Restoring balance: Advancing hormonal therapy for menopause through modern drug delivery



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Abstract

Menopause represents a pivotal transition in a woman's life, accompanied by multiple repercussions. Menopausal symptoms range from vasomotor instability to chronic diseases, like osteoporosis. While hormone replacement therapy (HRT) remains the cornerstone for providing symptomatic relief, conventional oral formulations pose substantial risks, including thromboembolism, stroke, and other malignancies. This has facilitated the development of innovative drug delivery systems, such as transdermal patches and intravaginal rings (IVRs). Transdermal systems are unaltered by first-pass metabolism, enabling controlled hormone release. IVRs offer localized and systemic benefits with extended efficacy. The integration of nanotechnology has refined drug penetration, optimizing therapeutic outcome. However, transdermal HRT faces various challenges, including erratic hormone absorption, dermal irritation, and compliance issues. Future advancements must employ personalized medicine to customize therapeutic regimens according to the patient's profile. As drug delivery technology evolves, it holds immense potential to redefine menopause management, enhancing safety, efficacy, and quality of life.

Keywords: Menopause, Hormonal Therapy, Transdermal Patch, Intravaginal ring

1. Introduction

Menopause is a significant stage in a woman's life, as it comprises almost one-third of their lifespan. From an evolutionary perspective, menopause is viewed as a survival tactic that protects women from the dangerous effects of late childbirth (1). However, changes during menopause makes women highly vulnerable to diseases, making it the second cause of disability-adjusted life among 45 to 60-year-old women (2). Thus, a majority of the population views menopause as a biological flaw, rather than an advantage. More than 80% of women face vasomotor symptoms that include hot flushes, night sweats, and others like osteoporosis, vaginal atrophy, and augmented anxiety (3). The severity and duration of these symptoms vary to a great extent among individuals, which may be a result of differences in genetic make-up, lifestyle and other factors. Thus, a 'one size fits all' approach is inefficient in easing navigation through menopause (4). Various commercial formulations currently available for hormonal replacement therapy (HRT) in the treatment of menopausal symptoms are showcased in Table 1.

Table 1. Comparative chart between different formulations of HRT

Route of administration	Advantages	Disadvantages	Active	Marketed formulations	References
Parenteral	Alleviate perimenopausal symptoms and improve overall well-being, help maintain bone density, balance hormone levels.	Invasive process, higher chances of side effects.	Progestin	Bioidentical hormone pellets, Nexplanon® implant	(5)
Parenteral	Provide symptomatic relief, low dosing frequency, long-term effect.	Requires medical supervision, invasive process.	Estradiol cypionate	Depo-Estradiol® injectable	(6)
			Progestin	Depo-Provera injectable	
Oral	High dosing flexibility, may prevent atherosclerosis.	Hepatotoxic, increases vascular fat.	Estrogen	Estrace and Estrofem tablets	(7)
			Progestin	Provera tablets	
Topical	Bypasses first-pass metabolism.	Skin irritation, allergic reactions, poor systemic effect.	Estrogen	Estrogel and Divigel	(8)
Vaginal	Treats vaginal dryness and discomfort associated with menopause.	Vaginal burning or irritation, Vaginal discharge or spotting.	Estrogen	Estrace cream	(9)

2. Conventional treatment and its risks

About 90% of perimenopausal women seek medical treatment for their symptoms. The management of vasomotor symptoms involves utilizing HRT, which includes orally administered ethinyl estradiol. Women's Health Initiative (WHI) has highlighted the several health risks such as increased risk of blood clots, stroke, breast cancer, endometrial cancer, etc. associated with orally administered HRT. Oral contraceptives undergo first-pass metabolism and require a high dosing frequency to receive satisfactory effectiveness. Higher frequency of dose reduces patient compliance and increases vulnerability towards adverse effects, like myocardial infarction. These issues have encouraged the administration of ethinyl estradiol through the transdermal route. Transdermal HRT has been widely explored during the last two decades. It is highly convenient and includes formulations like, creams, gels, lotions, patches to name a few (10).

3. Emerging therapeutic approaches

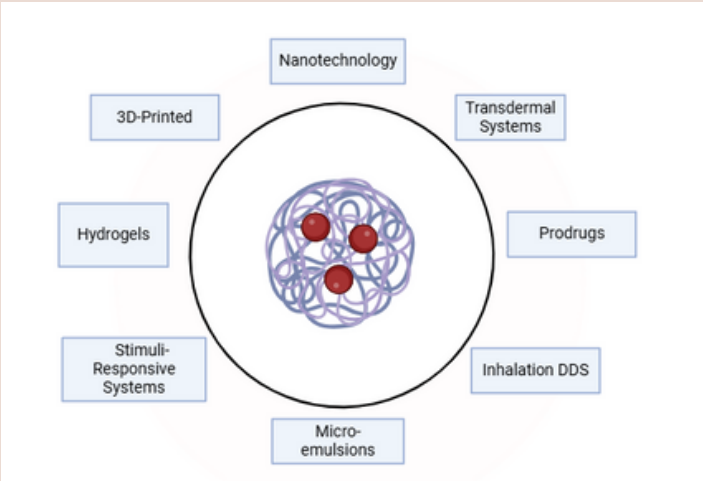

Figure 1. Plethora of emerging therapeutic approaches and novel drug delivery systems

3. Transdermal patches

Transdermal drug delivery systems are unaffected by first-pass metabolism and provide a long-term impact, resulting in reduced dosage frequency and better patient compliance (11). Transdermal patches are a non-invasive and effective method for delivering HRT to alleviate menopausal symptoms. The transdermal patches for HRT can be classified based on the mechanism of drug release as matrix-type, reservoir-type, microneedle-based, and ultra-thin patches. The basic mechanism of penetration of actives from transdermal patch through the skin are depicted in Figure 1.

In matrix-type patches, the drug is dispersed within a polymer matrix, which controls the rate of its release based on its diffusion through the polymer. Polymers such as ethylene-vinyl acetate, polyisobutylene and polyacrylate are widely used for their ability to efficiently control the drug release from the patch. Hydrogel-based matrix patches may also be fabricated to enhance skin hydration and permeation (12). In reservoir-types patches, the drug is contained in a liquid or gel reservoir, and separated from the skin by a membrane. The reservoir system is surrounded by an adhesive to ensure patch adherence to the skin. Drug release from the reservoir can be modified to suit the desired release profile, by utilizing the right blend of polymers for the membrane. Estraderm is a reservoir-type marketed formulation that delivers estradiol into the skin (13).

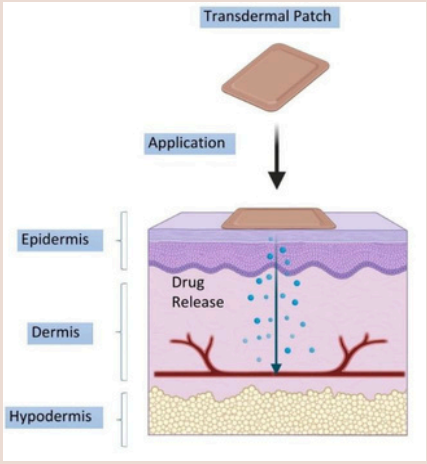

Figure 2. Penetration of actives from transdermal patch (14)

Microneedle patches comprise of micro-sized projections on the surface, which penetrate the outermost layer of the skin and deliver the drug directly into the dermis. These needles are usually dissolvable in nature, which release the drug as they dissolve upon contact with the skin. These patches are minimally invasive and can even deliver larger molecules through the transdermal route (15). Ultra-thin patches, on the other hand are patches with minimal thickness made up of polymers such as polyurethane and ethylene-vinyl acetate, which provide flexibility, better diffusion and adherence to the skin. They are non-irritant and improve patient compliance, making them ideal for long-term use. Minivelle is a commercially available ultra-thin patch that utilizes DOTMatrix technology to continuously release the drug from the patch. Ortho Evra is a transdermal patch that is composed of multiple layers. The outermost layer of the patch is a protective sheath and must be removed before application. The second layer comprises of drug-loaded adhesive layer. The innermost layer behaves like a 'cover' and is made up of flexible polymers. For the patch to stick firmly to the user's skin, its surface energy must be lower than that of clean, dry human skin, which is approximately 27 dyne/cm (16).

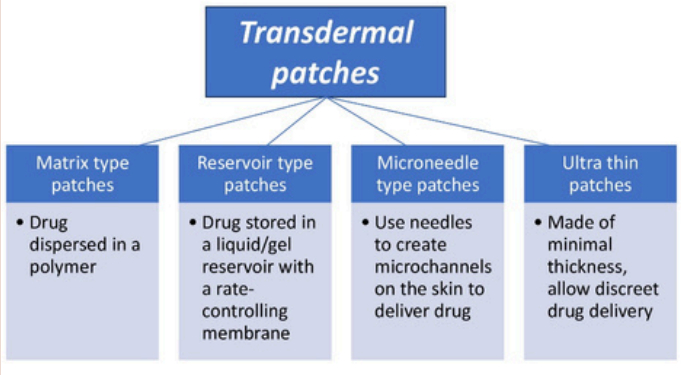

Figure 3. Systematic classification of various types of transdermal patches

In recent times, nanotechnology has been integrated into transdermal patches, wherein nanoparticles (NPs) are utilized to encapsulate the drug. NPs such as liposomes, nanostructured lipid carriers, metallic nanoparticles, polymeric nanoparticles, etc. are capable of disrupting the lipid bilayer membranes present in the stratum corneum, which would normally act as a barrier for drug penetration (17). NPs can be engineered to optimize skin-penetration through hair follicles, sweat glands or other pathways and provide sustained release of the drug, maintaining therapeutic levels for an extended period. Functionalized NPs, such as ligand-coated NPS, have been designed to provide increased affinity towards estrogen receptors, enhancing the therapeutic efficacy (17,18).

3.2. Intravaginal rings

Development of intravaginal rings (IVR) constitute a noteworthy advancement within the pharmaceutical sector. The series of processes involved in the manufacturing of IVR is displayed in Figure 2. The vaginal epithelium is highly vascularized, making it simpler for the drug to diffuse through the epithelial layer and enter systemic circulation (19). IVRs are used to relieve symptoms like vaginal atrophy and dyspareunia. Estring is a commercially available IVR that delivers a low dose of estradiol, which needs to be replaced every 90 days. IVRs such as Femring also protect the endometrium, which releases estradiol acetate. IVRs can be further classified based on their drug delivery mechanism as diffusion-controlled and erosion-controlled.

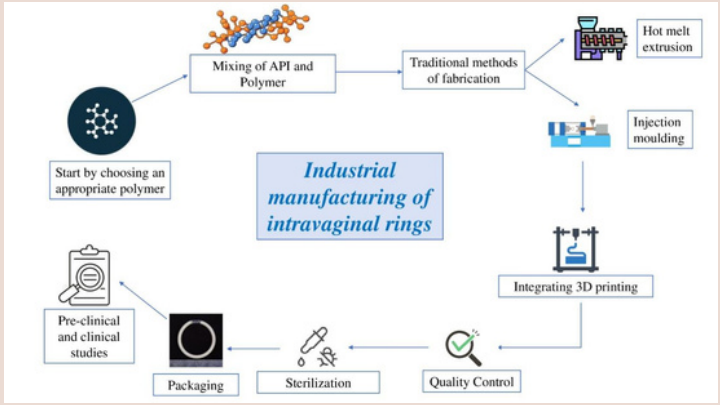

Figure 4. Industrial process for the manufacture of IVR (20)

In diffusion-controlled IVRs, the drug is dispersed in a polymer matrix, surrounded by a membrane. The drug diffuses through the polymer at a controlled rate, driven by the concentration gradient between the IVR and the surrounding tissue. These rings can be used to provide systemic as well as local action. In erosion-controlled IVRs, the drug is integrated within a biodegradable polymer matrix. The drug is released when the polymer undergoes degradation through hydrolysis or enzymatic action. Composition of the polymer is decided based on the rate of degradation required, which affects the rate of drug release. Poly(lactic-co-glycolic) acid (PLGA) is an extensively utilized polymer that is safe and biodegradable. IVRs composed of PLGA are environment-friendly and minimize chances of infection (21).

IVRs that can function on the basis of osmotic pressure are currently being studied to optimize drug delivery applications. The ring comprises of a semipermeable membrane, allowing water to enter, causing expulsion of the drug. The solubility of the drug and the permeability of the membrane affect drug release. These IVRs ensure consistent therapeutic levels of the drug, even for those with a narrow therapeutic index (22). Incorporation of 3D printing (3DP) has made it possible for researchers to develop IVRs with geometric accuracy. IVRs comprising multiple compartments can also be designed, enabling the administration of multiple hormones simultaneously.

NuvaRing was the first USFDA-approved IVR that provided the user with 120 µg of etonogestrel and 15 µg of estradiol per day (23). A more recently developed IVR is Annovera, designed for up to one year of use (24). In general, IVRs must be flexible, transparent and soft to facilitate insertion. They must also be of an appropriate size to prevent expulsion during regular activities (25,26). Certain IVRs possess multipurpose prevention technology, which enable the formulation to have an anti-viral action, especially against HIV (26).

4. Drawbacks of HRT

The application of HRT for perimenopausal symptoms is limited due to several drawbacks. HRT

substantially increases the occurrence of strokes by elevating blood pressure and causing inflammation in the blood vessels, along with other severe cardiovascular conditions. Venous thromboembolism is another prominent issue, which is directly linked with the increased production of clotting factors due to oestrogen. These effects are generally associated with long-term use of HRT (27). Venous thromboembolism is more prominent in oral HRT than transdermal therapies, owing to the lower ratio of estrone and estradiol (28). Clinical reports have also documented the increased susceptibility of women to breast cancer on long-term use of HRT. Combined HRT, especially estrogen and progesterone, aid in the growth of breast cancer cells, and making it challenging to detect the growth via mammography and biopsies (29). Moreover, the risks of breast cancer continue to exist even after the discontinuation of HRT. Furthermore, HRT also subjects women to minor side effects such as mood swings, breast tenderness, nausea, and migraines, among others, which can be managed via symptomatic treatment.

Notably, transdermal patches face a major challenge of drug penetration through the skin barrier, favouring the effective administration of smaller molecules over larger molecules (30). Additionally, patches may also cause inconsistent release of hormones, thus adversely affecting the patient. Another significant limitation includes minimal dose flexibility. Few minor setbacks include skin irritation caused by the patch and improper adhesion due to environmental reasons (31). While some of these challenges can be effectively mitigated through the integration of NPs, this approach also presents its own distinct set of challenges. Hence, it is crucial to navigate the hurdles associated with nanoparticle-integrated patches, prior to being considered as a standard of care. For IVRs, a major challenge is the discomfort and inconvenience associated with their insertion and removal, which can negatively influence patient compliance. Moreover, they may be less effective for systemic symptoms of perimenopause such as, hot flashes and sleep disturbances, hence rendering it incapable of broader management of perimenopause (32).

5. Conclusion

HRT has been a vital approach in the management of perimenopausal symptoms. However, research needs to be continued in order to optimise the therapeutic benefits of treatment and ensuring safety of the patient. It is essential for researchers to prioritize the development of treatment strategies that are tailored to the diverse needs of individual patients. Majority of the drawbacks of HRT can be evaded if the treatment is curated to suit the patient. Understanding the type of estrogen and progesterone that works best for a specific patient will potentiate the effects of the therapy. Artificial intelligence could be an effective tool for developing personalised therapy as it can efficiently analyse patient medical history and map out genetic profiles (33). Moreover, exploring different routes of administration has the potential to maximise the expected therapeutic outcomes of the treatment. As advancements in drug delivery technologies continue to evolve, they hold significant potential to enhance the safety, efficacy, and patient adherence towards HRT for menopause, ultimately improving quality of life for millions of women worldwide.

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