

A Review on Phosphodiesterase-5 Inhibitors as a Topical Therapy for Erectile Dysfunction



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ABSTRACT

Introduction: Due to the prevalence of erectile dysfunction and impotence among men in recent years, several pharmacotherapies have been considered for such problems. Systemic drug therapies in the treatment of erectile dysfunction have significant issues, including drug interactions and contraindications in a wide range of diseases, which makes researchers seek to design drugs and dosage forms with fewer side effects, interactions, and contraindications with maintained efficacy.

Objectives: 5-Phosphodiesterase inhibitors (5-PDEIs or PDE5Is), previously used systemically to treat erectile malfunction, are now appropriate candidates for topical application with considerable potency and fewer complications.

Methods: We sought to investigate the recent findings on the current subject in order to provide a comprehensive overview of the issue using an extensive literature search to pinpoint the latest scientific reports on this subject.

Results: In the present review, the function of 5-Phosphodiesterase inhibitors as topical formulations was evaluated with details including formulation type, adsorption, and comparative efficacy in all recent studies as an acceptable alternative therapy to systemic drugs.

Conclusions: Due to the fact that the influential factors in erectile dysfunction interact with many diseases and delinquent treatments, the use of topical therapeutic agents can be promising in mild to moderate cases. The utilization of 5-PDEIs through novel topical and transdermal drug delivery techniques plays a vital role in improving this effectiveness. **Hamzehnejadi M, Tavakoli MR, Abiri A, et al. A Review on Phosphodiesterase-5 Inhibitors as a Topical Therapy for Erectile Dysfunction. Sex Med Rev 2022;10:376–391.**

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Key Words: 5-Phosphodiesterase Inhibitors; Erectile Dysfunction; Topical Application; Drug Interaction; Sexual Dysfunction

INTRODUCTION

By definition, ED is the consistent or recurrent inability to get a sufficient erection and adequate penile hardness for sexual intercourse, causing vacuity in sexual pleasure.^{1,2} The issue of ED has

consistently been underestimated despite the great importance in the quality of life of patients and their partners and its high prevalence. One reason is that patients refuse to report such problems to their personal physician.² In the absence of treatment, the person usually loses self-confidence, and in addition to psychosocial issues, the overall quality of life of the patients and their partners also decreases.³ At this point, it is the physician's responsibility to examine the person regularly for sexual health, especially his erectile function. Examinations should include medical, sexual, psychological, and social records, as well as laboratory tests and physical examinations. Knowledge of culture, ethnicity, ethical and religious considerations can also be effective in prognosis, diagnosis, and treatment.⁴ Such studies lead to the early diagnosis of this disease, which in itself can be an indicator and criterion for the occurrence of several life-threatening diseases because the connection between ED and a specific range of morbidities has been proven.² Continuous monitoring of people with heart disease,

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hypertension, hyperlipidemia, diabetes, hypogonadism, hypothyroidism or hyperthyroidism, hyperprolactinemia, and other risk factors that we will address below is essential to prevent ED.^{2,4} Depending on the patient's condition and the severity of the ED symptoms, different treatment protocols (from traditional medicine to surgery) can be used. Reasons such as invasive treatment, drug interactions, treatment inefficiency, multiple contraindications, annoying side effects, and patients' personal preferences have made topical treatments a desirable choice in resolving this problem.^{5,6} Several compounds such as alprostadil,⁷ minoxidil,⁸ testosterone,⁹ papaverine,¹⁰ and PDE5 inhibitors, including sildenafil and tadalafil, have been evaluated for topical treatment of erectile dysfunction. These compounds with different formulations (classic or modern) have been studied in various studies. Classic formulations used to treat erectile dysfunction include sildenafil gel,¹¹ tadalafil gel,¹² sildenafil cream,¹³ and tadalafil cream.¹⁴ There is no study related to the treatment of erectile dysfunction using topical ointment of phosphodiesterase 5 inhibitors. Also, studies examining topical avanafil and vardenafil therapy (with both conventional and modern formulations) are very limited and have good potential for future research. Modern formulations of PDEIs used for inclusive drug delivery also include nano-emulsions, transfersomes, bilosomes, centrosomes, nano-ethosomes, liposomes optimized multilayer vesicles (MLVs) and nano-sized colloidal systems such as solid lipid nano particles (SLNs) and nano structured lipid carriers (NLCs). Still, in general, by examining the structure and anatomy of the penis, scrutiny of pathways affecting erection, detection of factors affecting transdermal absorption, and physicochemical properties of the drug and its carrier, it is possible to achieve the best formulation with the maximum therapeutic effect. Table 1. summarizes the phosphodiesterase 5 inhibitors formulations used to treat erectile dysfunction with their efficacy, classification, and complete description of the formulation. (Table 1).

Prevalence and Epidemiology

ED is the most common sexual disorder that occurs in older men. Due to the various and blurry definitions of ED, it is impossible to provide accurate statistics on its prevalence. Population, age, and risk factors can affect the majority and spread of the disease.^{15,16} Recent studies have shown evidence of ED due to alcohol abuse.¹⁷ ED is relatively common in the world. In 1995, more than 152 million people were registered with this disorder. This number is expected to reach over 300 million in the next 3 or 4 years, a very high number.^{18,19} If we calculate the prevalence of this disorder regardless of age, the figure is 12.9% in southern Europe and 20.6% in English-speaking countries.¹⁷ In a study conducted in Brazil, Italy, Japan, and Malaysia for all ages, the statistics were 9% for men aged between 40 and 44 years, 12% for 45 to 49 years, 18% for 50 to 54 years, 29% for 55 to 59 years, 38% for 60 to 64 years, and 54% for those between 65 and 70 years.²⁰ This percentage increases by 10% annually if associated with risk factors.²⁰ Due to the increasing average age, it is possible to accelerate this process worldwide.

Different studies indicated that age, diabetes, high blood pressure, heart disease, kidney disease, stroke, and prostate surgery often coincide with ED.^{19,21,22} Metabolic syndromes and smoking are among other risk factors.¹⁷ According to such studies, the prevalence and age of ED in different countries are different. European countries are ahead of other geographical locations regarding ED-related comorbidities.²³

Function and Physiology

Phosphodiesterases (PDE) are a large family of esterases responsible for hydrolyzing cyclic nucleotides.²⁴ If performed by PDE5, this process occurs mainly in the vascular smooth muscle of the corpus cavernosum. This enzyme has 2 subunits consisting of a catalytic domain and an allosteric domain. Following the binding of cyclic guanosine monophosphate (cGMP) to the catalytic domain and the hydrolysis of its bond, 5'-GMP is formed linearly, and this process reduces the amount of cGMP. Inhibition of this enzyme by the inhibitor can increase cGMP concentration by preventing its degradation.^{24,25} cGMP and cAMP are required to relax muscles and create an erection, but cGMP activity increases PDE5 expression, hydrolyzing cGMP and cAMP and controlling their concentration. Under normal conditions, an increase in cGMP increases the expression and amount of PDE5, which binds cGMP to the catalytic domain of PDE5, resulting in degradation of cGMP and decreased its level. As a result, a negative self-regulatory mechanism is established. However, in the presence of phosphodiesterase inhibitor, increasing cGMP concentration leads to increased PDE5 expression. The drug binds to the catalytic domain, where cGMP bind to the allosteric domain. This process prevents the degradation of cGMP, increases the affinity of the catalytic domain for the inhibitor, and increases the drug's effectiveness (Figure 1).²⁶

Sexual arousal is the beginning of the path to an erection. This stimulation releases NO from non-cholinergic and non-adrenergic neurons (NANCs) and stimulates the corpus cavernosum.^{25,27} Nitric oxide converts GTP to cGMP after penetrating vascular smooth muscle cells in the corpus cavernosum of the penis by activating soluble guanylate cyclase. cGMP activates a cascade of phosphorylation of intracellular proteins by activating protein kinase G (PKG). This process generally releases calcium ions from the cell or reduces its sensitivity to calcium. This lack of calcium and inhibition of its binding to relevant muscular proteins cause the smooth muscles to relax, dilating the arteries and amplifying blood flow, resulting in an erection. PDE5 inhibitors, by competing with cGMP in binding to the catalytic domain of PDE5, delay the degradation of cGMP and increase its level in the cell. This causes smooth muscle relaxation and increases blood flow to reach a complete erection.^{25,27}

Risk Factors and Pathophysiology

ED is defined in scientific resources as the inability to achieve or maintain an adequate erection for satisfactory sexual intercourse.

Table 1. Summary of topical formulations used to treat erectile dysfunction

| Formulation | Classification | Loaded Drug | Description | Efficacy |
|---------------------------------------|-------------------------------------|-------------|--|--|
| Gel | Classic | Sildenafil | Among the classic vehicles, gel-based formulations seemed more effective than creams and ointments. | up to 35% in topical application of cases can cause some degree of erection |
| | | Tadalafil | | - |
| Cream | Classic | Sildenafil | Topical cream 1% | Less effective than gel formulation. |
| | | Tadalafil | Topical cream 5% | |
| Ointment | - | - | - | - |
| Nano/micro emulsions | Modern | Sildenafil | Prepared with maisine 35-1 (16.4%), caproyl 90 (32.8%), cremophor RH40 (32.8%), and propylene glycol. (16.4%) | Long-lasting release and better penetration compared to drug suspensions. Sildenafil microemulsion has a double permeability coefficient compared to the pure drug solution. |
| Transfersomes | Modern Liposomal systems | Sildenafil | Transporter body of liposomes composed of phosphatidylcholine and an edge activator for the targeted drug delivery system that is involved in transporting transdermal drugs through phospholipid vesicles. 130 nm vesicular sizes and 94.74% entrapment efficiency. | Diffusion coefficients and computed permeability for the optimized batch were 1.57 and 1.25-fold higher than without the transfersomes, respectively. |
| Bilosomes | Modern Colloidal systems | Sildenafil | Novel colloidal delivery system similar to niosomes but incorporating bile salts into the vesicular lipid bilayer membrane | Rapid and adequate efficacy was reported in older mice due to its quick passage through the cutaneous fascia |
| Centrosomes | Modern Nano-liposomal systems | Tadalafil | Formed by the hydration-sonication method. penetration enhancer-containing tadalafil-loaded nanoliposomes. | - |
| Nano-ethosomes | Modern | Vardenafil | Made with the thin-layer evaporation technique. Nanocarriers of fat-based vesicles that contain a high percentage of ethanol and are used to deliver high-performance therapeutic agents to deep layers throughout the skin | In-vivo studies demonstrate that the bioavailability of transdermal nano-ethosome is 2-fold greater than the drug suspension. |
| Multilayer vesicles (MLVs) | Modern Liposomal systems | Avanafil | Optimized liposomal transdermal formulation | The permeability coefficient and diffusion coefficient were 4.59 and 21.11-fold compared to the suspension mode |
| Solid lipid nano particles (SLNs) | Modern Nano-sized colloidal systems | Sildenafil | Controlled release properties, improved transdermal penetration, and less skin sensitivity. | More stable than liposomes and polymeric nanoparticles. |
| | | Avanafil | This formulation has been suggested due to the low aqueous solubility of this drug. | HPMC transdermal film-loaded avanafil SLNs was more effective than oral therapy |
| Nano-structured lipid carriers (NLCs) | Modern Nano-sized colloidal systems | Tadalafil | Formulated using penetration enhancers such as ethanol and limonene to develop a new successful drug delivery system to improve the topical effectiveness of tadalafil. | - |

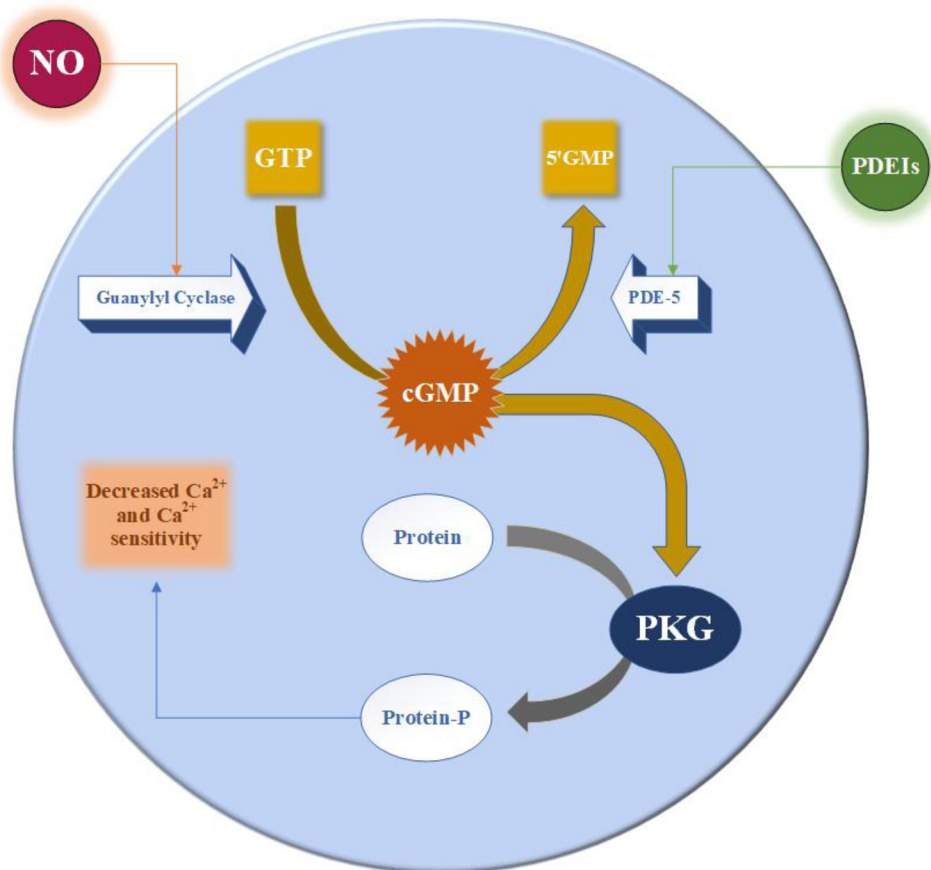


Figure 1. Molecular pathway of erection; the role of NO and 5-PDEIs in the functional cascade of cGMP.

It is estimated that 322 million people will have ED in the next 4 years (2025).²⁸ Anything that interferes with blood flow to the penis can cause ED.² Since ED increases with age, it can be surmised that this disease is often associated with other chronic diseases such as cardiovascular disease, type II diabetes mellitus, benign sexual hypertrophy, hypertension, etc. Any condition that interferes with the hypothalamic-pituitary-gonadal (HPG) axis signaling pathway or any disorder resulting in testosterone deficiency could contribute to the development of ED. Hypogonadism occurs for various reasons, from genetic to acquired—for example, Kalman syndrome, hereditary hemochromatosis, Prader-Willi, and Laurence-Moon-Biedl syndromes.²⁸ Other factors involved in the development of ED are very diverse and are generally divided into two categories: psychological and organic. These etiologies are listed in Table 2^{3,28}: cardiovascular disease, diabetes, depression, and emotional factors.¹ Poor body image, history of sexual, physical, psychological abuse, or even religious factors are other psychological causes of the disease.³

Pharmacology

The primary mechanism of erection is complex. A combination of tactile, olfactory, auditory, and mental stimuli that

include the spinal and supraspinal pathways are involved in this procedure and is controlled by different areas of the hypothalamus and cerebrum. There are various mechanisms for getting an erection, like a mechanism that works through the dopaminergic pathway. Dopamine and its receptors probably play a role through spinal regulation of penile reflexes.²⁹ Apomorphine is 1 of the drugs in this class that stimulates these receptors to cause sexual arousal.³⁰ Since its oral form was not effective, its sublingual form was used. However, numerous side effects of Apomorphine due to its easy passage through the blood-brain barrier and other complications such as headache, dizziness, nausea, and in rare cases, syncope significantly dissuaded its consumption.^{29,30}

Another critical pathway is the serotonin (5-hydroxytryptamine) pathway. It has been proposed that 5-hydroxytryptamine (5-HT) generally has an inhibitory effect on men's erection and sexual behavior, but this has not been thoroughly confirmed. We only know that 5-HT has several effects on sexual behavior. This may explain the improvement in erectile function after taking trazodone. Trazodone is an antidepressant that works by producing an active metabolite (m-chlorophenylpiperazine (mCCP)) through a 5-HT central absorption inhibition mechanism. According to studies, the noradrenergic pathway can also play a role in erectile function through the brain and spinal pathways.

Table 2. Classification of causes and risk factors for erectile dysfunction (ED)^{3,4}

| | |
|-------------------------|--|
| Neurogenic | stroke Parkinson Alzheimer temporal lobe epilepsy Spinal cord injury or associated CNS disorder Encephalitis Diabetic neuropathy Pelvic trauma or surgery |
| Drug-induced | Lithium 5 α -Reductase inhibitors Anxiolytics (benzodiazepines); newer anxiolytics not associated with sexual side effects Antidepressants Antihypertensives Antipsychotics Antiandrogens Alcohol abuse |
| Organic Vasculogenic | Pelvic/perineal trauma or irradiation Smoking Hypertension Hypercholesterolemia Atherosclerosis Diabetes mellitus Peyronie's disease Venous shunts (may be acquired after penile surgery) |
| Psychogenic Generalized | Primary lack of sexual arousability Age-related decline in sexual arousability |
| Endocrinological | Hyperprolactinemia Hypogonadism Hyper/hypothyroidism |
| Situational | Partner-related (lack of arousability, partner conflict) Performance anxiety Depression |

Different receptors can produce other stimulatory or inhibitory effects.²⁹ Therefore, the use of drugs such as yohimbine, which acts selectively as an α 2-adrenoceptor antagonist, can be effective in this way. The exact mechanism of action of yohimbine is not fully understood, but it is thought to play a role in eliminating ED by inhibiting penile vasoconstriction.³⁰ However, the results obtained from the treatment are not significant, and contradictory findings have been observed.

Prostanoids (locally acting hormones derived from arachidonic acid), namely prostaglandins (PG) like PGD₂, PGE, PGF, PGI₂, and thromboxane A (TXA), act by stimulating the thromboxane (TX) and prostaglandin F (FP) receptors.²⁹ The effects of prostanoids are mainly exerted through cAMP. This factor may explain the synergy between PGE1 and Forskolin. Forskolin is a direct stimulant of adenylate cyclase and thus can increase cAMP production within smooth muscle cells.³¹ PGE1 can cause an

erection by increasing the concentration of intracellular cAMP, similar to nitric oxide, and by relaxing the arteries. This makes PGE1 also a drug in this disorder.^{29,31} In addition to PGE1, other compounds such as papaverine, vasoactive intestinal polypeptide (VIP), and phentolamine can also be taken intracavernosally. Papaverine acts as a non-specific inhibitor of phosphodiesterase, phentolamine, a non-selective competitive antagonist of the α -adrenoceptors, and VIP as a potential neurotransmitter that leads to the elevated intracellular activity of cAMP.^{30,32}

Nitric oxide (NO) acts through a more direct mechanism. In fact, NO increases intracellular cAMP concentration by stimulating the cascading pathway with guanylate cyclase. This cAMP increases blood flow to the penis and causes an erection by relaxing the smooth muscles of the arteries. One of the most important mediators in this cascading pathway is cGMP-dependent protein kinase I (cGKI).²⁹ After releasing of NO following a sexual stimulus, it penetrates the vessels of the penis and smooth muscle cells of the corpus cavernosum and then stimulates the enzyme guanylate cyclase, which increases the conversion of guanosine triphosphate (GTP) to cGMP. This cGMP activates the protein kinase G (PKG) and alters cell channels by acting as a secondary messenger. This process results in dilation of the arteries of the penis and erection.³⁰ Any factor that in some way increases the amount of NO or the general activation of this pathway to relax the arteries can be considered a potential drug in the treatment of ED. For example, different families of phosphodiesterases can inactivate cAMP and cGMP by cleaving the 3'-ribose-phosphate bond, which can lead to ED or impairment. As a result, 1 of the best ways to treat ED is to inhibit these phosphodiesterases.³¹ PDE5, with its 3 isoforms, is 1 of the most effective phosphodiesterases in this field, and its inhibitors are available as acceptable drug candidates in the treatment of ED.²⁹ The endogenous NO-cGMP signaling pathway is the 1 used by drugs such as sildenafil.^{31,32} Other drugs such as tadalafil, vardenafil, and avanafil are the most widely used drugs in this category that work by a similar mechanism (increasing PDE5 concentration, followed by increased cGMP and local NO secretion, which relax smooth muscles).³³

Management and Therapies

Since the causes of ED are of both psychological and physical origins, its treatment is also possible through a variety of psychological, physical, and chemical (pharmacological) therapies. Psychiatric counseling, reducing pornographic content, using vacuum devices, diet correction, exercise, weight loss, and herbs and amino acids such as L-arginine and nutrients are recommended to treat and control ED.³⁴⁻³⁶ Apart from these, there are various medications *via* oral, injectable, or topical routes.

Apomorphine is 1 of the drugs used for ED treatment.³⁴ The use of prostaglandins is 1 of the treatment options in ED. For example, the use of alprostadil (PGE1) alone or in combination with papaverine and phentolamine has been suggested and

studied to treat erectile dysfunction.³⁷ PGE1 is also used topically.³⁷ Using PGE1 intracavernosally can even control severe ED. Also, for this administration route, phenoxybenzamine, atropine, nitroprusside, vasoactive intestinal peptide (VIP), and chlorpromazine are used.^{34,36,37} However, for hypogonadal men with milder ED, there is an option such as testosterone therapy (TTh or TRT).^{34,38,39} The most effective drugs for treating ED are phosphodiesterase type 5 inhibitors (5-PDEIs or PDE5Is).^{34,40} This category includes drugs such as sildenafil, vardenafil, tadalafil, etc., with sildenafil being their first approved one.^{34,40} By inhibiting phosphodiesterase type 5 enzyme, this class of drugs increases the stability of cGMP and enhances the duration of NO activity in the vessels of the penis.^{34–36,41} PDE5Is have been registered as 1 of the first-line drugs in the treatment of ED after passing several large and multifaceted clinical trials, and their efficacy and safety have been confirmed.^{34,40}

Other methods, such as stem cell injections or very low-intensity shock therapy, are sometimes used.^{34,35} Another type of treatment is intraurethral therapy, performed by placing PGE1 in the urinary tract, which is less commonly used.³⁷ Surgery is also an acceptable first-line treatment option (Penile implant).^{36,40}

Topical Applications of PDEIs

Along with significant effects in confronting ED, various results of topical application of PDEIs have been reported to date. In 1 study, high-dose sildenafil increased lipolysis in adipose tissue cultures. One of the types of PDE that is likely to be effective on adipose tissue lipolysis is PDE-5A which is present in adipose tissue along with PDE-3b. It seems that a group of PDEIs can be effective on cellulite. Due to the 50% inhibition of PDE-3B activity in pretreated adipocytes, sildenafil (transdermal or local) can have undeniable effects on skin microcirculation such as tissue hypoxia.⁴² Studies have been conducted based on a presumption that topical PDEIs may affect alopecia areata in children. Still, the final results vindicate that sildenafil 1% twice a day for 3 months has no tangible effect on these cases.⁴³

Another corroborated usage of PDE inhibitors is reducing sphincter hyperactivity. This feature is critical in patients with anal fissures. Maximum resting anal pressure (MRP) is significantly reduced with sildenafil, and fewer side effects are expected than topical nitroglycerin.⁴⁴ In the following, after a series of specified examinations, it was found that topical sildenafil is optimistically effective in the clinical improvement of hand-foot syndrome (HFS) and hand-foot skin reaction (HFSR).⁴⁵ Sildenafil also has an indubitable effect on the healing resistant skin wounds and skin ulceration in patients with antiphospholipid syndrome.⁴² Data indicate the effect of sildenafil citrate hydrogel (SCH) on wound healing without the footprints of skin toxicity and severe side effects, but to understand the mechanism and more accurate conclusions about the effectiveness of sildenafil citrate, more detailed studies are necessitated.⁴⁶ Palmar-Planter Erythrodyssthesia (PPE) is a complication of chemotherapies

such as intravenous 5-fluorouracil (5-FU) that typically results in dermal toxicities and skin attenuation. Clinical observations performed in a double-blind, placebo-controlled manner have shown the positive effects of 1% sildenafil topical cream in reducing such adverse effects.¹³ In infants, sildenafil is prescribed topically to treat pulmonary hypertension, but in adults, due to less skin penetration, we have to use adjuvant methods to observe this effect.⁴² Recent studies also support using topical PDEIs to treat pulmonary hypertension besides healing wounds such as digital wounds of Raynaud's syndrome.¹³ PDE5Is and calcium channel blockers (CCBs) are suitable options for the treatment of active digital ulcers. Tadalafil 5% was compared with nifedipine 5% cream in secondary Raynaud's phenomenon patients and generally showed positive effects in accelerating the recovery process. In general, tadalafil cream has demonstrated positive outcomes for improving Raynaud's phenomenon (RP) and digital ulcers (DU) in systemic sclerotic patients.¹⁴

MATERIALS AND METHODS

This project was done based on the manner of effectiveness, clinical applications, and formulation of topical phosphodiesterase-5 inhibitors in various forms to reduce or cure ED. The intended searches were done in Scopus and PubMed search engines. To search for each drug's clinical application and trials, the combined keywords [drug name] + [X] + [erectile dysfunction] have been used (Table 3). The results of this 3 word search are integrated and categorized in the results and discussion section. PubMed searches were limited to advanced search in titles and abstracts. Other investigations have been done based on the general focus of the content of each section or on an ad hoc basis. From a scientific and literary point of view, the text's coherence was then re-evaluated and revised accordingly.

RESULTS AND DISCUSSION

Phosphodiesterase-5 Inhibitors (PDE5Is)

PDE5Is are the first-line treatment for most men with ED (unless specifically contraindicated). These drugs are taken orally and are usually taken on-demand before intercourse. Unlike other medications, such as Apomorphine, which act on the CNS, they work inside the penis.^{25,47} Caffeine, theophylline, and papaverine were among the first PDE inhibitors, but their activity was inadequate and non-selective. Their structure is similar to cGMP, and their core structure led to the production of

Table 3. The search strategy of the manuscript

| DRUG NAME | X | ERECTILE DYSFUNCTION |
|------------|-------------|----------------------|
| SILDENAFIL | Topical | (ED) |
| TADALAFIL | Transdermal | |
| VARDENAFIL | Gel | |
| AVANAFIL | Cream | |

more specific and potent inhibitors for PDE5.^{24,26} Zaprinast was the first orally active isoenzyme selective PDE5 inhibitor given to humans to relax vascular smooth muscle. The function of Zaprinast is to enhance NO-induced relaxation. As a result, it was used to treat allergies. This function of Zaprinast led to the development of PDE5 inhibitors to treat certain diseases.²⁴

One of the side effects of sildenafil in early research was erection, and it changed the subject of Pfizer's research in 1993 to go to ED and work on its treatment. Sildenafil has about 240 times more inhibitory effect than Zaprinast. But because it has a short half-life, tadalafil (less interfering) and vardenafil (more potent) were developed.²⁴ Significant research efforts have led to the production and development of selective and potent compounds in inhibiting specific PDEs. Some of these inhibitors have a general structure similar to sildenafil, and others, such as tadalafil, have entirely different structures. Part of the structure of any PDE5 inhibitor is identical to the structure of cGMP. This is important because these drugs are cGMP antagonists for PDE5, and it is believed that they also have some of the same molecular interactions that cGMP forms with amino acids in PDE5.²⁵ Three PDE5 inhibitors, sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis), are currently licensed for worldwide use. Several newer drugs are available in some countries, such as udenafil (Zydena) and mirodenafil. Others are being developed, such as avanafil, ludenafil, and SLX-2101.^{25,47} Sildenafil, vardenafil, and udenafil belong to a group of compounds called pyrazolopyrimidines with a structure similar to cAMP, while tadalafil has an entirely different structure.⁴⁷ PDE5 inhibitors are effective, safe, and tolerable medications for secondary ED caused by other diseases. Almost all available documentation relates to sildenafil, tadalafil, vardenafil, and avanafil (Table 4). There is no evidence of significant differences in efficacy, safety, and tolerability between PDE5 inhibitors.²⁵

Dose Adjustment

Patients taking ketoconazole, itraconazole, erythromycin, clarithromycin, and HIV protease inhibitors (eg, ritonavir, saquinavir) may need lower doses of PDE5Is because they are cytochrome P450 CYP3A4 inhibitors (The enzyme that degrades PDE5 inhibitors). Higher doses of PDE5 inhibitors may be required in patients taking rifampicin, phenobarbital, phenytoin, or carbamazepine. In patients with impaired renal or hepatic function, the dose of these drugs may need to be adjusted. In patients with hypogonadism, androgen supplementation improves the erectile response.⁶²

Systemic Interactions and Contraindications

The multiplicity of drug interactions and contraindications of PDEIs dosage forms with systemic absorption are among the reasons that lead patients to resort to topical therapy. Such interactions may increase the concentrations of PDE5Is to more than ten times of their usual (interaction-free) concentrations.⁶³ Despite good tolerance of this class of drugs in patients due to

Table 4. Characterization of well-known PDE5 inhibitors. IC₅₀ values are for PDE-5

| Drug | Dose (mg) | Bioavailability | Half-life (hr) | Side effect | IC ₅₀ (nmol/L) | Vd (L) | Metabolism | Onset of action (min) |
|------------|-----------------------|--------------------------|---|--|---------------------------|----------------------------|--|-------------------------|
| sildenafil | 25 | 40% ⁴⁹⁻⁵¹ | 3-5 ²⁵ | headache (7%-32%), flushing (7%-33%), dyspepsia/ nausea (1%-13%), nasal congestion/rhinitis (1%-19%), dizziness (2%-9%), visual disturbance (1%-10%) ⁴⁹ | 1.6 ^{52,53} | 105 ⁵⁴ | ~79% CYP3A4, ~20% CYP2C9, <2% CYP2C19 and CYP2D6 ⁴⁹ | 15-60 ⁵⁵ |
| | 50 | | | | | | | |
| | 100 ⁴⁸ | | | | | | | |
| tadalafil | 5 | 80% ⁵¹ | in normal healthy men: 17.5 hours elderly men: 21.6 hours ⁵¹ | headache (66% of 65 subjects), back pain (60%), myalgia (4.3%) dyspepsia (19%), nausea (19%), dizziness (17%), fatigue (12%), eye pain (11%) and spontaneous penile erection (11%) ⁵⁶ | 4.0 ^{52,53} | 62.6 ⁵⁷ | CYP3A4 ⁵¹ | 15-120 ^{50,51} |
| | 10 | | | | | | | |
| | 20 ⁵⁰ | | | | | | | |
| vardenafil | 2.5 | 15% ^{51,58} | 3.94- 4.79 ⁵⁸ | Headache 16%, Flushing 12%, Dyspepsia 4%, Nasal congestion 10%, Dizziness 2%, Abnormal vision <2% ⁴⁸ | 0.08 ^{52,53} | 208 ^{54,58} | Major: CYP3A4 Minor: CYP3A5 / CYP2C ^{50,58} | 25-60 ⁵⁵ |
| | 5 | | | | | | | |
| | 10 ⁵⁰ | | | | | | | |
| avanafil | 50 | Not tested ⁵⁰ | 1.07- 1.23 ⁶⁰ | headache (2.7% to 12.1%), flushing (1.4% to 13%), nasopharyngitis (0.6% to 5.1%), nasal congestion (0.6% to 4.3%), and back pain (0.6% to 3%) ⁵⁴ | 5.2 ^{52,53} | not reported ⁵⁴ | Major: CYP3A4 Minor: CYP2C ⁵⁹ | 15-30 ^{59,61} |
| | 100 200 ⁵⁹ | | | | | | | |

their mild side effects such as headaches, hot flashes, indigestion, and respiratory infections in a limited percentage of patients, interactions with these drugs can be hazardous and even deadly. Due to their mechanism, the interaction of PDEIs with CYP3A4 inhibitors or inducers seems reasonable. According to studies on the interactions of CYP3A4 with sildenafil, a CYP3A4 inducer such as rifampin reduces the serum concentration of sildenafil. This pattern of interactions may also exist among other members of the phosphodiesterase inhibitor family with drugs such as erythromycin, ketoconazole, itraconazole (by increasing AUC of sildenafil), ritonavir, saquinavir (by increasing sildenafil C_{max} and AUC), or cimetidine.^{64,65} Macrolide antibiotics, antifungals, and cimetidine are other P450 3A4 inhibitors that increase the concentration of sildenafil. Antiviral protease inhibitors such as nelfinavir inhibit the metabolism of sildenafil, increase its serum half-life by 1 hour, and increase the time required to reach maximum concentration by about 3 hours.⁶⁶ Some drugs do not affect sildenafil metabolism despite their influence on CYP3A4. For example, although omeprazole and quinidine inhibit CYP3A4, they do not affect the metabolism of sildenafil (not quinine, quinine increases its concentration by inhibiting CYP3A4 and inhibiting the metabolism of sildenafil).⁴⁹ Numerically, taking a single dose of 100 mg sildenafil with CYP3A4 inhibitors increases the exposure to sildenafil. This was reported to be an increase of 1000% with ritonavir at a dose of 500 mg twice daily, 210% with saquinavir at a dose of 1200 mg 3 times a day, or 182% with erythromycin at a dose of 500 mg twice a day.⁶³

Contrary to the above, bosentan has the mechanism of induction of CYP3A4 and CYP2C9. In the simultaneous use of sildenafil 80 mg 3 times a day and bosentan 125 mg twice, a 63% reduction in dose-interval AUC for sildenafil was observed.⁶³ Due to the effects of sildenafil on vasodilation, other interactions and contraindications can be expected for it.

One of these interactions with amyl and butyl nitrites can have serious consequences. These outcomes include a sudden and severe drop in blood pressure. They can also cause acute myocardial infarction, especially in people with a history of heart disease, and pose risks to heart and brain blood flow in patients with the previous pathology. As a result of this dangerous interaction, the concomitant use of phosphodiesterase with nitrates and nitrites is prohibited.^{48,66} However, PDEIs such as sildenafil themselves do not directly affect cardiovascular disease. They do not increase the patients' cardiovascular risk and will not pose a particular risk unless used with nitrates.⁶⁷ Sildenafil can also cause a sharp drop in blood pressure if taken with alpha-adrenergic blockers such as doxazosin.^{65,68} Alpha-adrenergic blockers are mainly used to treat benign prostatic hyperplasia (BPH). According to these studies, for administering sildenafil above 25 mg, a minimum interval of 4 hours with alpha-adrenergic blockers should be set.⁶⁸ In general, in addition to the prohibition of concomitant use of nitrates and PDEIs, cautions should be considered when co-administering sildenafil or tadalafil with alpha-adrenergic blockers. In the United States, concomitant use

of vardenafil with this class of drugs has contraindication.^{48,68,69} In cases related to hematology, 1 study showed that a dose of 100 mg of sildenafil could increase bleeding time because it inhibited collagen-induced accumulation. This effect starts after 1 hour and lasts up to 4 hours but has not been seen in lower doses (50 mg).⁷⁰ Sildenafil does not directly affect platelets, but it will increase bleeding by increasing the impact of nitrite oxide donors on platelet aggregation due to adenosine diphosphate. Even though sildenafil is not inherently connected to cardiovascular toxicity, it is considered contraindicated in people with certain conditions⁷¹:

- Patients with active coronary ischemia
- Patients with a positive exercise stress test
- Patients with congestive heart failure or hypertension and borderline low volume
- Patients taking a complex multidrug regimen for their blood pressure and the drugs that increase the half-life of sildenafil.

In addition to taking nitrates and nitroglycerin, these drugs should not be used in people with severe liver or kidney failure or retinitis pigmentosa of the eyes.⁷² The interaction of sildenafil and PDEIs with some fruits and juices is also significant. Such as the interaction of sildenafil with pomelo juice or fresh fruit, which, contrary to expectations, leads to a decrease in bioavailability and a potential reduction in the drug's effect, and its mechanism is not yet fully understood.⁷³ If we want to investigate this interference to some extent, the rate and bioavailability of sildenafil in concomitant use with pomelo water decreases from 212.44 ng/ml to 134.07 ng/ml. It will be reduced by about 40%.⁷⁴ In this regard, interaction with grapefruit juice is also essential in the interactions that increase its bioavailability.^{63,75,76} Grapefruit juice can increase sildenafil exposure by up to 23% as a weak inhibitor.⁶³ Interactions between the new drug GT-CV (green tea (GT) - cardiovascular (CV)) and sildenafil have been reported. This interference is probably due to the inhibitory effect of green tea on CYP3A. However, these interactions are mild to moderate. Concomitant use of a single dose of green tea with sildenafil increased sildenafil exposure by up to 50%.⁷⁶ No trace of alcohol interaction up to 80 mg/dL has been observed. There has also been no interaction with tricyclic antidepressants. Contrary to popular belief, sildenafil does not interfere with active platelet drugs such as ticlopidine.⁶⁶ There is also no significant interaction between sildenafil and warfarin, atorvastatin, acenocoumarol, or acetylsalicylic acid.⁶³ There are no effects of the interaction of this class of drugs with magnesium hydroxide antacids and/or aluminum hydroxide, thiazide diuretics, ACE inhibitors, or calcium antagonists.⁶⁴ In general, most drugs that affect CYP3A4 activity interact with PDEIs.⁴⁹ However, in some drug groups, such as oral contraceptives, this interaction is minuscule to some extent and even neglected in some studies. No severe interaction has been reported between these medications.⁶⁶ In summary, the number

of systemic interactions of these drugs is not small, and it interferes with most of the cases that affect the activity of CYP3A4, which includes a relatively wide range of drugs.

Topical PDE5Is and Erectile Dysfunction (ED)

Male sexual dysfunction is a common complaint in men all around the world. It is estimated that about 50% of men between 50 and 70 suffer from 1 of 3 major sexual dysfunctions, which are ejaculatory dysfunction, erectile dysfunction (ED), and a decreased libido (hypoactive sexual desire disorder).^{77,78} Although survey findings vary considerably, premature ejaculation is considered the most common male sexual disorder besides ED.⁷⁷ Due to the WHO second International Consultation on Sexual Dysfunction, premature ejaculation is considered as persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration, and before the person wishes it, over which the sufferer has little or no voluntary control which causes the sufferer and his partner bother or distress.⁷⁷ Not only human's social life is affected by ED, but also ED is closely linked with a wide variety of diseases. As previously mentioned, it is associated with an increase in the risk of myocardial infarction or angina and even many more jeopardies.⁷⁹ Stress could also cause ED, but the stress-induced ED mechanism has yet to be fully uncovered.⁸⁰ Oral PDE5Is are the first-line treatment of ED. In the following, the topical effectiveness of drugs in this classification is examined in detail.

Sildenafil

Sildenafil citrate (SC), a selective PDE5 inhibitor that increases NO level and stops cGMP destruction,⁸¹ is the first oral drug approved to treat ED. However, efforts are being made to increase this selectivity for new PDE5 inhibitors (based on structure-function discoveries) because sildenafil also affects PDE6 and PDE1, causing visual impairment, headaches, and hot flashes. More than 90% of drug sales for ED treatment are sildenafil. Numerous studies on sildenafil in men with cardiovascular complications have shown no synergistic effect with antihypertensive drugs (ACEIs, diuretics, calcium channel blockers, alpha, and beta-adrenoceptor blockers) other than natural nitrates.²⁷ Sildenafil affects 30 to 60 minutes after use until 12 hours after use, but the peak effect is 1 hour after use. An empty stomach makes the onset of action faster, but fatty foods reduce or prolong its absorption.^{62,82} The potency of sildenafil is strong only for families 1, 5, and 6 PDEs but very weak for other PDE enzymes. Families 1 and 6 are very similar to 5 and are very specific to cGMP.²⁶ Sildenafil is sold in two commercial forms: Revatio, which reduces pulmonary artery blood pressure (PAH), and Viagra, used to treat ED. Sildenafil is a treatment but not a cure, and thus, it must be administered for a long time.^{47,83} The effectiveness of sildenafil doses over 24 weeks of use is as follows: 25 mg: 56% - 50 mg: 77% - 100 mg: 84% - placebo: 25%.⁶² Its oral absorption is reported to be about 92%.⁸⁴

Patients prefer methods that are less invasive and easier to use. This is why topical phosphodiesterase inhibitors (PDEIs) have been proposed today as a treatment option; 1 of the most important is sildenafil.⁵ The topical application does not have systemic problems and is better accepted by the patient. However, barriers need to be addressed, such as toxicity or non-toxicity for the sexual partner.⁶ Even though there is no approved topical medication in the United States for ED, many studies have been done on topical sildenafil. These studies have shown good penetration and few side effects.^{85–88} One of the products available in pharmacies as a manufactured drug is a combination of sildenafil and topical alprostadil.⁸⁵ Dermal delivery of sildenafil citrate at a dose of 28–56 mg appears to erect for 30 minutes if sexual arousal continues.⁸⁹ Oral administration of SC faces many obstacles such as a short duration of action, a prolonged onset of action, and intestinal and hepatic first-pass metabolism,⁹⁰ and as mentioned before, systemic SC has serious side effects such as hypotension, arrhythmia, headache, nasal congestion, priapism, emesis, disturbed vision, and even retinitis.⁷⁹ Patients with moderate to severe cardiovascular disease or those undergoing nitrate therapy are at increased risk with SC oral therapy, documented as a substantial contraindication in medical references.⁹⁰ Oral SC has many advantages, like a double-edged sword, but its significant disadvantages cannot be ignored. The topical form also faces problems such as poor membrane permeability and the need for appropriate pH and particular drug delivery forms, which are much easier to solve by the topical form. In a study with a sample population of 80 people who were divided into two halves to compare oral and topical sildenafil, in the topical group, 4 people (10%) complained of mild headache.⁹¹ A suitable nanocarrier can greatly alleviate some of the problems of the oral form, for example, SC-loaded self-nano emulsifying drug delivery system (SNEDDS) and nanoemulsions. Additionally, an optimized nanoemulsion can also manifest promising effects on topical drug delivery.⁹²

The most critical interaction for this class of drugs is their X-class interaction with nitrates to reduce arterial pressure, even leading to death.⁹³ All possible side effects, interactions, and contraindications to systemic PDE5Is lead patients to topical administrations that are less venturesome in nature. Transdermal delivery of SC is another way to use SC. It has advantages such as fewer side effects, shorter onset time, and sustainable outcomes for more extended periods.⁹⁰ With the penetration of the minimum effective dose into the cavernous tissue of the penis, adequate efficacy (due to avoiding extensive first-pass metabolism) along with minimal side effects will be expected.⁷⁹ Transdermal SC effects depend on its ability to penetrate through the skin to the target receptor. The main challenge for the drug to reach the cavernous tissue of the penis is to cross the barrier of different layers of skin and then pass-through Tunica albuginea, a bilayer structure of condensed collagen. Designing a drug delivery system that can cross both mentioned layers can revolutionize topical treatment for ED.⁷⁹ The stratum corneum (the outermost layer

Table 5. Information on topical forms of sildenafil nanoparticles⁸⁴

| Drug | Nanocarrier | Preparation method | Components | Description |
|------------|--|-----------------------------|--|---|
| Sildenafil | Transdermal Transfersomes | Lipid film hydration | l- α -Phosphatidylcholine Tween 80 Span 80 | - Particle size of 610nm - Entrapment efficiency of 97.21% - Enhancement of in-vitro permeation up to 5-fold compared to the drug suspension. |
| | Transdermal nanoemulsion Self-nano emulsifying System | Precipitation Sonication | Maisine 35-1 Caproyl 90 Cremophor RH40 Propylene glycol | - Globule size of 70 nm - Enhancement of in-vitro release, followed by a sustained pattern for 24 hours, compared to the drug suspension. - Enhancement of ex-vivo permeation rate, with prolonged profile, when compared to the drug suspension. |

of skin) hinders drug penetration and is the main barrier of drug permeation.^{11,94} Also, personal differences in skin types and penile tissues in different races and individuals, along with allergic reactions, can be challenging.⁹⁵ At this point, the importance of the formulation methods, the type of vehicle (gel, cream, ointment, etc.), and the adsorbents used are all discussed, all of which are very effective on the absorption of the drug through the skin layers and thus its effectiveness in creating an erection. In animal experiments, it was found that the highest skin absorption of sildenafil occurs in the pH range of 8-11.⁷⁸ In a study on 94 patients with symptoms of ED to compare the effectiveness of 1% sildenafil gel and 100 mg sildenafil tablet, it was found that up to 35% in topical application of cases can cause some degree of erection. Oral use was also 70% successful, but some patients had side effects such as severe headaches and dyspepsia. The results show that despite the lower success rate in improving the complication using topical gel, the shorter onset of action and less severe side effects are expected.⁷⁸ Utilizing modern drug delivery systems can also help increase the efficiency of topical products. Nano-sized colloidal carriers such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been studied for topical use more than other systems, which are more stable than liposomes and polymeric nanoparticles and can be used on an industrial scale without consumption of organic solvents. According to Hosny et al., The particle size of topical sildenafil citrate SLNs depends on the time it is exposed to ultrasound.⁹⁶ Compared to conventional carriers, such systems, besides providing more protection to the drug, have controlled release properties, improved transdermal penetration, and less skin sensitivity.

In a study conducted by Badr-eldin et al. comparing sildenafil citrate loaded transfersomal transdermal patch using a modified lipid hydration technique with sildenafil citrate film without transfersomes (the transfersome is a transporter body of liposomes composed of phosphatidylcholine and an edge activator for the targeted drug delivery system that is involved in transporting transdermal drugs through phospholipid vesicles), results were obtained that showed greater clinical efficacy of the compound. Diffusion coefficients and computed permeability for the

optimized batch were 1.57 and 1.25 times higher without the transfersomes, respectively. 130 nm vesicular sizes and 94.74% entrapment efficiency were the features of this optimized category. Due to their properties, transfersomes can cross the stratum corneum barrier and enter the systemic circulation. This can be considered a positive point because oral sildenafil citrate has a problem with poor bioavailability and short duration of action, and increasing bioavailability in this way can reduce repeated prescriptions.^{91,97} Transdermal nanoemulsion of sildenafil citrate with self-nano emulsifying drug delivery system prepared with maisine 35-1 (16.4%), caproyl 90 (32.8%), cremophor RH40 (32.8%), and propylene glycol (16.4%) in in-vitro and ex-vivo created a long-lasting release and better penetration compared to drug suspensions (Table 5).⁸⁴

Regarding sildenafil, it can be said that due to the amphoteric structure, low solubility in both aqueous and oily phases, pH-dependent characteristics, and poor membrane permeability, relying on new systems such as SC-loaded NLCs and SLNs can be a logical solution.⁹⁰ It has been shown that the hydrogel formulation of sildenafil microemulsion has a double permeability coefficient compared to the pure drug solution.⁸¹ Among the classic vehicles, gel-based formulations (like Carbopol based gels) seemed more effective than creams and ointments.⁷⁷ In 1 study using sildenafil topical bilosomes (bilosomes are a novel colloidal delivery system similar to niosomes but incorporating bile salts into the vesicular lipid bilayer membrane), rapid and adequate efficacy was reported in older mice due to its quick passage through the cutaneous fascia, increased cGMP levels in cavernous tissue, and to a lesser extent increased NO.⁷⁹

Tadalafil

Along with sildenafil, tadalafil is a recently approved PDE5 inhibitor. It was designed in 2000, and in 2003 it was approved by FDA for the treatment of ED. Tadalafil has a significant selectivity in binding to PDE5,²⁷ and in comparison, with other PDE5 inhibitors, it is at least 9,000 times more selective with a better duration.^{12,98} One of the significant drawbacks of PDE5Is

is the inhibition of PDE6, which causes visual disturbances. Tadalafil has less of this property than sildenafil and vardenafil, resulting in fewer visual disturbances. Tadalafil (Cialis) duration of action lasts from 30 minutes to 36 hours after use, but the peak effect is 2 hours after use. Food does not affect its absorption. The effectiveness of tadalafil doses over 12 weeks of use is as follows: 10 mg: 67% - 20 mg: 81% - placebo: 35%.⁶²

In addition to its long duration of action, this case leads to high consumption and clinical acceptance of this drug. However, similar to avanafil, tadalafil also faces the problem of low dissolution and variable bioavailability. Tadalafil absorption through the biological membranes is even lower than that of avanafil; it has the lowest absorption among PDE5Is.¹² To solve the low topical adsorption of tadalafil, a solution similar to avanafil was used, that is, nanoparticle bearers. This method was performed as penetration enhancer-containing tadalafil-loaded nanoliposomes (centrosomes) were formed by the hydration-sonication method.^{99,100} The combination of sialorphan, tadalafil, and NO is 1 of the most suitable compounds to produce nanoparticles and has received promising responses.¹⁰¹ Receiving an erectile response and increased intracavernous pressure (ICP) is usually received 60 minutes after topical administration. However, both topical applications of tadalafil nanoparticles and oral administration are practical.^{102,103} In one study, the drug penetration into human skin was determined by sensitive HPLC. This study used an RP column with UV detection at 290 nm, and acetonitrile-water mobile phase containing 20 mM pH 7 phosphate buffer (65.35, V / V), and finally a perfect linear calibration curve in the concentration range of 5 2000 ng/ml was obtained for tadalafil with a coefficient of determination (R²) of 0.998.¹⁰⁴ Studies show that adding alpha-lipoic acid to topical tadalafil can protect endothelial cells from oxidative stress damage. This damage causes a dose of hyperglycemia, making this combination a more suitable option for people with diabetes. This nanotransdermal compound also increases the cumulative release of the drug.¹⁰⁵

Recently, using a unique formulation containing a mixed solution of HPCD (2-hydroxypropyl-beta-cyclodextrin), PEG 400, and Tween 80, the permeability of tadalafil has been improved by 223% compared to its conventional gel.¹² As with sildenafil, topical administration of tadalafil, in addition to preventing the first-pass metabolism, resolves gastrointestinal problems and other possible systemic complications, including headache, upset stomach, back pain, muscle aches, nasal congestion, hot flashes, and dizziness. The effect of the solvent used in the formulation on the permeability of tadalafil is undeniable. In a group study, it was found that N-methyl pyrrolidone (NMP) as a solvent can increase the efficacy and local absorption of tadalafil.⁹⁴ In another research work, the solubility of tadalafil in different vehicles was investigated, and PEG 400, propylene glycol, ethanol, ethyl oleate, isopropyl myristate, and water had more suitable solubility, respectively. Also, the highest rates of transdermal drug delivery were observed in isopropyl myristate, ethyl

oleate, ethanol, propylene glycol, PEG, and water vehicles, respectively. In general, solubility and drug delivery in binary vehicles have been better than pure solvents.¹⁰⁶ In 2015, Baek et al. Designed nanostructured lipid-based carriers (NLC) made from tadalafil using penetration enhancers such as ethanol and limonene to develop a new successful drug delivery system to improve the topical effectiveness of tadalafil. A few studies about transdermal delivery of tadalafil, but further studies are required to verify its effectiveness.¹⁰⁶

Vardenafil

Vardenafil (Levitra) effects after 30 minutes, but the peak effect is 1 hour after use. Fatty foods reduce or prolong its absorption.^{62,82} The effectiveness of Vardenafil doses over 12 weeks of use is as follows⁶²: 5 mg: 66% - 10 mg: 76% - 20 mg: 80% - Placebo: 30%. Vardenafil is another PDE5 inhibitor that can be used for ED, but it should be used with caution in patients with prolonged QT intervals.⁹⁵ This potent and selective PDE5 inhibitor is similar in structure to sildenafil.³¹ In-vitro, vardenafil is about ten times more potent than sildenafil in efficacy, but it can't be said in clinical terms.⁶² Vardenafil is effective in cases where sildenafil does not work.²⁵ The design of the Vardenafil imidazotriazenone ring system was based on the hypothesis that this ring system inhibits its metabolism by the enzyme xanthine oxidase. The replacement of the phenyl pendant ring with piperazine sulfonamide led to the development of vardenafil, which is more potent and selective than sildenafil for PDE5 in-vitro.²⁷ The choice between these 3 drugs depends on the patient's condition, number of intercourses, experience, method of use, duration of action, and side effects. Although these drugs have been introduced for on-demand service, research has shown that continuous use of sildenafil and tadalafil can solve erectile problems even after discontinuation. As a result, it is suitable for couples who have frequent and unanticipated sex. This sustained effect has not been mentioned for vardenafil.⁶² It is noteworthy that these drugs interact with nitrates due to hypotension. For this reason, the time gap for sildenafil and vardenafil is 24 hours and 48 hours for tadalafil.⁶² Vardenafil is available in Europe, the US, and other countries in forms such as aqueous suspension and orodispersible tablets (ODTs).^{99,107,108}

During ex-vivo studies, transdermal nano-ethosomes made with the thin-layer evaporation technique for vardenafil showed more than 3 times the permeability of the film prepared with vardenafil powder. (Ethosomal systems are actually nanocarriers of fat-based vesicles that contain a high percentage of ethanol and are used to deliver high-performance therapeutic agents to deep layers throughout the skin). In vivo studies also demonstrate that the bioavailability of transdermal nano-ethosome is twice the drug suspension.^{84,105,109,110} More detailed statistics for comparison are as follows:

Vardenafil transdermal film⁸⁴:

— AUC: 271.67 ng/mL·h

- $t_{1/2}$: 14.40 h
- T_{max} : 2 h
- C_{max} : 25.76 ng/mL

Oral aqueous suspension⁸⁴:

- AUC: 128.30 ng/mL·h
- $t_{1/2}$: 3.89h
- T_{max} : 4h
- C_{max} : 14.54 ng/mL

These statistics show that this transdermal form can be a reliable option for ED. Still, credible research on the efficacy and efficacy of topical vardenafil for ED has not yet been performed, and it may be an exciting topic for research in the future.^{84,99}

Avanafil

Avanafil is a type of PDE5I that has been utilized to treat ED. But there are obstacles and challenges to achieving this goal with avanafil. These barriers include low solubility in water and consequent inadequate bioavailability, altered drug uptake in the presence of food, and high pre-systemic metabolism.⁹⁷ The attempts to use topical medications to reduce invasive therapies have led to topical research on avanafil. One of the proposed methods for topical application of avanafil is solid lipid nanoparticles (SLN) in hydrogel films, which have been tested in-vitro and ex-vivo and have indicated successful results.⁵ This formulation has been suggested due to the low aqueous solubility of this drug, and SLNs can help by augmenting the solubility and bioavailability. One study claimed that topical treatment with HPMC (hydroxypropyl methylcellulose) transdermal film-loaded avanafil SLNs was more effective than oral therapy.¹¹¹

One study on avanafil showed that the drug exhibited greater potency than a suspension when used as a liposome-optimized multilayer vesicle (MLVs). This increase in penetration was reported to be 4-fold after 12 hours (52.30% of the cumulative amount versus 12.36%). In general, the permeability coefficient and diffusion coefficient were 4.59 and 21.11-fold compared to the suspension mode.^{84,99} More accurate numerical statistics include the following reports:

Optimized liposomal transdermal formulation^{84,100}:

- C_{max} : 8.42 ng/mL
- T_{max} : 3.5 h
- AUC0-t: 108 ng·h/mL

Suspension formulation^{84,100}:

- C_{max} : 3.64 ng/mL
- T_{max} : 1.5 h
- AUC0-t: 13.10 ng·h/mL

This statistic shows that the bioavailability in the liposomal form is 7.3-fold greater ($P < .05$) than in the suspension form.^{99,112} Additional studies by Güven et al. reported the best state and highest efficiency at a particle size of 135.6 nm, encapsulation efficiency of 65.2%, and steady-state flux of 8.2 $\mu\text{g} / \text{cm}^2 \text{ h}$.¹⁰⁵

CONCLUSION

In recent decades, with the advancement of technology and human science, human has been able to find a solution to many of the rare and intractable diseases that have spread in societies. Unaware that many diseases that humans are struggling with have specific and proven symptoms and causes, but for some reason, they have not been considered seriously despite their high prevalence in the population. Erectile dysfunction (ED) is among underestimated issues in human welfare. The expansion of this disease is undeniable and probably has an intimate connection with today's lifestyle of humans. Men may also refuse to visit a physician and try to treat the condition due to a lack of self-confidence, lack of knowledge about the disease and its causes and symptoms and possible treatment approaches, lack of trust in the doctor, embarrassment and timidity, lack of confidence in modern therapies, and relying on traditional methods and self-medication. Also, under no circumstances can this disease be described as a superficial disease because ED is bilaterally associated with several dangerous diseases such as cardiovascular disease and diabetes. Its rapid diagnosis and treatment can be a salvation and remarkably improve the patients' quality of life. As a first-line treatment for ED in many guidelines, PDE5Is are often taken orally and have systemic absorption. Apart from some significant contraindications and interactions with drugs like ritonavir, saquinavir, and erythromycin through CYP3A4 enzymes, following this method of administration, many people develop various complications, and therefore, treatment may not be continued.

On the other hand, patients often have backgrounds such as cardiovascular disease, and meaningful drug interactions, such as nitrate interactions with PDEIs, may limit treatment. PDEIs are also contraindicated in many of the conditions and diseases mentioned earlier. In such cases, topical use of these drugs will be promising if they have sufficient absorption and effectiveness because there will no longer be the issue of systemic absorption, so interactions and contraindications will be minimized. Among the benefits of transdermal use of PDEIs are as follow⁷⁷:

- Lack of problems with gastrointestinal absorption due to gastrointestinal pH, enzymatic activity, and drug-food interaction.
- Avoiding the first-pass effect.
- Non-invasive nature of this dosage, higher acceptability for the patients, and raised compliance.
- Ease of removal from the skin and minimal side effects due to diminished oscillations in drug concentrations.
- Affordability and cost-effectiveness of this dosage form

- Providing the minimum dose to create a sufficient effect compared to oral administration.
- Localized effect besides the negligible side effects.

Unfortunately, studies in this area have been limited to sildenafil and tadalafil, and other PDE5Is have not been well studied and evaluated. Further research into new phosphodiesterases, as well as their topical use with other drugs used for ED, including prostaglandins, could be promising in the future to treat this global problem.

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