nanoparticles that were coated with the mucoadhesive polymer chitosan to form hybrid nanogels for vaginal delivery. The nanogels displayed particle sizes between 420 and 850 nm and drug entrapment efficiencies of 50%–83%. The chitosan coating imparted mucoadhesion, thermal gelling, and sustained-release properties, demonstrating release rates that were up to 4.4 times faster than control estradiol suspension. *Ex vivo* permeation studies indicated that estradiol permeation through vaginal mucosa was up to 2.2-fold enhanced. Tolerability of the system was acceptable and, at most, caused mild to moderate irritation, indicative of potential novel localized estrogen delivery for improved permeability and retention [6].

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Recent advances from 2024 to 2025 featured hybrid nanocarriers that combine liposomes with polymeric nanocarriers to generate stimuli-responsive hybrid systems for transdermal patches. Hybrid nanoparticles take all the biocompatibility and sustained release of liposomes while generating the mechanical strengths and controlled release of polymers. The hybrid platforms that utilize sustained, controlled hormone release should improve bioavailability and patient compliance compared to current conventional patches. In addition, smart patches have surface modifications guided by artificial intelligence (AI) to improve skin penetration and expand the patch response systems to stimulate hormone release profiles based on physiological stimuli (e.g., a change in pH or temperature). Such applications show promise to improve the efficacy and versatility of transdermal estrogen therapy that will be responsive and personalized delivery [7].

In early 2025, a multicenter phase II clinical trial evaluated a hybrid lipid-polymer nanocarrier-based estradiol patch using computer-aided design to promote sustained release. The estradiol patch formulation comprised PEGylated liposomes embedded in a film of biocompatible polymer, with the intention of increasing skin penetration and reducing fluctuations in hormonal levels. In clinical outcomes of 120 postmenopausal individuals, there was a 54% reduction in vasomotor symptoms in less than 6 weeks, sustained levels of serum estradiol (35–45 pg/ml), and a significant reduction in follicle-stimulating hormone (FSH) (42%). There were no thromboembolic or dermatologic events, highlighting improved safety and adherence to the estradiol patch [8].

In 2025, a randomized controlled trial compared transdermal estrogen as a novel nanocarrier plus micronized progesterone (P4) against standard oral treatment in perimenopausal women. The transdermal patch, based on new patented nanotechnology, produced better clinical outcomes overall: 82.3% of the treatment group had a reduction in vasomotor symptoms compared with 76.5% of women who had a reduction with oral conjugated estrogen/medroxyprogesterone acetate therapies. The trial also reported improvements in metabolic outcomes and predictors of treatment response with baseline levels of FSH and genetic polymorphisms identified as important features in this treatment response. Importantly, there were no major adverse events identified in this trial position, which makes the nanocarrier patch ideal for the resolution of symptoms and for risk reduction implications [9].

2. TRANSDERMAL DELIVERY OF ESTROGEN

Human estrogens include estrone, 17 β -estradiol, estriol, and estretol. Estrone and 17 β -estradiol are produced in the ovaries, while estriol and estretol are produced during pregnancy by the placenta. 17 β -estradiol exhibits the most significant binding affinity towards estrogen receptors out of these endogenous estrogens. 17 β -estradiol represents one of the most vital estrogens, which is primarily secreted by the ovaries and being circulating naturally in females [3,10]. It plays a major role in hormone-dependent breast carcinoma and is potent at the estrogen receptor compared to estrone or estriol. During menopause, secretion of estrogen from the ovaries depletes, but local and peripheral androgen tissue aromatization

to estrogens continues, thereby providing a major estradiol source [11]. Estradiol is often used clinically to supplement the lack of estrogen and to treat different disease conditions like bilateral oophorectomy, vulvar dryness, metastatic breast cancer, atrophic vaginitis, advanced androgen-dependent prostate cancer, osteoporosis, type 2 diabetes, endometriosis, cardiovascular, neurodegenerative diseases, and menopausal syndrome [12–16].

2.1. Case studies on nanocarrier-based estrogen delivery

The following section explores the different case studies related to estrogen delivery through topical/transdermal routes, with a focus on research involving nanocarriers for transdermal drug delivery (Fig. 1).

Tang et al. developed and formulated a Microemulsion (ME) entrapped long-acting Microneedle (MN) system for transdermal delivery of lipophilic drugs using Estradiol (Es) as a model drug. The formulation and optimization of Es-loaded ME were carried out using the D-optimal design, and the resulting Es-ME-MN loaded system was further fabricated using the freeze-thaw cycle method and optimized by Box-Behnken design. *In vitro* drug release studies showed that the conventional microneedles released the drug within 72 hours, while the Es-ME-MN drug release occurred over 192 hours. Methylene blue staining confirmed that Es-ME-MN effectively permeated the cuticle and epidermis in the skin, forming cone-shaped microporous channels. The Es-ME-MN achieved 95.29% drug penetration with drug residue ($4.71\% \pm 3.71\%$), higher than commercial patch ($25.26\% \pm 1.71\%$) and conventional microneedles ($14.28\% \pm 5.18\%$). Additionally, the Es-ME-MN caused no irritation with recovery of the skin within 8 hours post-application. The *in vivo* drug release pattern of Es in the group of Es-ME-MN was 2.47 and 3.65 times greater than the Es commercial patch at 6hrs and conventional MN at 12 hours, respectively [17].

3. PATENTS ON ESTRADIOL DELIVERY USING TRANSDERMAL ROUTE

The filed patents delve into enhancing the treatment efficacy, delivery method, and patient compliance, covering the advancements for transdermal estradiol delivery (Table 1). Kulakofsky and Liano [18] studied that for maintaining a stable matrix of polymer with drug solubility, the acrylic polymers with hydroxy groups, mainly vinyl acetate, are helpful to overcome the challenges associated with levonorgestrel, such as low solubility and low permeability in pressure-sensitive adhesives. The enhancers such as Glyceryl Monooleate, Dipropylene Glycol, Isopropyl Myristate, and Diethylene Glycol Monoethyl Ether (Transcutol®) were found to be effective, particularly in various combinations or alone. The addition of humectants like crospovidone and polyvinyl pyrrolidone was found to suppress the crystallization of levonorgestrel and improve adhesion properties. Additionally, an adhesive layer containing silicone face can enhance both adhesion and physical properties without affecting the flux of the drug. Thus, the study encompassed a transdermal delivery system with effective delivery of therapeutically active ethinyl estradiol and levonorgestrel amounts for at least 3–4 days.

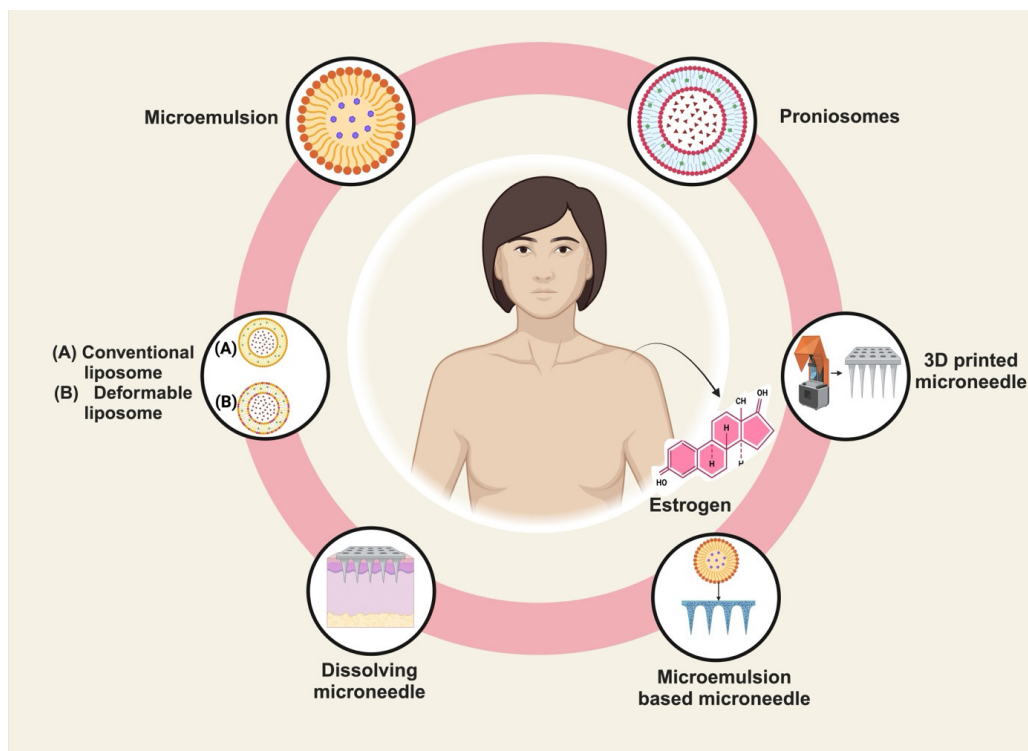


Figure 1. Nanocarriers-based transdermal delivery of estrogen.

Table 1. Patents on estradiol on transdermal delivery.

Patent number	Patent title	Applicant	Assignees	Technological/clinical impact Summary
W02017004507A1	Ethinyl estradiol and Levonorgestrel transdermal delivery systems	Noven Pharmaceuticals, Inc	Brinckerhoff, Courtenay [18]	Focuses on combined hormonal contraceptive delivery via transdermal route, potentially improving compliance and steady dosing.
US9682087B2	Transdermal gel of NESTORONE®/Estradiol	-	The Population Council, Inc; Antares Pharma IPL AG [19]	Introduces gel formulation facilitating HRT with possibly enhanced skin permeation and convenience.
US9248136B2	Transdermal therapies for hormone replacement	TherapeuticsMD, Inc.	TherapeuticsMD, Inc. [20]	Covers HRT options via transdermal systems likely targeting postmenopausal symptoms with controlled release.
US9526736B2	norelgestromin-based transdermal therapeutic system for HRT and contraception	LTS Lohmann Therapie-Systeme AG	LTS Lohmann Therapie-Systeme AG [21]	Emphasizes <i>norelgestromin</i> delivery for contraception with potential for improved efficacy and patient compliance.
WO2015031552	Transdermal drug delivery compositions and systems containing estradiol	-	3M Innovative Properties Co [22]	Develops compositions enhancing drug delivery efficiency of estradiol through the skin, supporting better systemic absorption.
WO2010006143	Estradiol transdermal delivery and device	-	Noven Pharmaceuticals, INC [23]	Focuses on device innovation for estradiol delivery, possibly improving patient comfort and dosing precision.
US20060078601A1	Methods and composition for estradiol delivery in transdermal drug delivery systems	-	Noven Pharmaceuticals, Inc.[24]	Covers formulation methods enhancing transdermal estradiol delivery, aiming for optimized bioavailability and sustained action.

4. CLINICAL TRIALS WITH THE LIMITATIONS OF THE STUDY

Although several clinical studies have demonstrated the therapeutic potential of transdermal estrogen formulations and their limitations, the findings from these studies have

inspired the development of new nanocarrier-based formulations to help bypass these limitations. The following section explains the clinical trials and is represented in the Table 2. Multiple clinical studies have demonstrated the efficacy and safety of transdermal estrogen delivery systems, for example, estradiol

Table 2. Clinical trial of estradiol on transdermal drug delivery.

Study title	ClinicalTrials.gov ID	Phase	Study type	Sponsor
Transdermal Estradiol Spray for Treating Vasomotor Symptoms	NCT01389102	Phase 3	Interventional	Lumara Health, Inc.[27]
A Pharmacokinetic Study of Bioidentical Compounded Natural Progesterone Estrogen Cream in Hormone Replacement Therapy	NCT00864214	Phase 1	Interventional	Mayo Clinic [28]
Transdermal Hormone Replacement Therapy for relieving Postmenopausal Symptoms	NCT02033512	Phase 2	Interventional	University Potiguar [29]
Using Ultra-low Dose Estradiol Patch Management of Hot Flushes in Asian Women	NCT00185237	Phase 3	Interventional	Bayer [30]
Comparison of Nanoparticulate and Micronized Steroid Delivery in Transdermal Hormone Replacement Therapy	NCT02467673	Phase 2	Interventional	University Potiguar [31]
PERT	NCT01308814	Phase 2 Phase 3	Interventional	University of North Carolina, Chapel Hill [32]
Impact of 17 β -estradiol on Immune Responses and Inflammatory Responses in Postmenopausal Women Based on Administration Route	NCT00701337	Phase 4	Interventional	University Hospital, Toulouse [33]
Comparative Study of Transdermal and Oral Estrogen Therapies in Adolescent Girls with Ovarian Failure	NCT01023178	Not applicable	Interventional	Stanford University [34]
Primary Ovarian Insufficiency: Optimal Treatment and Phenotype	NCT03568708	Phase 3	Interventional	Children's Hospital Medical Center, Cincinnati [35]

patches, gels, and sprays. For instance, in a 12-week double-blind clinical trial ($N = 220$) randomized to receive estradiol and norethindrone acetate patch applied continuously in comparison to a patch placed on a placebo group. The investigational subjects demonstrated a clinically significant reduction in menopausal vasomotor symptoms (e.g., hot flushes and/or sweating) without adverse events, compared to the placebo group. A second prominent study, referred to as the UK PATCH trial, included individuals with advanced prostate cancer who received a transdermal estradiol patch compared to those receiving luteinizing hormone-releasing hormone agonists. The rate and severity of cardiovascular events were similar in both treatment groups and demonstrated secondary outcomes of low rates of treatment discontinuation and high adherence rates—13 patients needed to be enrolled to achieve one patient withdrawal in comparison to the placebo group. This totality of evidence reinforces the connection between transdermal estradiol precautions and indications, supporting the incorporation of transdermal estradiol into the long-term treatment portfolio. In addition to the studies referencing patches, both sprays and gels were recently demonstrated to effectively control symptoms without significant adverse events, including severe skin irritation. The implications of these clinical studies support the incorporation of transdermal delivery systems, including transdermal estradiol enhanced with nanocarriers, as an effective, safe, and most importantly, tolerable option for HRT, to improve both adherence and levels of systemic hormone [25,26].

5. ADVANCEMENTS IN TRANSDERMAL ESTROGEN DELIVERY SYSTEMS

The transdermal route is a method of drug administration that involves administering a medicine via the skin

to achieve local or systemic effects [36]. Transdermal delivery technologies for estrogen therapy are rapidly advancing within the pharmaceutical sector, capturing significant market value in biomedical applications. These technologies enhance drug delivery through topical and transdermal routes, transitioning from painful therapies to painless treatments via innovative dosage forms [37] (Fig. 2). The initial approach for transdermal hormone therapy was the reservoir patch, which consists of multiple layers, including a backing layer, a rate-controlling membrane, and a drug reservoir [38]. These patches provide a stable release of estrogen, maintaining more consistent blood levels compared to oral hormone therapy. However, they are associated with high rates of local skin irritation, reported in up to 46% of cases, often due to the adhesive formulation or alcohol in the membrane [39–41]. Matrix patches represent a significant advancement, utilizing a textile pad or polymer containing the active ingredient in direct contact with the skin. This design allows for a more consistent drug delivery rate and typically results in fewer skin reactions, as it lacks alcohol and offers better air circulation [41]. The latest innovation in this category is dot matrix technology, which integrates the adhesive and drug into a single layer, resulting in thinner patches with a lower incidence of local irritation [41,42]. Transdermal patches are designed to improve patient adherence with once or twice weekly dosing. However, certain types, particularly reservoir patches, can lead to application site reactions, including erythema and pruritus, and may detach prematurely, disrupting the dosing schedule.

State-of-the-art advancements in nanocarrier-based transdermal delivery of estrogen now include an innovative methodology to optimize the formulation according to patient data, using AI. AI algorithms provide an opportunity to

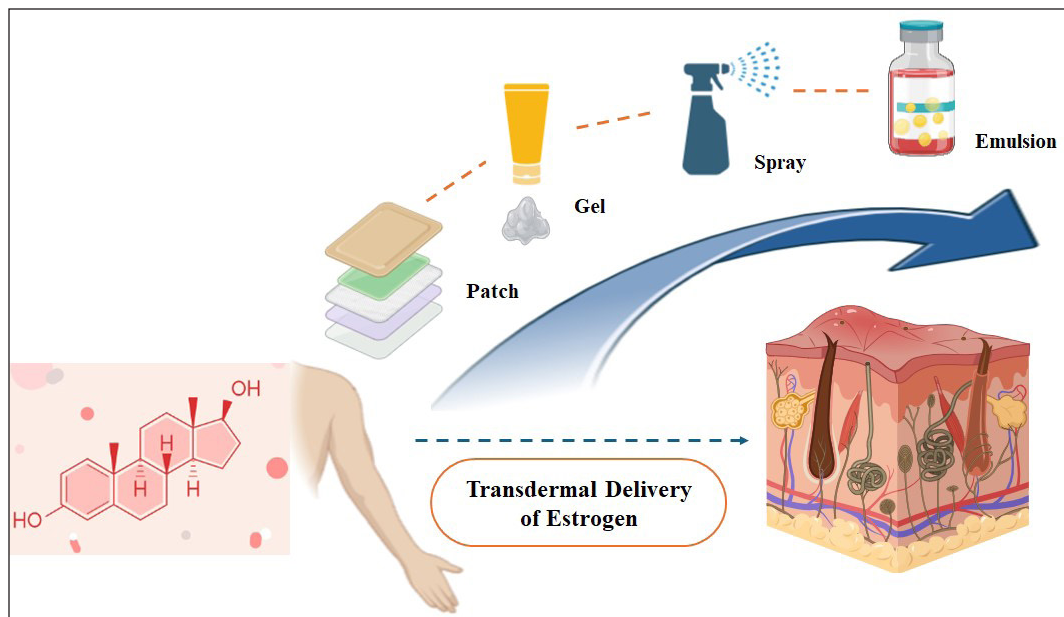


Figure 2. Evolution of dosage forms for transdermal estrogen therapy.

optimize the composition of the nanocarrier and drug release properties through patient-specific data for more potent and safer hormone delivery [43]. This emerging interaction of AI, newer patents, and clinical insights is increasing the progress toward personalized medicine and associated outcome prediction, putting transdermal delivery of estrogen at the forefront of personalized medicine and precision medicine [44].

6. CONCLUSION AND FUTURE PROSPECTS

The article reviews the evolution of transdermal delivery of estrogen starting with traditional systems (i.e., reservoir, matrix, and dot matrix) while acknowledging typical limitations of traditional systems that include skin irritation, patches falling off, and localized side effects. Next, it reviews advancements of nanocarrier platforms, vesicular technology, and new patch designs with an unbiased introduction of new technology consideration issues including stability, dosage, and adherence. In the conclusion, the article looks toward the evolving role of personalization and pharmacokinetic enhancements in the delivery of safer, and more effective therapeutics. Since the discussion combines new technology advances with clinical evidence data collection such as the KEEPS study, the conclusion describes future application of nanocarrier transdermal systems as potentially transforming estrogen therapies that are both more precise and patient-centered.

7. ABBREVIATIONS

CEC, cholesterol efflux capacity; CT, computed tomography; CRS, Confocal Raman Spectroscopy; T-DMN, conventional DMN; DMN, dissolving microneedle; EM, emulsion; Es, estradiol; ER β , estrogen receptor beta; ERT, estrogen replacement therapy; FMD, Flow-mediated dilatation; FDA, Food and Drug Administration; FTIR, Fourier-Transform

Infrared Spectroscopy; FDM, fused deposition modelling; HDL, high-density lipoprotein; HRT, hormone replacement therapy; IGF-1, Insulin-like Growth Factor; Jmax, maximum flux; KEEPS, Kronos Early Estrogen Prevention Study; LDL, low-density lipoprotein; MISS, membrane-initiated steroid signaling; MNPEE, micellar nanoparticle estradiol emulsion; ME, microemulsion; MN, microneedle; MNAs, microneedle arrays; OBE, oral 17 β estradiol; OCEE, oral conjugated equine estrogen; PS, particle size; PERT, perimenopausal estrogen replacement therapy; PC, phosphatidylcholine; PDI, polydispersity index; PLA, polylactic acid; PVA, polyvinyl alcohol; PLGA, poly (lactide-co-glycolide); rGH, recombinant growth hormone; SEM, scanning electron microscopy; TRZ, thermoregulatory zone; TTS, transdermal therapeutic system; TS, turner syndrome; VMS, vasomotor symptoms; WHI, Women's Health Initiative; ZP, zeta potential.

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9. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be authors as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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11. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

12. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

13. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

14. PUBLISHER'S NOTE

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15. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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