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USE OF TRANSDERMAL GEL OF SILDENAFIL CITRATE IN SEXUAL DYSFUNCTION

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ABSTRACT

Premature Ejaculation (PE) is one of the most common forms of Sexual Dysfunction and is thought to affect up to 30 % of men. This is the most frequently encountered sexual complaint of men and couples. The physical problem associated with premature ejaculation can be simply described as "over-sensitivity" of the penis. Psychological causes of PE are often associated with "performance anxiety" – anxiety relating to sexual intercourse. The most common treatment today is the oral treatment with phosphodiesterase -5 (PDE-5) inhibitors. There are currently three different inhibitors available Sildenafil, Vardenafil, and Tadalafil. Sildenafil citrate is a drug of choice used in the treatment of premature ejaculation disorder. It was licensed for use in the United States in 1998; Sildenafil has shown in studies that it improves ED in men regardless of disease etiology, severity of disease, or even age. Transdermal gel has gained more and more importance because the gel based formulations are better percutaneously absorbed than creams and ointment bases**.** *Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation.* Present Status - A review by Barry in 2001 showed, the transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery.

INTRODUCTION: There are three major forms of male sexual dysfunction are ejaculatory dysfunction, erectile dysfunction (ED) and decreased libido (hypoactive sexual desire disorder). While survey findings vary considerably, most epidemiological studies suggest that premature ejaculation (PE) may be the most common male sexual disorder. Data from the National Health and Social Life Survey have revealed a prevalence of 21 % in men ages 18 to 59 in the United State [1]. Using various definitions, other studies report prevalence ranging from less than 5 % to greater than 30 % [2, 3, 4].

The WHO second International Consultation on Sexual Dysfunction proposed a multivariate definition for PE: "Premature ejaculation is 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/or his partner bother or distress."

Premature ejaculation is defined as a male sexual climax/orgasm that happens before a man wants it to happen or too quickly during intercourse to satisfy his

partner. Most couples enjoy the sensations of intercourse, but it usually ends when the man 'comes' or ejaculates. This is the most frequently encountered sexual complaint of men and couples. It is estimated to occur in 30 % of all men.

Epidemiologically, in a random survey of 1511 men in the USA, about one third considered that they had ejaculated prematurely over the past year [5]. Data from the National Health and Social Life Survey have revealed a prevalence of 21 % in men ages 18 to 59 in the United States [6]. In general, however, the prevalence of PE is reported as being between 22–38 % of adult male population [5, 7]. In addition the psychiatric literature on the prevalence of such disorders is suggestive of family or genetic origins [8, 9].

Physiologically, penile erection is a hemodynamic event regulated by relaxation of arteriolar and trabecular smooth muscle cells in the corpora cavernosa mediated via the NO-cGMP pathway. Following sexual stimulation neuronal impulses causes the release of NO into the corpora cavernosa. As a result of which the penile blood flow increases and sinusoidal spaces expand, preventing venous outflow and producing an erection.

The phosphodiesterase inhibitors used for ED treatment are selective competitive inhibitors of phosphodiesterase type 5 (PDE-5), an enzyme that breaks down cGMP. By inhibiting cGMP breakdown, PDE-5 inhibitors enhance the vasodilatory effect of NO and restore the ability to achieve an erection in patients with ED. PDE-5 inhibitors are thus only effective in case of a simultaneous sexual stimulation. There are currently three different inhibitors available Sildenafil, Vardenafil, and Tadalafil [10-14].

Drug Profile [15]:

DRUG	SILDENAFIL CITRATE
Synonyms	Sildenafil Citrate
Chemical Formula	$C_{22}H_{30}N_6O_4S$
IUPAC Name	5-[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-propyl- 1H,4H,7H-pyrazolo[4,3-d]pyrimidin-7-one
Molecular Weight	474.576 g / mol
BCS Class	Class I (High Solubility, High Permeability)
Side effect	Headache, flushing, dyspepsia, nasal congestion and impaired vision
pKa value	8.7
Categories	Phosphodiesterase Inhibitor, Vasodilator Agent
Physical form	White to off-white crystalline powder
Solubility	3 mg/ml in water
Melting point	189-190 °C
Half Life	4 hours
Bioavailability	Absolute bioavailability is 25-63 %
Dose	25 mg – 100 mg
Route of excretion	Sildenafil is cleared predominantly by the CYP3A (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. Sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13 % of the administered oral dose).

Transdermal Drug Delivery Systems: Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation [16].

Advantages [16]:

(1) It delivers a steady infusion of a drug over an extended period of time.

(2) It increases the therapeutic value of drugs by avoiding specific problems associated with drug.

(3) The simplified medication regimen leads to improved patient compliance.

(4) Self-administration is possible with these systems.

(5) The drug input can be terminated at any point of time by removing transdermal patch.

Transdermal Gel: Transdermal gel preparations are intended for superficial skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action. Gels are typically formed from a liquid phase that has been thickened with other ingredients. The continuous liquid phase allows free diffusion of molecules through the polymers scaffold and hence release might be equivalent to that from a simple solution.

Transdermal gel reduces the adverse drug reaction associated with oral formulations. Transdermal application of gels at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compare to creams and ointments [18].

Advantages: The transdermal administration of drug to achieve optimal cutaneous and percutaneous delivery has recently gained an importance because of various advantages:

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
2. They can substitute for oral administration of medication when that route is unsuitable.
3. To avoid the first pass effect.
4. They are non-invasive and have patient compliance.
5. Less greasy and can be easily removed from the skin
6. Cost effective
7. Reduction of doses as compare to oral dosage forms.
8. Localized effect with minimal side effects.

Aim and Objectives: In the recent years extensive efforts have been made in various pharmaceutical research laboratories for the development of transdermal drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment of many diseases.

The aim of present work was that to evaluate use of transdermal gel of Sildenafil Citrate as a first choice of drug used in treatment of erectile dysfunction.

Material Used: There are many pharmacological materials used like Sildenafil Citrate, Carbopol 934 P, PEG 400, HPMC K100M, sodium chloride, 95% ethanol, triethanolaine, potassium dihydrogen phosphate, sodium hydroxide pellets, distilled water.

CONCLUSIONS: As Premature Ejeculation is a major psychological problem & many people are caught by this problem, it should be relieved by any simpler & effective drug.

Sildenafil citrate is the drug of choice in the treatment of premature ejaculation.

So, transdermal gel of Sildenafil Citrate was prepared with aim to deliver the drug through transdermal route as it provide quick onset of action in comparison of oral route. Carbopol was found to be suitable polymer as it gives better consistency, viscosity, spreadability, pH, homogeneity and *in-vitro* drug release.

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