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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF SILDENAFIL CITRATE

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ABSTRACT

The objective of this study was to formulate and evaluate a transdermal patch of sildenafil citrate to enhance its bioavailability, reduce first-pass metabolism, and provide sustained release. Sildenafil citrate, a phosphodiesterase type 5 inhibitor, is commonly used in the treatment of erectile dysfunction but faces limitations related to its oral bioavailability and short half-life. Transdermal drug delivery offers an alternative route of administration that can bypass the gastrointestinal tract and liver metabolism, thereby improving therapeutic outcomes. The sildenafil citrate patches were prepared using different polymers hydroxypropyl methylcellulose,and plasticizers polyethylene glycol to optimize the release characteristics. The patches were evaluated for various physicochemical properties, including thickness, weight uniformity and drug content. In vitro drug release studies were conducted using a Franz diffusion cell to determine the release profile of sildenafil citrate. The results showed that the patches exhibited a controlled release over 24 hours, with a significant increase in drug permeation across the skin compared to conventional oral formulations. The stability studies indicated that the patches were stable under accelerated conditions, with no significant degradation of sildenafil citrate. The formulation demonstrated potential for effective transdermal delivery, providing a novel approach for sustained-release sildenafil therapy, which could improve patient compliance and therapeutic efficacy.

KEYWORDS: Sildenafil citrate, hydroxypropyl, phosphodiesterase.

INTRODUCTION

The transdermal drug delivery is one most important of the novel drug delivery system. The transdermal drug delivery is one of the most effective methods of application. Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing one or more active substances. They are intended to be applied to the unbroken skin in order to deliver the active substance(s) to the systemic circulation after passing through the skin barrier. In this, drug delivery system across the skin to have an effect on the adjacent to the site of application or to have an effective distribution of the systemic circulation.

TDDS has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin as well as for systemic delivery of drug.

TDDS has provide many advantages over conventional method are frequency excessive toxic and sometimes ineffective. The conventional drugs are in the form of tablets, capsules, injectables and ointment of in the body as pulses that usually produce large fluctuations of drug concentration in the blood stream and tissues. Transdermal delivery system has provide an improved approach to the administration of drug by maintaining therapeutic constant concentration of the blood for deired period of time, high bioavailability and the fact that is non-invasive.

Transdermal delivery enables enables avoidance of gastro intestine absorption and hepatic first pass metabolism. It produce not only controlled constant administration of the drug, but also continues input of drugs with short biological half life and eliminates the pulses into systemic circulation which often cause undesirable side effect.[1,2]

Transdermal Patches

A transdermal patch is a medicated adhesive patch that is Placed on the skin to deliver a specific dose of medication Through the skin and into the bloodstream. Often, this Promotes healing to an injured area of the body. An Advantage of a transdermal drug delivery route over other Types of medication delivery such as oral, topical, Intravenous, intramuscular, etc. is that the patch provides a Controlled release of the medication into the patient, usually Through either a porous membrane covering a reservoir of Medication or through body heat melting thin layers of Medication embedded in the adhesive. The main disadvantage to transdermal delivery systems Stems from the fact that the skin is a very effective barrier; As a result, only medications whose molecules are small enough to penetrate the skin can be delivered by this Method. A wide variety of pharmaceuticals are now available in transdermal patch form.

The first commercially available prescription patch was approved by the U.S. Food And Drug Administration in December 1979 these patches Administered scopolamine for motion sickness. Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for Dermatological disorders. The occurrence of systemic side-Effects with some of these formulations is indicative of Absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically Administered drug formulations intended to deliver the Active ingredient into the general circulation. Transdermal Therapeutic systems have been designed to provide Controlled continuous delivery of drugs via the skin to the Systemic circulation. Moreover, it over comes various side Effects like painful delivery of the drugs and the first pass Metabolism of the drug occurred by other means of drug Delivery systems. So, this Transdermal Drug Delivery System has been a great Field of interest in the recent time.

Many drugs which can be injected directly into the blood stream via skin have been formulated. The main advantages of this system are that there is controlled release of the drug and the medication is Painless. The drug is mainly delivered to the skin with the Help of a transdermal patch which adheres to the skin. A Transdermal Patch has several components like liners, Adherents, drug reservoirs, drug release membrane etc. Which play a vital role in the release of the drug via skin. Various types of patches along with various methods of Applications have been discovered to delivery the drug from the transdermal patch. Because of its great advantages, it has become one of the highly research field among the various Drug delivery system. Here, a general view over the Transdermal patch has been discussed along with its Advantages, disadvantages, methods of applying, care taken While applying, types and applications of transdermal patch And recent advances along with recent patents and market Products On left is a 'reservoir' type, on the right a 'Single-layer Drug-in-Adhesive' version. Both contain exactly the same Level of the same active ingredient with identical release Rates.[3,4]

Figure 1: Transdermal patches.

ADVANTAGES OF TDDS[5]

The advantages of transdermal drug delivery system as follow as

- To avoid first pass metabolism, salivary metabolism and Intestinal metabolism.
- It is very useful for self-medications to patients.
- In case of any emergency or reactions produced means removing the patch at any point of time during therapy can instantly stop drug input.
- Drugs showing gastrointestinal irritation and absorption can be suitably administered through the skin.
- It is convenient to noninvasive route.
- Avoid the risk and Inconvenience of IV therapy.
- Bypass Variation in absorbance permits continues drug administration.
- Reduce the chances of over dose or under dosing through prolonged, Preprogrammed delivery of drug at the required therapeutic rate.
- It provides reduce the dose frequency, so there is better patient compliance.
- Therapeutic failures associated with irregularities in the dosing with conventional therapies can be avoided.
- The adverse effects are minimized due to a steady and optimum blood concentration time profile.
- The release rate more prolong than compared to oral sustained drug delivery systems.
- The daily doses require is lower than that with conventional therapies.
- The drug release is such that there is a predictable and extended duration of activity.

- It can be used for chronic conditions where drug therapy is desired for a long period of time. E.g. Hypertension, Angina and Diabetics etc.
- Transdermal therapy is not feasible for ionic drugs.
- It cannot deliver drug in pulsate fashion.

FACTORS AFFECTING TDDS

1. Physicochemical properties of permeation

1.1. Partition coefficient

For molecules with intermediate partition coefficient and for highly lipophilic molecules, the intercellular route will be almost the pathway used to traverse the stratum corneum. These molecules are ability of partition out of the stratum corneum into the aqueous viable epidermal tissues. For more hydrophilic molecules, the transcellular probably predominates. A water partition coefficient of 1 or garter is generally required for optimal transdermal permeability. It may be altered by chemical modification without affecting the pharmacological activity of the drug.

1.2. Molecular size

In this factor in determine the flux of a material through human skin is the size of the molecule. Molecular size is inversely relationship existed between transdermal flux and molecular weight of the molecules. In transdermal delivery the drug used within narrow range of molecular weight (100-500).

1.3. Solubility/Melting point

The most organic materials with high melting points have relatively low aqueous solubility at normal temperature and pressure. The lipophilic molecules tend to permeate though the skin faster than more hydrophilic molecules. Lipophilicity is a desired property of transdermal candidates, it is also necessary for the molecule to exhibit some aqueous solubility since topical medicaments are generally applied from an aqueous formulation.

1.4. Ionization

A unionized form drug can more permeate though the lipid barrier than compare to ionized drugs.

1.5 Other factors

Interactions between drug substance and their tissue can vary from hydrogen bonding to weak Vander Waals forces, and the effect of drug binding on flux across the tissue will vary depending on the permeate. Depending on the type of formulation selected, other may be important in a transdermal delivery system.[10]

2. Physiological factors

2.1. Skin barrier property in the neonate and young infant

The skin of new born is known to relative susceptible to irritants, other variables related to stratum corneum function such as p" and stratum corneoum hydration may enhance the irritant potential to newborn skin. Skin surface pH values in new born are significantly higher in all body sites than those in adult skin. There are also changes in the metabolic capacity are not observed until 2 months or even 6-12 months of age which may additionally account for the sensitivity of baby skin to irritants. The skin surface of the newborn is slightly hydrophobic and relatively dry and rough when compare to older infants.

2.2. Skin barrier properties in aged skin

The aged has no of physiological changes than compare to other skins. The corneocytes area shown to increase in surface area which may have implications for stratum corneum function due to resulting decrease the volume of inter neomeoctye space per unit volume of stratum corneum. The moisture content of human skin is decrease with age. There is flattening of the dermo epidermal junction.

2.3. Race

Radical differences between black and white skins have been shown in some anatomical and physiology functions of the skin. In black skin, increased intracellular cohesion, higher lipid content and higher electrical skin resistance levels compared to whites have been demonstrated. Black skin suggesting the stratum corneum modulates the different radical response to irritant.

2.4 Body

The relative permeability of different skin sites is not simply a function of stratum corneum thickness as a different premeants exhibit varied rank orders through different skin sites It is apparent that genital tissue usually provides the most permeable site for transdermal drug delivery. The skin of the head and neck is also relatively permeable compared to other sites of the body such as the arm and legs.

3. Physiological factors[6]

Numerous disorders result in an eruption of the skin surface. In this case, the harrier properties of the stratum corneum are compromised, allowing the passage of drug into and through the skin. The skin disease associated with reduced barrier skin function with trans epidermal water loss up to twenty times higher in active disease. The reduced barrier function, which correlated with signs of scaling, enables increased absorption of topically applied compounds. The plagues are largely devoid of intercellular lipid, reducing the convoluted lipid pathway to the dermo epidermal junction, thus enhancing permeation.

TYPES OF TRANSDERMAL PATCHES

The different type of transdermal systems was developed and fabricated such as,

- Matrix type
- Reservoir type
- Membrane matrix type
- Micro reservoir type
- Drug in adhesive type

Matrix type[7]

Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer. The required quantity of plasticizer and permeation enhancer is then added and mixed properly. The medicated polymer formed is then molded into rings with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Most of the matrix patches are prepared by

solvent evaporation method. Commonly used of matrix are cross linked polyethylene glycol, cudregit, ethyl cellulose, polyvinyl pyrrolidone and hydroxyl propyl methyl cellulose.

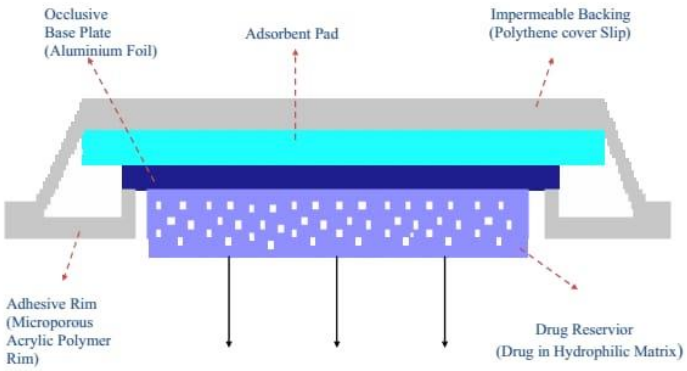


Figure 2: Matrix type transdermal patches.

Reservoir type transdermal patches[8]

Drug reservoir prepared by homogeneously dispersing drug particle in a rate controlling polymer matrix fabricated from either a lipophillic or a hydrophobic polymer. The drug dispersion in the polymer matrix is accomplished by either (1) blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross linking of the polymer chains, or (2) mixing drug solids with a rubbery polymer at elevated temperature. The resultant drug-polymer dispersion is then molded or extruded to form drug delivery device of various shape and sizes designed for specific applications. It can also fabricated by dissolving the drug and polymer in a common solvent, followed by solvent evaporation at an elevated temperature.

The drug reservoir is made up of homogenous dispersion of drug particle suspended in an unreachable viscous liquid medium to form a paste like suspension or gel or a clear solution of drug in an evaporating solvent. The drug reservoir is made by sandwiched between rate controlling membrane and backing laminate layer. Rate controlling membrane materials are such as EVA, ethyl cellulose, silicon rubber, and polyurethanes.

The rate controlling membrane may be prepared by solvent evaporating method. The solvent evaporation by polymer is dissolved in solvent with or without plasticizer. The solution poured on the horizontal surface and left for evaporation of solvent in order to obtain a thin film. The main advantage of reservoir type patches is that this patch design can provide at zero order release pattern to achieve a constant serum drug level.

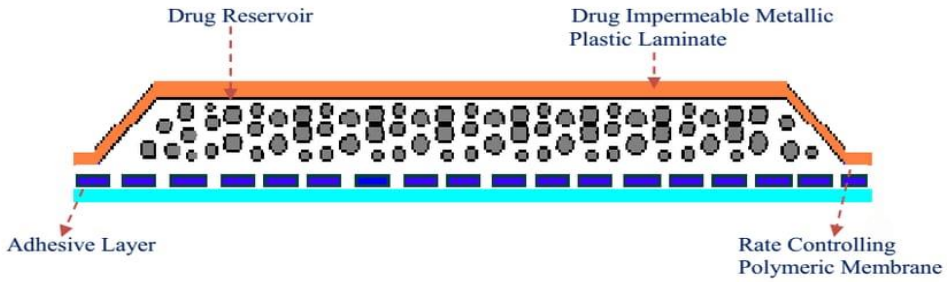


Figure 3: Reservoir type transdermal patches.

Membrane matrix hybrid type patches[7]

This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix which is sandwiched between rate controlling membrane and backing laminate.

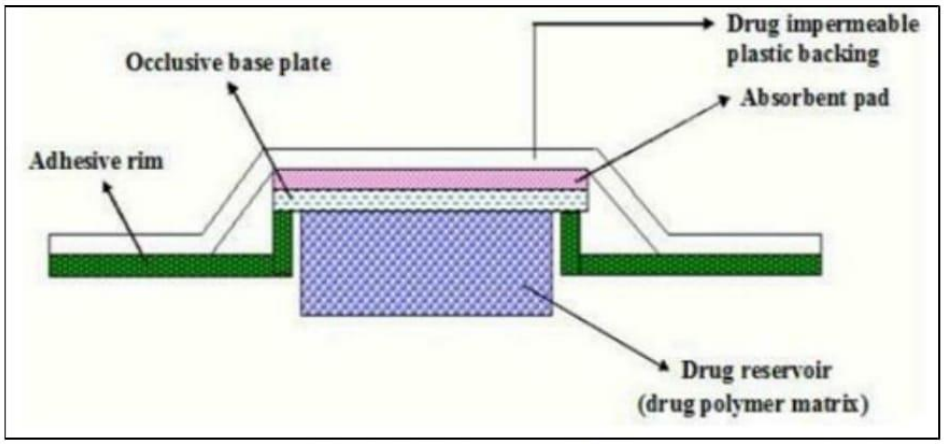


Figure 4: Membrane matrix hybrid type patches.

Micro reservoir type transdermal patches[9]

The drug reservoir is formed by suspending the drug in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogenously dispersed by a high shear mechanical force in liphophilic polymer, forming thousands of unleachable microscopic drug reservoirs. The dispersion is quickly stabilized by immediately cross linking the polymer chains in situ which produces a medicated polymer dise of specific area and fixed thickness.

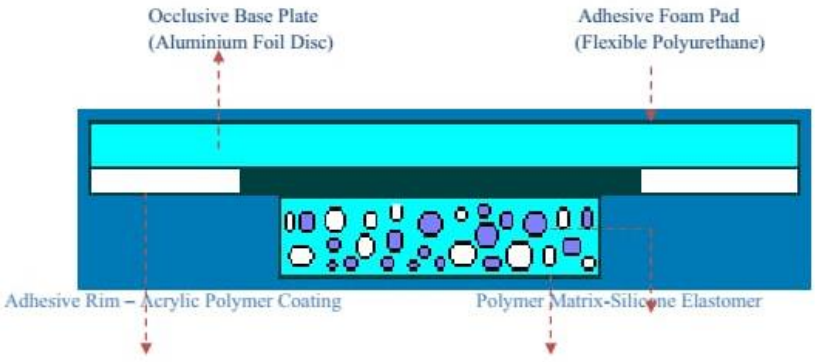


Figure 5: Micro reservoir type transdermal patches.

Drug in adhesive type transdermal patches[7,5]

The drug and others selected excipients, if any, are directly incorporated into the organic solvent-based pressure sensitive adhesive solution, mixed cast as a film and dried to evaporate the solvents, leaving adried adhesive matrix film containing the drug and exicipents. This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug-in- adhesive patch may be single layer or multi-layer. The multi-layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane.

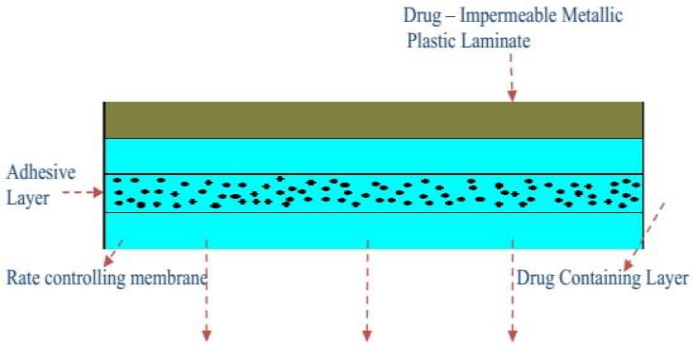


Figure 6: Drug in adhesive type transdermal patches.

Conditions which Transdermal patches are used[10]

- When the patient has intolerable side effects and who is unable to take oral medication and is requesting an alternative method of drug delivery.
- Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self medicate with their analgesia.
- It can be used in combination with other enhancement stregiges to produce synergistic effects.

Mechanism of drug delivery in transdermal drug delivery system

Transdermal absorption occurs through a slow process of diffusion driven by the gradient between the high concentration in the delivery system and the zero concentration prevailing in the skin. The delivery system must kept continuous contact with the skin for a considerable time. It is a formulation or device that maintains the blood concentration of the drug within the therapeutic window. The drug levels neither fall below the minimum effective concentration not exceeding the minimum toxic drug.

A transdermal drug delivery system is a device that is made of one or more types of polymers] embedded with drugs to deliver the embedded drug through the skin over a period of time. In this delivery system with the patch and its different layers are involved.

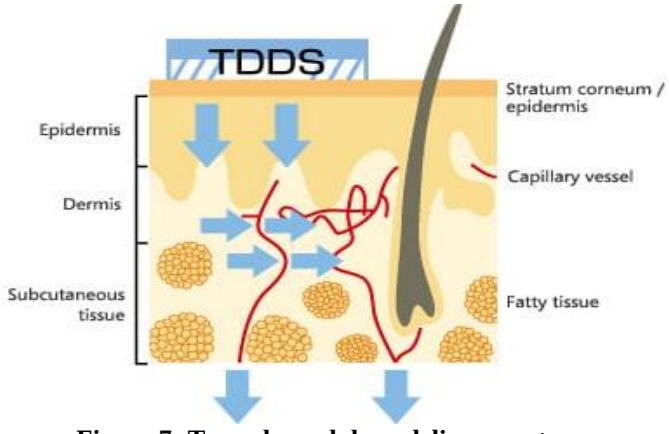


Figure 7: Transdermal drug delivery system.

The drug penetrate the skin obey's the fick's first law where steady-state flux (J) is related to the diffusion coefficient(D) of the drug in stratum corneum over a diffusional path length or membrane thickness(h), the partial coefficient(P) between the stratum cornuem and the vehicle and the applied drug concentration(CO) which is assumed to be constant.

ANATOMY AND PHYSIOLOGY OF SKIN

The potential of using the intact skin as the port of drug administration tre the human body has been recognized for several decades. However, the skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. In order to design a drug delivery system, one must first understand the skin anatomy ший its implication of drug-of choice and method of delivery. The human skin is the largest organ in our body with surface area of 1.2-2.0m2. It is composed of three main layers; the epidermis, dermis and hypodermis (subcutaneous layer) The skin is a well energized organ that protects the organism against environmental factors and regulates heat and water loss from the body.

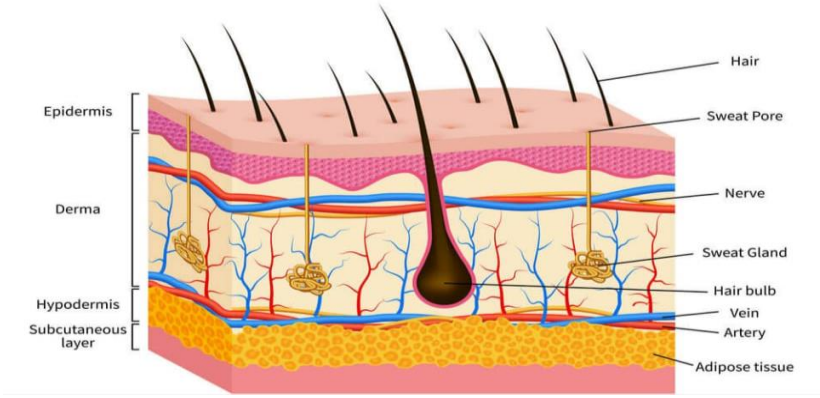


Figure 8: Anatomy of Skin.

Routes of drug penetration through the skin

The permeation of drugs through the skin involves the diffusion through the intact epidermis through the skin appendages (hair follicles and sweat glands). These skin appendages form shunt pathways through the intact epidermis, occupying only 0.1% of the total human skin. It is known that drug permeation through the skin is usually limited by the stratum corneum. Three main penetration routes are recognized.

The intercellular lipid route[13]

Inter lamellar regions in the stratum corneum, including linker regions, contain less ordered lipids and more flexible hydrophobic chains. This is the reason for the nonplanar spaces between crystalline lipid lamellae and their adjacent cells' outer membrane. Fluid lipids in skin barrier are crucially important for transepidermal diffusion of the lipidic and amphiphilic molecules, occupying those spaces for the insertion and migration through intercellular lipid layers of such molecules. The hydrophilic molecules diffuse predominantly "laterally" along surfaces of the less abundant water-filled interlamellar spaces or through such volumes; polar molecules can also use the free space between a lamella and a corneocyte outer membrane to the same end.

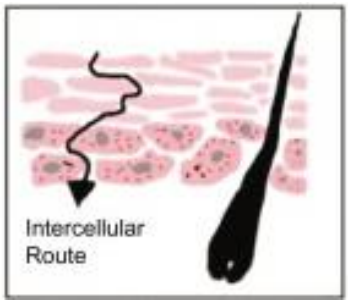


Figure 9: The intercellular lipid route.

The transcellular route[12]

Intracellular macromolecular matrix within the stratum corneum abounds in keratin. Which does not contribute directly to the skin diffusive barrier but supports mechanical stability and thus intactness of the stratum corneum. Transcellular diffusion is practically unimportant for transdermal drug transport. The narrow aqueous transepidermal pathways have been observed using confocal laser scanning microscopy. Here, regions of poor cellular and intercellular lipid packing coincide with wrinkles on skin surface and are simultaneously the sites of lowest skin resistance to the transport of hydrophilic entities.

This lowest-resistance pathway leads between clusters of corneocytes at the locations where such cellular groups show no lateral overlap. The contribution to transdermal drug transport can increase with pathway widening or multiplication, e.g., that which is caused by exposing the stratum corneum to a strong electrical (electroporation / iontophoresis), mechanical (sonoporation / sonophoresis), or thermal stimulus, or suitable skin penetrants.

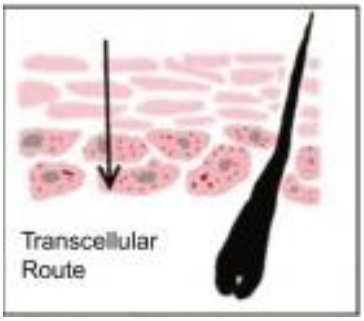


Figure 10: The transcellular route.

Follicular penetration[13]

Recently, follicular penetration has become a major focus of interest due to the fact that drug targeting to the hair follicle is of great interest in the treatment of skin diseases. However, follicular orifices occupy only 0.1% of the total skin surface area. For this reason, it was assumed to be a non-important route for drug penetration. But a variety of studies have shown that hair follicles could be an interesting option for drug penetration through the skin. Such follicular pathways have also been proposed for topical administration of polystyrene nanoparticles.

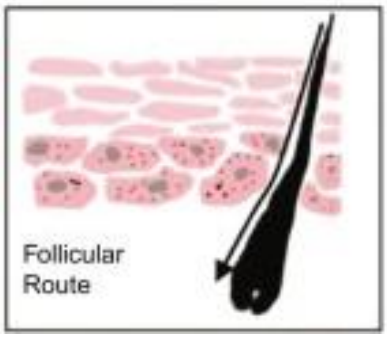


Figure 11: The Follicular route.

They were investigated in porcine skin (ex vivo) and human skin (in vivo). Surface images revealed that polystyrene nanoparticles accumulated preferentially in the follicular openings. This distribution was increased in a time-dependent manner, and the follicular localization was favored by the smaller particle size. The study also confirmed similarity in

the penetration between both membranes (porcine and human skin). In other investigations, the influence of microparticle size in skin penetration has been shown by differential stripping. Nanoparticles can act as efficient drug carriers through the follicle or can be utilized as follicle blockers to stop the penetration of topically applied substances.

Disease introduction

Erectile dysfunction (ED), formerly termed impotence, is defined as the failure to achieve or maintain a rigid penile erection suitable for satisfactory sexual intercourse.[28] While no specific time is part of this definition, some have suggested that the condition needs to persist for six months. ED is a common condition in men who are 40 years and older; prevalence increases with age and other co-morbidities.[32]

ED can be a symptom of a wide range of underlying pathologies and is an essential but underutilized cardiovascular risk factor.[15,29,16,9,24] Any disease process that affects penile arteries, nerves, hormone levels, smooth muscle tissue, corporal endothelium, or tunica albuginea can cause erectile dysfunction. This condition is closely related to cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension, among other disorders. Endothelial dysfunction appears to be the other common pathway in patients with this condition.[25]

While the vast majority of patients with ED will have organic disease, some may have a primary psychological issue, particularly younger men. Even when the underlying cause is organic, there are almost always psychological consequences to ED regarding marital and relationship issues, cultural norms and expectations, loss of self-esteem, shame, anxiety, and depression, among others. ED can cause considerable emotional damage to the patient and their partner, as well as have a significant impact on their quality of life. Fortunately, ED is almost always treatable.

Symptoms[21]

Erectile dysfunction symptoms might include persistent:

- Trouble getting an erection
- Trouble keeping an erection
- Reduced sexual desire

Causes[21]

Male sexual arousal is a complex process that involves the brain, hormones, emotions, nerves, muscles and blood vessels. Erectile dysfunction can result from a problem with any of these. Likewise, stress and mental health concerns can cause or worsen erectile dysfunction.

Sometimes a combination of physical and psychological issues causes erectile dysfunction. For instance, a minor physical condition that slows your sexual response might cause anxiety about maintaining an erection. The resulting anxiety can lead to or worsen erectile dysfunction.

Physical causes of erectile dysfunction[21]

In many cases, erectile dysfunction is caused by something physical. Common causes include:

- Heart disease
- Clogged blood vessels (atherosclerosis)
- High cholesterol
- High blood pressure

- Diabetes
- Obesity
- Metabolic syndrome - a condition involving increased blood pressure, high insulin levels, body fat around the waist and high cholesterol
- Parkinson's disease
- Multiple sclerosis
- Certain prescription medications
- Tobacco use
- Peyronie's disease - development of scar tissue inside the penis
- Alcoholism and other forms of substance abuse
- Sleep disorders
- Treatments for prostate cancer or enlarged prostate
- Surgeries or injuries that affect the pelvic area or spinal cord
- Low testosterone

Pathophysiology[30,31,32]

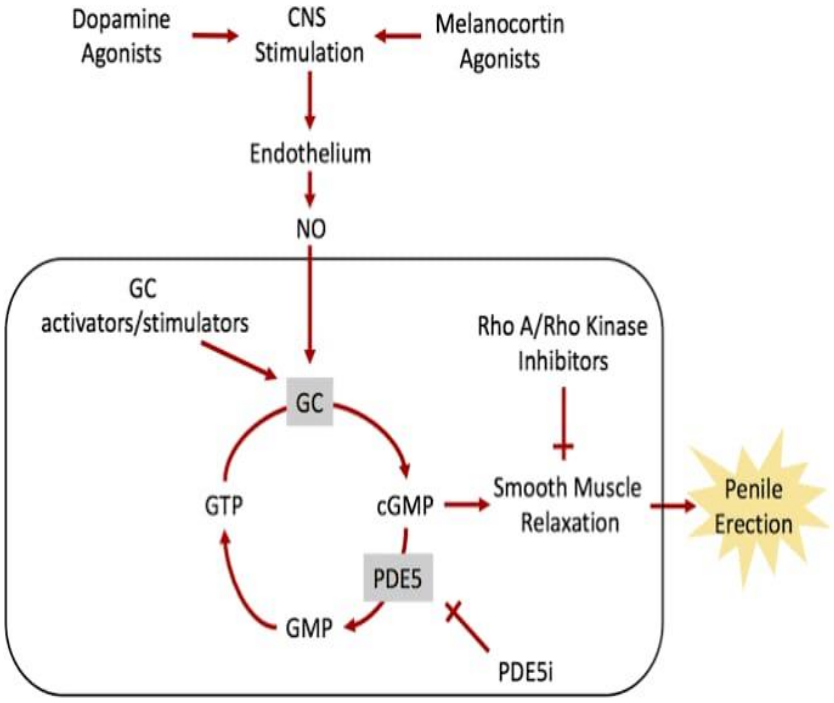


Figure 12: Pathophysiology of erectile dysfunction.

Psychological causes of erectile dysfunction[21]

The brain plays a key role in triggering the series of physical events that cause an erection, starting with feelings of sexual excitement. A number of things can interfere with sexual feelings and cause or worsen erectile dysfunction. These include:

- Depression, anxiety or other mental health conditions
- Stress
- Relationship problems due to stress, poor communication or other concerns

Risk factors[21]

As you get older, erections might take longer to develop and might not be as firm. You might need more direct touch to your penis to get and keep an erection.

Various risk factors can contribute to erectile dysfunction, including:

- **Medical conditions,** particularly diabetes or heart conditions
- **Tobacco use,** which restricts blood flow to veins and arteries, can — over time — cause chronic health conditions that lead to erectile dysfunction.
- **Being overweight**, especially if you're obese
- **Certain medical treatments**, such as prostate surgery or radiation treatment for cancer
- **Injuries**, particularly if they damage the nerves or arteries that control erections
- **Medications**, including antidepressants, antihistamines and medications to treat high blood pressure, pain or prostate conditions
- **Psychological conditions**, such as stress, anxiety or depression
- **Drug and alcohol use**, especially if you're a long-term drug user or heavy drinker

Prevention[21]

The best way to prevent erectile dysfunction is to make healthy lifestyle choices and to manage any existing health conditions. For example:

- Work with your doctor to manage diabetes, heart disease or other chronic health conditions.
- See your doctor for regular checkups and medical screening tests.
- Stop smoking, limit or avoid alcohol, and don't use illegal drugs.
- Exercise regularly.
- Take steps to reduce stress.

Get help for anxiety, depression or other mental health concerns.

Mechanism of sildenafil citrate

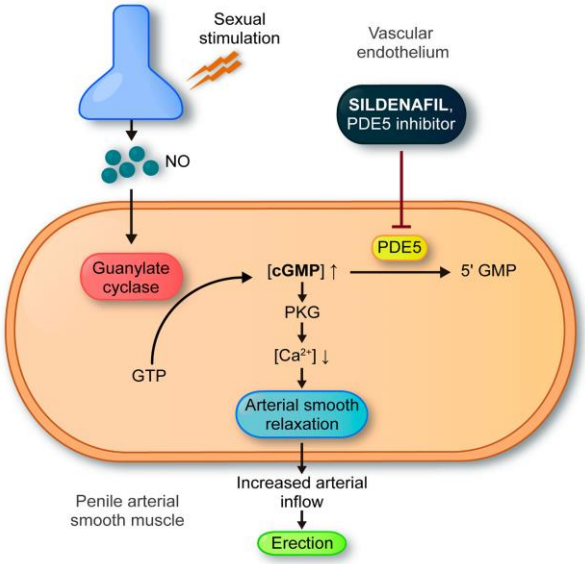


Figure 13: Mechanism of Sildenafil Citrate.

1. PDE5 Inhibition: Sildenafil and other PDE5 inhibitors bind to the PDE5 enzyme, inhibiting its activity.
2. Nitric Oxide (NO) Release: During sexual arousal, NO is released from the endothelial cells lining the blood vessels of the penis.
3. cGMP Accumulation: With PDE5 inhibited, cGMP accumulates, leading to prolonged smooth muscle relaxation.
4. Smooth Muscle Relaxation: cGMP causes relaxation of the smooth muscle cells in the corpus cavernosum, allowing blood to flow into the penis.
5. Increased Blood Flow: Increased cGMP levels cause increased blood flow into the penis, resulting in an erection.

Aim

The aim of this study is to formulate and evaluate a transdermal patch for the of sildenafil citrate with sustained delivery, utilizing biocompatible polymers such as Hydroxypropyl Methylcellulose (HPMC) and Polyethylene Glycol (PEG) to enhance drug permeability, sustained release (prolong release), and improve bioavailability while minimizing first-pass metabolism and systemic side effects.

Objectives

1. To develop a transdermal patch using suitable polymers and excipients to achieve sustained drug release.
2. To evaluate the physicochemical properties of the prepared patch, including thickness, weight variation, and drug content uniformity.
3. To assess the in vitro drug release profile of sildenafil citrate from the transdermal patch.
4. To conduct diffusion studies to determine the permeability and sustained release characteristics.
5. To perform stability studies under different environmental conditions to ensure formulation integrity.

DRUG AND EXCIPIENT PROFILE

SILDENAFIL CITRATE[58-60]

Sildenafil citrate is a medication primarily used to treat erectile dysfunction (ED) and pulmonary arterial hypertension (PAH). Here's a detailed drug profile:

Generic Name: Sildenafil Citrate

Brand Names

- Viagra (for ED)
- Revatio (for PAH)

Drug Class

- Phosphodiesterase type 5 (PDE5) inhibitor

Chemical structure

IUPAC name: **(1R,2R)-N-[(3S,4S)-4-(2-ethoxyphenyl)-3-(ethylamino)thio]-1-methyl-2-pyrimidin-5-yl]-3,4-dihydro-1H-quinazoline-2-carbaldehyde.

Here’s a general breakdown of its structure:

Molecular Formula: C22H30N6O4S

Structure:

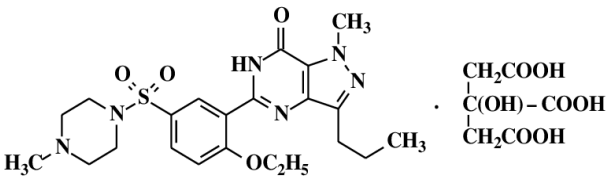


Figure 14: Sildenafil Citrate Structure.

Mechanism of Action

Sildenafil works by inhibiting the enzyme PDE5, which breaks down cyclic guanosine monophosphate (cGMP). By inhibiting PDE5, sildenafil helps to increase the levels of cGMP, leading to relaxation of smooth muscle and dilation of blood vessels in the penis (for ED) or the lungs (for PAH). This helps to improve blood flow, either enhancing erectile function or reducing pulmonary pressure.

Indications

- Erectile Dysfunction: Treatment of ED in adult men.
- Pulmonary Arterial Hypertension: To improve exercise capacity and delay clinical worsening in PAH.

Dosage

- Erectile Dysfunction

The typical starting dose is 50 mg taken about 1 hour before sexual activity, though it can range from 25 mg to 100 mg based on effectiveness and tolerability. It should not be taken more than once a day.

- Pulmonary Arterial Hypertension

The starting dose is generally 5 mg three times a day, but it can be adjusted depending on response and tolerability.

Onset and Duration of Action

- Erectile Dysfunction

Onset: Typically within 30-60 minutes

Duration: Can last up to 4-6 hours, though its effectiveness for ED may diminish over time.

- Pulmonary Arterial Hypertension

Onset: Within 30-60 minutes.

Duration: Effects can last for several hours, depending on individual patient response.

Side Effects

- Headache
- Flushing
- Dyspepsia (indigestion)
- Nasal congestion
- Dizziness
- Vision disturbances (e.g., blurred vision, color tinge)
- Priapism (a prolonged, painful erection) is a rare but serious side effect that requires immediate medical attention.

Contraindications

- Nitrates: Sildenafil should not be used in combination with nitrate medications (e.g., nitroglycerin), as this can cause a significant drop in blood pressure.
- Severe cardiovascular conditions: People with certain heart conditions should avoid sildenafil, especially if they have unstable angina or have had a recent heart attack or stroke.

Precautions

- Renal and Hepatic Impairment: Dose adjustment may be necessary in patients with liver or kidney problems.
- Blood Pressure: Sildenafil can cause a slight drop in blood pressure, so caution is advised for people with low blood pressure or those on antihypertensive medications.
- Vision Issues: Some individuals may experience temporary changes in vision, particularly a blue tinge or increased sensitivity to light. This is typically short-lived.

Drug Interactions

- Alpha-blockers: Using sildenafil with alpha-blockers (used for high blood pressure or prostate problems) can enhance blood pressure-lowering effects.
- Antifungals and Antibiotics: Certain drugs like ketoconazole or erythromycin can increase sildenafil levels in the blood, increasing the risk of side effects.
- Ritonavir (a protease inhibitor): This can increase sildenafil levels significantly, requiring dosage adjustments.

Pregnancy Category

- Category C (Risk cannot be ruled out) – There's no evidence of teratogenic effects in humans, but sildenafil should only be used during pregnancy if absolutely necessary.

Excretion

Sildenafil is primarily excreted in the urine, with a half-life of about 4 hours. This means it stays in the body for several hours before being cleared.

Considerations for Special Populations

- Elderly: Older adults may be more susceptible to side effects, so the lowest effective dose is typically recommended.
- Children: Sildenafil is not recommended for children under the age of 18 unless prescribed for a specific medical condition, such as pulmonary hypertension.

EXCIPIENT PROFILE

Hydroxypropyl Methylcellulose (HPMC)[61-62]

Synonyms

Hypromellos, Methyl Hydroxypropyl Cellulose Hydroxypropyl Methyl Cellulose, Hydroxypropyl Methyl Ether.

Chemical Structure

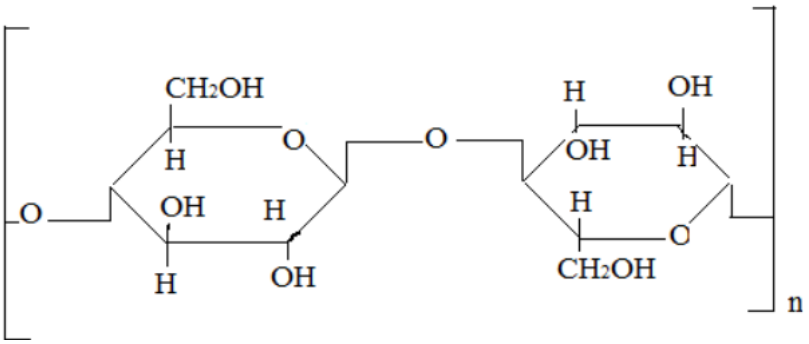


Figure 15: HPMC Structure.

Molecular Formula

C12H22O7

Molecular Weight

50,000-1,000,000 Da)

Physical Properties

1. **Appearance**: White or off-white powder
2. **Solubility:** Soluble in cold water, forming a clear, colloidal solution
3. **Viscosity:** Varies depending on grade and concentration (typically 50-100,000 mPa·s)
4. **pH:** Neutral (pH 5.5-8.5)
5. **Density**: 0.5-0.7 g/cm3

Applications

1. Pharmaceuticals: Excipient in tablets, capsules, and ointments; binder, film-former, and controlled-release matrix.
2. Food Industry: Food additive, stabilizer, and thickener in ice cream, sauces, dressings, and more.
3. Cosmetics: Personal care products, such as toothpaste, hair care, and skin care creams.
4. Construction: Building materials, such as cement, mortar, and drywall.
5. Textiles: Sizing agent and finisher for textiles.

Storage

Store in a cool, dry place, away from direct sunlight and moisture.

ETHANOL[63]

Chemical Name: Ethanol

Chemical Structure:

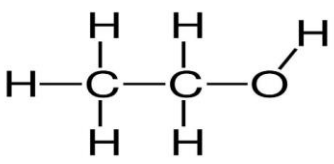


Figure 16: Ethanol Structure.

Molecular Formula: C2H5OH

Physical Appearance: Colourless, clear liquid

Solubility: Miscible with water and most organic solvents

Boiling Point: 78.3°C (173.1°F)

Melting Point: -114.1°C (-173.4°F)

Uses and Applications

1. Pharmaceuticals: Ethanol is used as a solvent, preservative, and antimicrobial agent in various pharmaceutical formulations.
2. Beverages: Ethanol is the primary psychoactive ingredient in alcoholic beverages.
3. Industrial Applications: Ethanol is used as a solvent, cleaning agent, and fuel additive in various industries.
4. Medical Applications: Ethanol is used as an antiseptic and disinfectant in medical settings.

Pharmacokinetics

1. **Absorption:** Ethanol is rapidly absorbed from the gastrointestinal tract.
2. **Distribution**: Ethanol is distributed throughout the body, with high concentrations in the brain and liver.
3. **Metabolism:** Ethanol is metabolized by the liver enzyme alcohol dehydrogenase.
4. **Excretion:** Ethanol is excreted through the kidneys, lungs, and skin.

Safety and Toxicity

1. Toxicity: Ethanol is toxic at high concentrations, causing CNS depression, respiratory depression, and death.
2. Addiction: Ethanol is addictive, and chronic use can lead to dependence and withdrawal symptoms.
3. Interactions: Ethanol interacts with various medications, including sedatives, antidepressants, and antihistamines.

Contraindications and Precautions

1. Pregnancy and Breastfeeding: Ethanol is contraindicated in pregnancy and breastfeeding due to its potential for fetal harm and infant exposure.
2. Liver Disease: Ethanol is contraindicated in patients with liver disease due to its potential for hepatotoxicity.
3. Medication Interactions: Ethanol should be used with caution in patients taking medications that interact with ethanol.

Storage

Ethanol should be stored in a cool, dry place, away from direct sunlight and heat sources.

POLYETHYLENE GLYCOL (PEG)[64-66]

Synonyms

Macrogol, Polyethylene oxide

Chemical structure

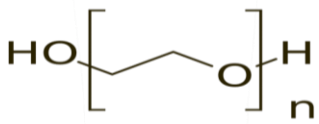


Figure 17: Polyethlene Structure.

Molecular Weight

- PEG can have a wide range of molecular weights, from as low as 200 Da to several million Da. The properties of PEG vary significantly depending on its molecular weight.

Molecular Formula

$(C_2H_4O)_n$

Appearance

- Low molecular weight PEG: A Colourless, Odourless Liquid (E.G., PEG 200, PEG 400).
- High Molecular Weight PEG A Waxy, White, Or Off-White Solid (E.G., PEG 6000).

Solubility

- Water solubility: PEG is highly soluble in water. The solubility increases as the molecular weight decreases.
- Solubility in organic solvents: It is also soluble in many organic solvents, such as alcohols, acetone, and chloroform.

Melting Point

1. The melting point varies with molecular weight. For instance:
2. Low molecular weight PEG (e.g., PEG 400): Has a melting point below room temperature (liquid form).
3. High molecular weight PEG (e.g., PEG 6000): Can have a melting point ranging from 60°C to 65°C (solid form).

Viscosity

- PEG exhibits low viscosity at lower molecular weights and becomes increasingly viscous as the molecular weight increases. This makes it useful for different applications, such as thin liquids for pharmaceuticals or thicker gels for ointments.

Non-toxicity

- PEG is generally considered non-toxic, biocompatible, and hypoallergenic, which is why it is widely used in medical and cosmetic applications.

Biodegradability

- PEG is biodegradable by microorganisms, but the rate at which it degrades depends on the molecular weight and environmental conditions (e.g., temperature and microbial activity).

Hydrophilicity

- PEG is highly hydrophilic (water-attracting), which is why it is often used as a humectant in cosmetics, personal care products, and food.

Stability

- PEG is chemically stable and resistant to oxidation, making it suitable for long-term use in various formulations (medicines, cosmetics, etc.).

pH Sensitivity

- PEG is neutral to mildly alkaline in nature and maintains stability across a wide pH range, making it a versatile ingredient in many formulations.

Freezing Point

- Low molecular weight PEGs generally have a freezing point below 0°C, while higher molecular weights have higher freezing points.

Storage

PEG should be stored in a cool, dry place, away from direct sunlight and moisture.

Uses and Applications

- Pharmaceuticals: PEG is used in various pharmaceutical formulations, including tablets, capsules, injections, and ointments.
- Biotechnology: PEG is used in biotechnology applications, such as protein purification and conjugation.
- Cosmetics: PEG is used in personal care products, such as skin creams, lotions, and shampoos.

OLEIC ACID[67-68]

Synonyms: Octadecenoic acid, Cis-9-octadecenoic acid, 9-octadecenoic acid, Omega-9 fatty acid.

Chemical structure:

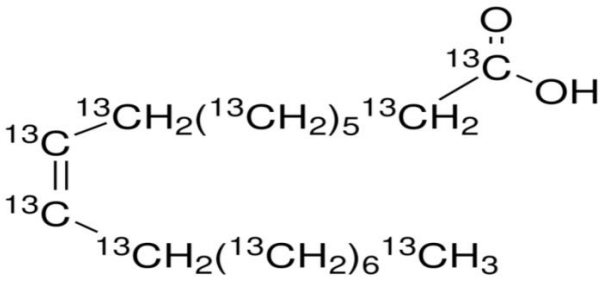


Figure 18: Oleic Acid Structure.

Chemical formula

C18H34O2

IUPAC name: (9Z)-Octadec-9-enoic acid

Sources

- **Plant sources:** Olive oil (55-83%), avocado oil, canola oil, and some nuts and seeds (like almonds).
- **Animal sources**: It can also be found in animal fats but in lower quantities compared to plant oils.

Molecular Formula

C18H34O2

Physical Appearance

Colourless or pale yellow liquid

Solubility

Soluble in ethanol, ether, and other organic solvents

Melting Point

13-14°C (55-57°F)

Boiling Point

223-225°C (433-437°F)

Uses and Applications

- Pharmaceuticals: Oleic acid is used in various pharmaceutical formulations, including topical creams, ointments, and injections
- Cosmetics: Oleic acid is used in personal care products, such as skin creams, lotions, shampoos, and conditioner
- Food Industry: Oleic acid is used as a food additive, flavoring agent, and texture modifier in various food products

Pharmacokinetics

1. Absorption: Oleic acid is absorbed from the gastrointestinal tract
2. Distribution: Oleic acid is distributed throughout the body, with high concentrations in adipose tissue
3. Metabolism: Oleic acid is metabolized by beta-oxidation
4. Excretion: Oleic acid is excreted primarily through the kidneys

Storage: Oleic acid should be stored in a cool, dry place, away from direct sunlight and moisture.

MATERIAL UTILIZED

SOURCE OF API

The sildenafil citrate in this experiment was sourced from nice chemical, Mumbai, India.

MATERIAL USED

The following materials were used for the preparation of sildenafil citrate transdermal patch and their evaluation in their best quality available.

Table 1: Material used for the research work.

S. no.	Name	Manufacture / Supplier
1.	Sildenafil citrate	Nice chemical ,Mumbai
2.	Hydroxypropyl methylcellulose	Lobo chemie, Mumbai
3.	Ethanol	Lobo chemie, Mumbai
4.	Polyethylene glycol 400	Lobo chemie, Mumbai
5.	Oleic acid	Lobo chemie, Mumbai

Table 2: Instrument used for research work

S. no.	Instrument	Manufacture / Supplier
1.	Magnetic stirrer	Adarsh magnetic stirrer, Haryana
2.	Franz diffusion cell	ABGIL initiative,UP
3.	Electronic digital balance	Satorious 21.00 (max 220g)
5.	FT-IR 8400	SHIMADZU Scientific instruments, Japan
6.	Uvspectorophotometer	SHIMADZU Scientific instruments, Japan
7.	Hot air oven	Servewell industries, INDIA

PREPARATION OF CALIBRATION CURVE[69]

25 mg of Sildenafil citrate was weighed and solubility of this sample was checked in 25 ml distilled water, methanol, ethanol. It is freely soluble in water, hence solvent selected as a distilled water.[3] B) To identify the λ max of Sildenafil citrate: Weigh 10mg of the pure drug and dissolve it in small portion of distilled water and make up the volume up to 10 ml using distilled water give a standard stock solution of 1000µm/ml. From above solution 2.5 ml of the standard solution was withdrawn in volumetric flask and diluted to 25ml with distilled water to prepare 100ppm solution. Suitable dilutions were made with methanol to get standard solutions of concentrations: 5, 10, 15, 20, 25µm/ml.

PREPARATION OF STANDARD GRAPH[69]

Start by preparing a series of known concentrations of sildenafil citrate by dissolving a precise amount of the pure sildenafil citrate powder in an appropriate solvent. For example, you could prepare concentrations such as 1.0 mg/mL, 2.0 mg/mL, 5.0 mg/mL, 10.0 mg/mL, etc., in a solvent (e.g., methanol or ethanol).

COMPATIBILITY STUDIES[69]

FTIR

Fourier-transform infrared (FTIR) spectroscopy is commonly used to analyze the molecular structure of various compounds, including sildenafil citrate Obtain a pure sample of sildenafil citrate. Grind the sample into a fine powder using a mortar and pestle. Mix the powdered sample with a suitable matrix (e.g., potassium bromide) and compress into a pellet. Use a Fourier Transform Infrared spectrometer. Use a suitable detector, such as a deuterated triglycine sulfate (DTGS) detector. Measure the spectrum over a range of 4000-650 cm^{-1}.Set the resolution to 4-8 cm^{-1}. Perform 32-64 scans. Spectral Interpretation: Interpret the obtained spectrum to identify characteristic peaks corresponding to sildenafil citrate. Peak Assignment: Assign the peaks to specific functional groups, such as:

- N-H stretching (3300-3500 cm^{-1})
- C-H stretching (2800-3000 cm^{-1})
- C=O stretching (1650-1750 cm^{-1})
- C-N stretching (1000-1200 cm^{-1})

Formula for solution preparation

$$\textbf{Concentration} = \frac{\textbf{Mass of Sildenafil Citrate}}{\textbf{Volume of Solvent}}$$

Place each of these solutions in a sample holder (or cell) that is compatible with your FTIR instrument. Record the FTIR spectra of each standard solution. Focus on the peaks that are characteristic of sildenafil citrate (e.g., C-H stretching, N-H stretching, C=O stretching, etc.). You can use a specific absorption peak for analysis, such as the C=O stretch around 1650 cm^{-1} or aromatic C-H stretching near 3000-3100 cm^{-1}.From the FTIR spectra of each standard solution, identify and record the intensity (absorbance) of the specific peak that corresponds to the active component (sildenafil citrate). Ensure that you're consistent in selecting the same peak for all measurements.

PREPARATION OF SILDENAFIL CITRATE TRANSDERMAL PATCHES[9]

Sildenafil citrate weighing

Precisely weigh a set quantity of pure sildenafil citrate. For instance, weigh about 10 mg of sildenafil citrate (employ a balance capable of reading up to 0.001g for accuracy).

Prepare solvent

Select a proper solvent in which sildenafil citrate is well dissolved (e.g., methanol or ethanol). The solvent should not interact with the FTIR peaks of concern.

Dissolve sildenafil citrate

Dissolve the weighed sildenafil citrate in a measured volume of solvent. For instance, dissolve 10 mg sildenafil citrate in 10 mL methanol to obtain a 1 mg/mL solution.

Prepare serial dilutions

Prepare standard solutions with known concentrations by serial dilution of the stock solution. For instance, prepare solutions with the following concentrations:

- mg/ml
- 2.0 mg/ml
- 5.0 mg/ml
- 10.0 mg/ml
- 15.0 mg/ml

To make these, pipette a known volume of the stock solution and dilute it with the same solvent to achieve the required concentrations.

Table 3: Composition of Sildenafil Citrate Transdermal Patch.

Formulation	Drug (sildenafil citrate) (mg)	Polymer(HPMC) (mg)	Solvent (ethanol) (ml)	Plasticizer (peg)	Permeation enhancer (oleic acid)
F1	50	150	10ml	1ml	0.5ml
F2	50	200	10ml	1ml	0.5ml
F3	50	250	12ml	1ml	0.5ml
F4	50	300	`12ml	1ml	0.5ml
F5	50	350	15ml	1ml	0.5ml
F6	50	400	15ml	1ml	0.5 ml

Prepare the FTIR instrument

Switch on the FTIR spectrometer and let it warm up (refer to the manufacturer's guidelines).Calibrate the FTIR if necessary, by performing a background scan with the solvent or air (make sure there is no contamination).

Transfer the solution to the sample holder

- Fill the sample holder with 1-2 mL of standard solution. A clean cuvette or appropriate sample holder should be used for FTIR measurement.
- If a liquid sample holder is used, check that it is free from bubble and contamination.

Record the FTIR spectra

- Position the cuvette/sample holder in the FTIR instrument.
- Obtain the FTIR spectrum of each solution. The scan should include the 4000 cm^{-1} to 400 cm^{-1} wavenumber region.
- Target a particular absorbance peak associated with sildenafil citrate. For instance, observe the C=O stretch at about 1650 cm^{-1} or aromatic C-H stretch at about 3000 cm^{-1}.

Repeat for every concentration

- For every standard concentration, take the FTIR spectrum under identical experimental conditions (same path length, solvent, etc.).
- Record the absorbance or peak height at the selected wavenumber (e.g., 1650 cm^{-1}).

Method of preparation of silidinafil citrate patch

- Weigh the required amount of sildenafil citrate. Dissolve it in an appropriate solvent (ethanol or isopropyl alcohol) to create a concentrated solution. The solvent should be enough to dissolve the drug completely, creating a homogenous solution or suspension. In a separate container, dissolve the HPMC in a solvent (water or a mixture of water and alcohol) under stirring to ensure it fully dissolves.
- Add the desired amount of Polyethylene Glycol (PEG) to the solution (typically between 5-10% of the total formulation weight). PEG acts as a plasticizer, increasing the flexibility and handling of the patch. Stir the mixture well to achieve homogeneity.
- Once the HPMC solution is ready, add oleic acid (typically around 2-5% of the total weight of the formulation). Oleic acid helps to enhance the permeation of sildenafil citrate through the skin by temporarily disrupting the skin's lipid barrier. Mix thoroughly to ensure uniform distribution of the penetration enhancer.
- Slowly add the sildenafil citrate solution into the HPMC matrix solution, ensuring uniform dispersion of the drug in the polymer matrix. Use gentle stirring to avoid air bubbles. Ensure the drug is evenly distributed in the polymer matrix for consistent drug release.
- Allow the cast patch to dry at room temperature or in an oven under controlled conditions (preferably at low heat to avoid damaging the polymer or drug). After drying, the patch can be cut into the desired shapes and sizes, depending on the dose you wish to administer and the size of the skin area to be covered. After drying, the patch can be cut into the desired shapes and sizes, depending on the dose you wish to administer and the size of the skin area to be covered.

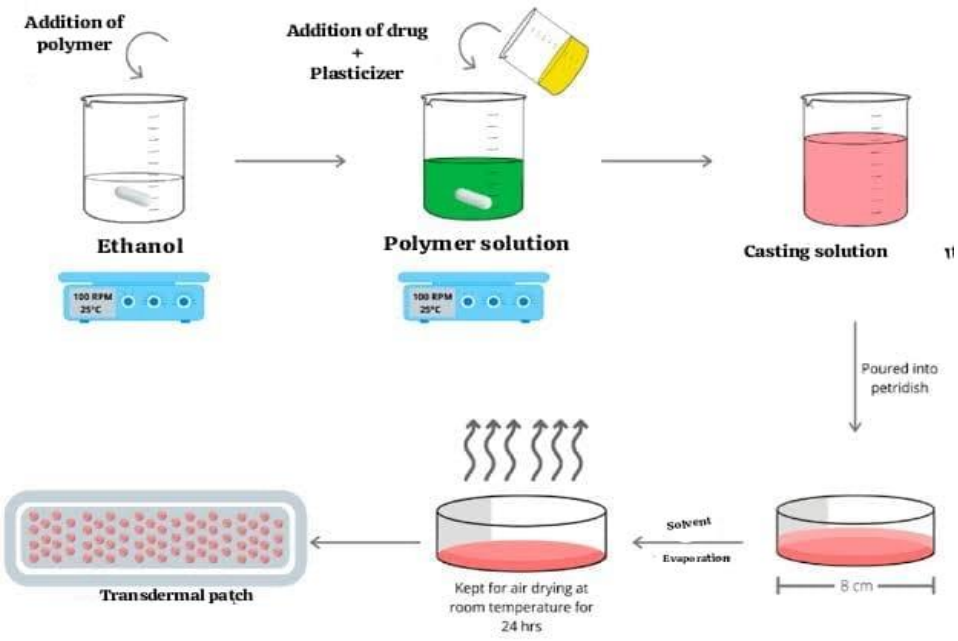


Figure 19: Methods Of Preparation Ofsildenafil Citrate Patch.

Evaluation parameter of transdermal patch of sildenafil citrate

pH measurement

The pH of various gel formulations was determined by using digital pH meter. 1 g of gel was dissolved in 100 mL freshly prepared distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

Drug content

Weigh individual patches to ensure that you have an accurate starting weight for each one. This is important as variations in the weight of the patches can influence the drug content. Choose a suitable solvent to dissolve the transdermal patch and extract the drug.

A common solvent is ethanol, but depending on the composition of the patch, other solvents such as methanol or phosphate buffer (pH 7.4) can also be used. Prepare the solvent in a volumetric flask, ensuring the solvent is sufficient to completely dissolve the active ingredient and matrix of the patch.

Cut the patch into smaller pieces if necessary to ensure complete extraction. Place the weighed patch into a clean container (such as a beaker) and add the solvent. The amount of solvent used should be enough to dissolve the drug and matrix completely.

Typically, use 50 mL to 100 mL of solvent per patch. Stir the solution continuously for a specific period (usually 30 minutes to 1 hour) at room temperature or under gentle heating (if necessary) to ensure the complete dissolution of the drug.

This step is critical to ensure the sildenafil citrate is thoroughly extracted from the matrix. Prepare a standard calibration curve by diluting known concentrations of sildenafil citrate in the same solvent. Measure the absorbance of the sample solution at the appropriate wavelength (usually 290 nm, which is the maximum absorption wavelength for sildenafil citrate).Compare the sample absorbance with the standard curve to calculate the concentration of sildenafil citrate in the patch extract. The sildenafil citrate content in each patch should be **90%–110%** of the labeled claim. The % Relative Standard Deviation (RSD) of triplicate measurements should be ≤2%. The correlation coefficient (R^2) of the calibration curve should be ≥0.999.

Physical Appearance and Thickness

Appearance: Check for uniformity, smoothness, transparency, and color of the patch.

Thickness Measurement

- Select at least five patches randomly from the batch.
- Use a micrometer screw gauge or digital caliper for measurement.
- Place the patch between the caliper jaws and gently close it to measure the thickness.
- Record the readings at five different points (center and four corners) of each patch.
- Calculate the average thickness for each patch.

Weight Uniformity

- Select 10 patches randomly from the batch.
- Weigh each patch individually using an analytical balance and record the values.
- Calculate the average weight of the patches.
- Determine the % weight variation using the formula:

$$\% \text{ weight variation} = \frac{individualweight - averageweight}{averageweight} \times 100$$

In-Vitro Drug Release Study (Dissolution Test)

1. Preparation of the Diffusion Cell*

- Fill the receptor compartment with phosphate buffer pH 7.4 or another suitable dissolution medium (50–100 mL).
- Place a magnetic stirrer bead in the receptor compartment and maintain stirring at 100–300 rpm.
- Adjust the temperature to 37°C ± 0.5°C to simulate body temperature.

2. Membrane Preparation

- Use either a synthetic membrane (e.g., cellulose acetate, dialysis membrane) or excised rat skin as the diffusion barrier.
- Carefully mount the membrane between the donor and receptor compartments.

3. Drug Release Study

- Cut the transdermal patch to a standard size (e.g., 2×2 cm^2).
- Place the patch on the donor compartment (drug side facing the membrane).
- Seal the donor compartment with Parafilm or a clamp to prevent evaporation.
- Start the stirring (100–300 rpm) and maintain a temperature of 37°C.
- Withdraw 1 mL of sample from the receptor compartment at fixed time intervals (e.g., 0, 1, 2, 4, 6, 8, 12, 24 hours).
- After each withdrawal, replace the same volume of fresh buffer to maintain sink conditions.

4. Drug Quantification

- Analyze the withdrawn samples using HPLC or UV-Vis spectrophotometry at 290 nm (wavelength for sildenafil citrate).
- Plot a cumulative % drug release vs. time graph.

RESULT AND DISCUSSION

Present study was done on formulate and evaluate a transdermal patch for the of sildenafil citrate with different formulation F1 to F6 by solvent evaporation method with using polymers such as Hydroxypropyl Methylcellulose (HPMC), Polyethylene Glycol (PEG), Oleic acid to enhance drug permeability, sustained release (prolong release).

Determination of λmax of Sildenafil citrate

The absorption maxima (λmax) of the sildenafil citrate were estimate by scaning the solution between 200-400 nm region on UV-Vis spectrophotometer. The obtain spectrum showed that the absorption maxima (λmax) was 290 nm in methanol which was shown in figure.

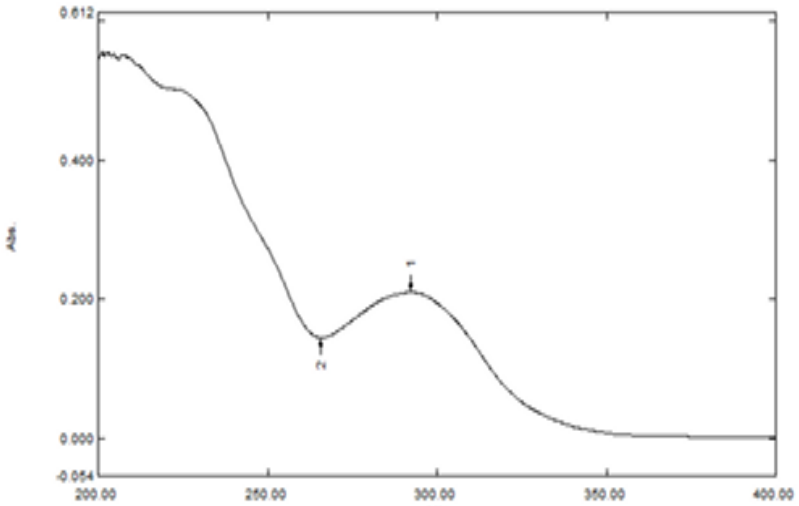


Figure 20: λ max of Sildenafil citrate.

Standard curve of sildenafil citrate

Standard graph was prepared for concentration of 5- 10mg at 293nm. The graph of absorbance vs concentration was plotted and data were subjected to linear regression analysis. The standard graph of drug in phosphate buffer shown in Table 11.

Table 4: Calibration curve of sildenafil citrate.

S. No.	Concentration (µg/ml)	Absorbance (nm)
1.	5	0.109
2.	10	0.211
3.	15	0.323
4.	20	0.431
5.	25	0.526

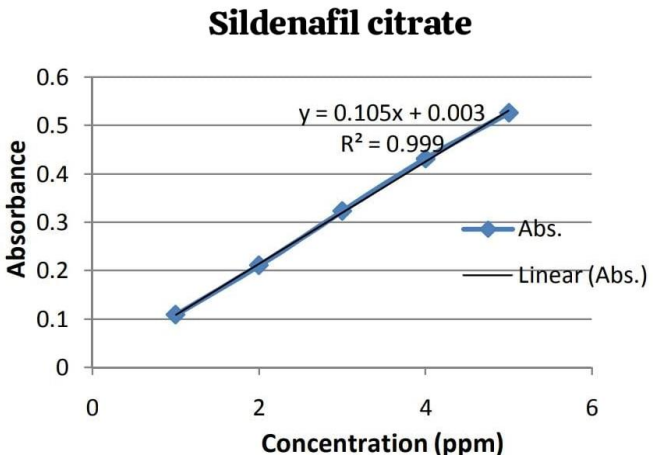


Figure 21: Linearity of sildenafil citrate.

DRUG EXCEPIENT COMPATIBILITY STUDY

To ensure that the active pharmaceutical ingredient (API) remains stable in the presence of these excipients during storage and use.

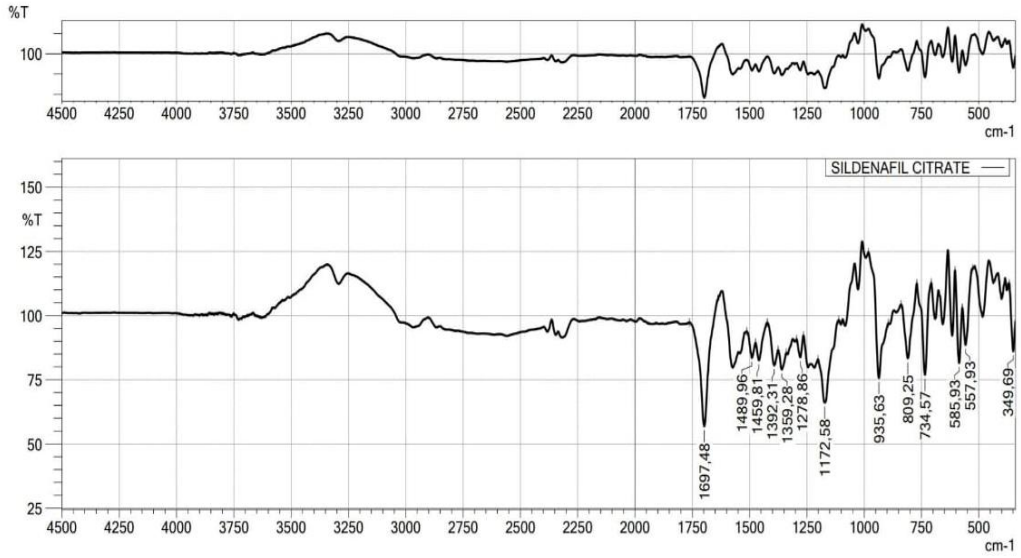


Figure 22: Spectrum of pure drug of sildenafil citrate.

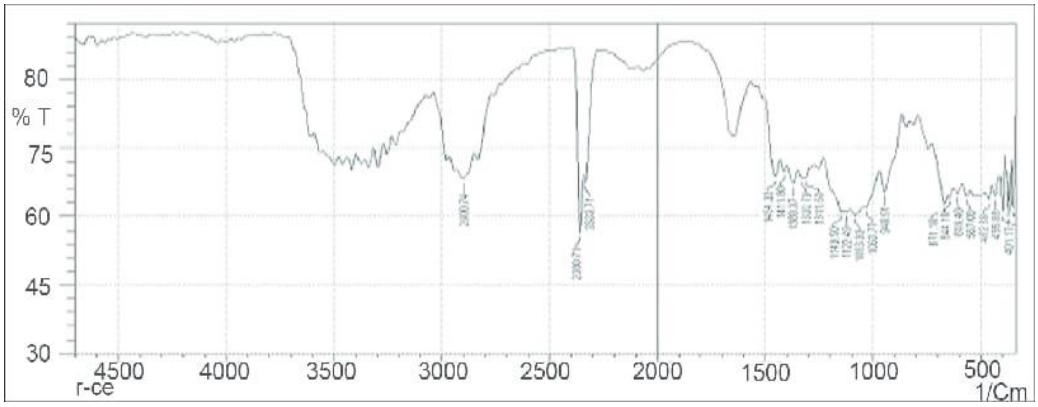


Figure 23: Spectrum of FTIR of HPMC.

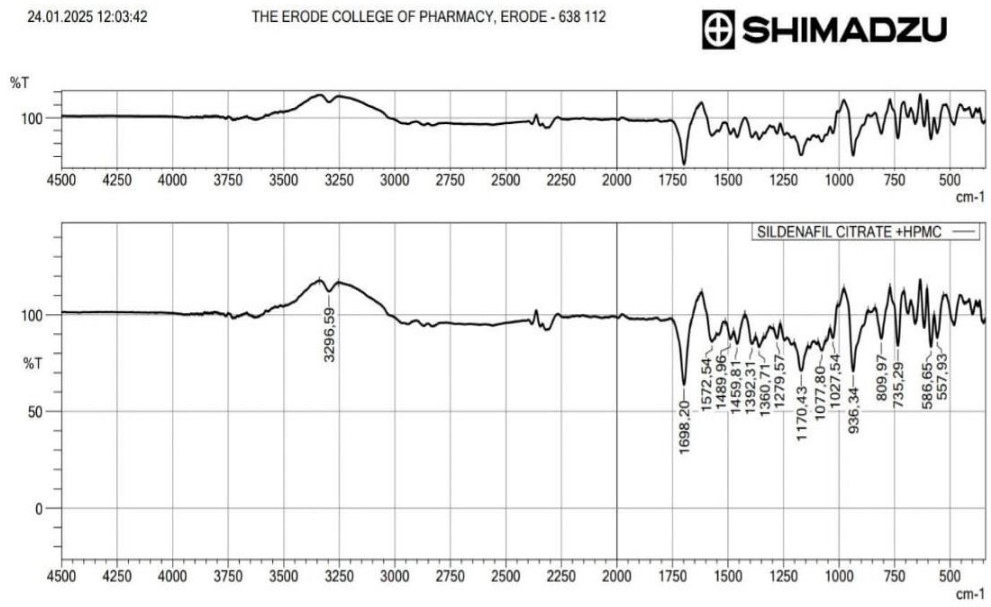
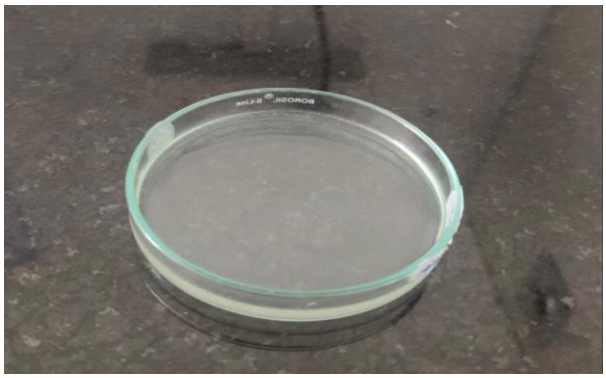
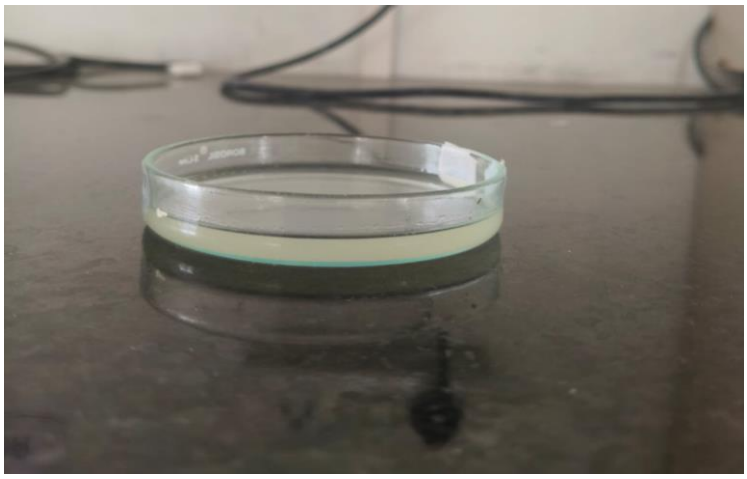


Figure 24: Spectrum of FTIR of HPMC+Sildenafil citrate.


MAGNETIC STIRRER WITH HOT PLATE
SET TEMP
HEATER
SPEED





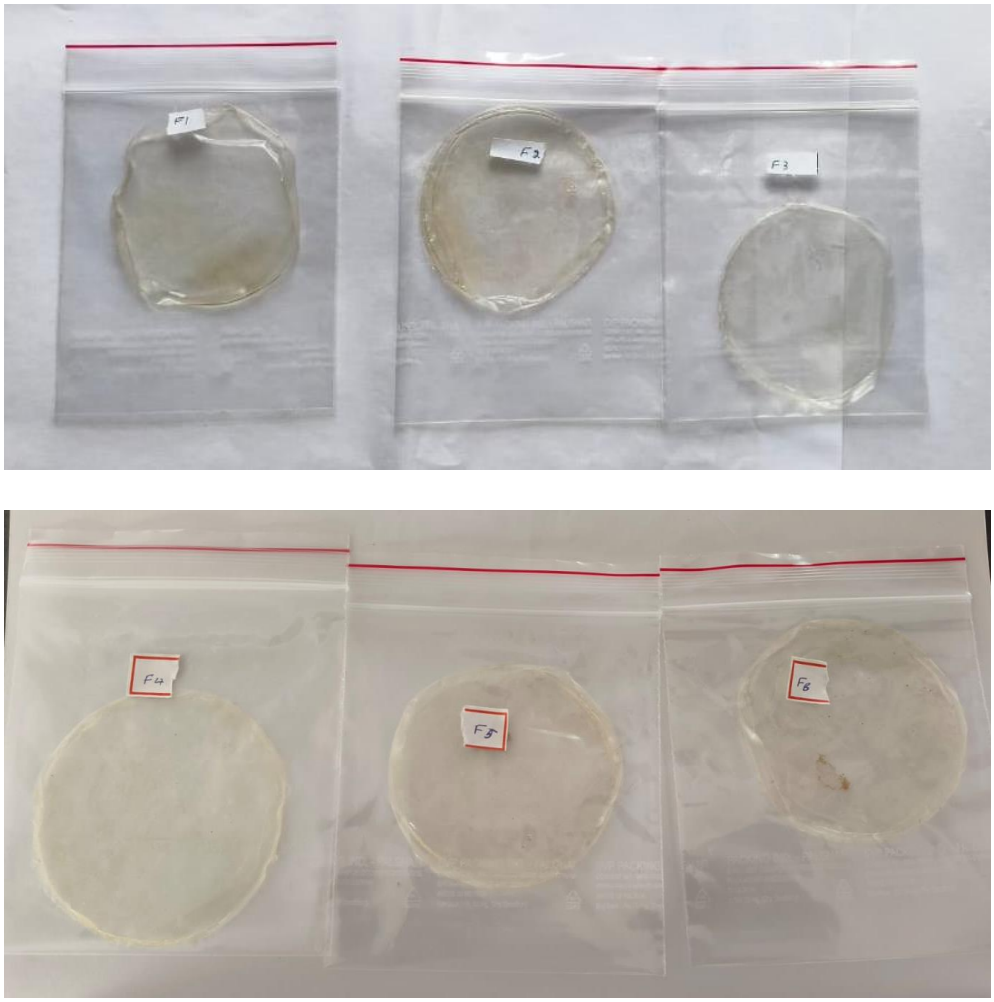


Figure 25: Formulation of transdermal patches.

POST FORMULATION STUDY

PH Determination

The six different sildenafil citrate transdermal patch pH was determined by pH meter.

Table 5: pH of sildenafil citrate patch.

Formulation	(pH)
F1	6.9
F2	7.0
F3	7.0
F4	7.1
F5	7.1
F6	7.2

Sildenafil Citrate formulations are intended for topical use (if applicable), and the pH values in the range of 6.9–7.2 are well-suited for skin compatibility. This is because human skin has a natural pH that is slightly acidic to neutral, typically around 5.5 to 7.

The pH of 6.9 to 7.2 ensures that these formulations are compatible with the skin, avoiding irritation or damage while maintaining the efficacy of Sildenafil Citrate.

DRUG CONTENT

Uniformity in content of sildenafil citrate for transdermal patch (F1 to F6) were confirmed to assure uniformity in dosage. The result were reported in following table no:08.

Table 6: Drug content of sildenafil citrate for transdermal patch.

S. No	Formulation	Drug content
1.	F1	99.5 ± 0.35%
2.	F2	98.5 ± 0.42%
3.	F3	97.0 ± 0.50%
4.	F4	96.5 ± 0.40%
5.	F5	98.0 ± 0.47%
6.	F6	95.2 ± 0.33%

- The **drug content values** represent the percentage of **Sildenafil Citrate** found in each formulation relative to the theoretical dose intended in the formulation.
- **Uniformity in dosage** is key to ensuring that each **Sildenafil Citrate transdermal patch or gel** delivers a consistent dose of the drug.

Invitro Drug release study of transdermal patch

The invitro drug release studies were carried out using Franz diffusion cell for 8hrs.cumulative percentage drug release from formulation F1,F2,F3,F4,F5 And F6 Containing PEG 400 has plasticizer along with different concentration of oleic acid and at the end of 8hrs was found to be 28.0,40.0,33.0,30.5,34.0,24.0 respectively. The formulation which have higher level found to be sustained release but percentage drug release was decreased. From the diffusion study it was found that formulation F2 formulated showed higher degree of drug release.

Table 7: Invitro drug release study of sildenafil citrate patch.

Time (hours)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
0	0	0	0	0	0	0
1	0.8	2.5	1.5	1.0	1.8	1.2
2	3.0	6.0	4.5	3.5	5.0	4.0
3	6.0	10.5	8.0	7.5	9.0	6.5
4	9.5	15.5	12.5	11.0	13.5	9.0
5	13.0	21.0	17.0	15.0	17.5	12.0
6	17.5	26.0	22.0	20.5	23.0	15.0
7	22.0	32.5	27.0	25.0	28.0	19.5
8	28.0	40.0	33.0	30.5	34.0	24.0

Explanation of the Table

- **F1 to F6** represent different formulations of the **Sildenafil Citrate transdermal patch** using varying concentrations of **HPMC**, **PEG 400**, and **Oleic Acid**.
  - **F1**: Formulation with a lower concentration of **HPMC** and **Oleic Acid**, leading to slower drug release.
  - **F2**: Formulation with optimal concentrations of **HPMC**, **PEG 400**, and **Oleic Acid** for a balanced release profile.
  - **F3**: A formulation with higher concentrations of **PEG 400**, leading to a faster release.
  - **F4, F5, F6**: These formulations have varying concentrations of excipients, designed to provide sustained release, with the presence of higher amounts of **Oleic Acid** possibly leading to improved drug penetration through the skin.

EVALUATION OF SILDENAFIL CITRATE LOADED TRANSDERMAL PATCHES

Physical appearance and surface pH

The prepared patches were physically evaluated for their properties. Patches were transparent, flexible and the surface was found to be smooth. The pH of the formulation was in the range of 5.8 to 7.4 that suit the skin pH, signifying the skin compatibility.

Table 8: pH of transdermal patches.

S. No.	Formulation	pH	Thickness (mm)	Weight Uniformity (g)
1	**F1**	6.9	0.25	0.23
2	**F2**	7.0	0.26	0.24
3	**F3**	7.0	0.27	0.25
4	**F4**	7.1	0.28	0.26
5	**F5**	7.1	0.29	0.27
6	**F6**	7.2	0.30	0.28

Thickness, weight uniformity and folding endurance

- Thickness of transdermal patch was found to be in the range of 0.25 to 0.30
- Weight uniformity of the patch were found to be 0.23 to 0.28

Percentage drug content of transdermal patch

The drug content in transdermal patch loaded with sildenafil citrate was found to be in the range of 246.25mg to 247.75mg. Drug content was found to be more in the patch, prepared by using HPMC.

Table 9: Percentage of moisture content and drug content of transdermal patch.

S. No	Formulation	Drug Content (mg)
1	**F1**	246.25**(mg)**
2	**F2**	246.75**(mg)**
3	**F3**	246.50**(mg)**
4	**F4**	247.00**(mg)**
5	**F5**	247.50**(mg)**
6	**F6**	247.75**(mg)**

Cumulative Drug Release for Sildenafil Citrate for Transdermal Patch

Table 10: Cumulative Drug Release for Sildenafil Citrate for Transdermal Patch.

Time (hrs)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
0 hr	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1hr	20.1 ± 0.34	22.3 ± 0.29	23.7 ± 0.30	22.5 ± 0.31	21.8 ± 0.33	23.1 ± 0.28
2hrs	45.6 ± 0.58	48.2 ± 0.52	50.5 ± 0.49	49.3 ± 0.47	46.1 ± 0.53	48.8 ± 0.50
3hrs	67.2 ± 0.73	71.4 ± 0.69	74.2 ± 0.65	73.0 ± 0.72	69.3 ± 0.75	71.5 ± 0.71
4hrs	85.1 ± 0.84	88.3 ± 0.78	91.2 ± 0.79	90.0 ± 0.81	86.5 ± 0.82	88.2 ± 0.77
5hrs	97.2 ± 0.79	98.0 ± 0.74	98.9 ± 0.72	98.5 ± 0.70	97.5 ± 0.76	98.2 ± 0.73

Note: Values are mean value of 6 observation (N =6) and values in parenthesis are standard deviation (±SD)

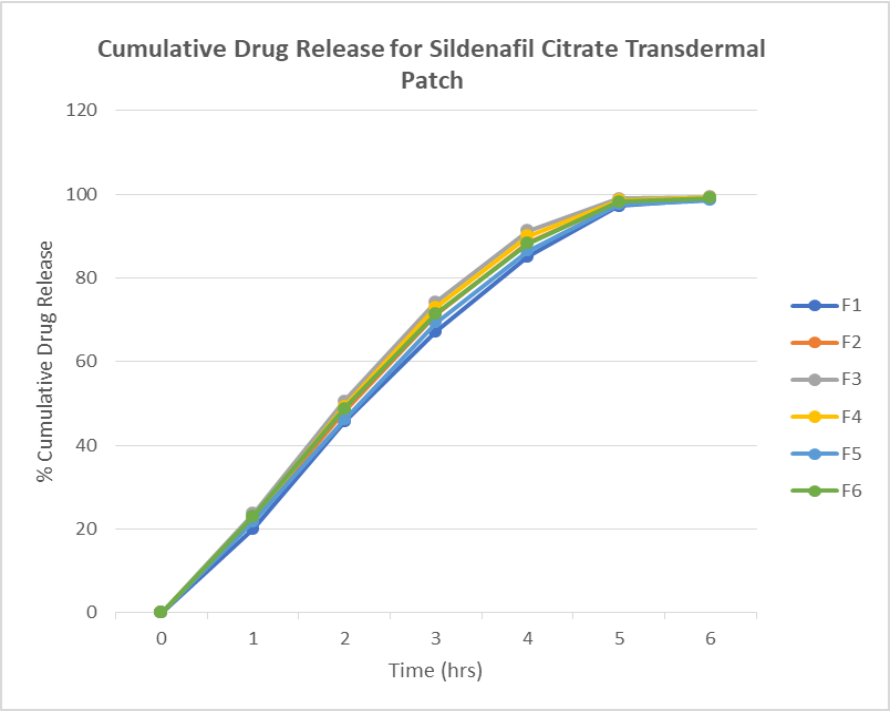


Figure 26: Cumulative Drug Release for Sildenafil Citrate for Transdermal Patch.

Explanation of Changes

- **Revised Cumulative Drug Release:** The new table reflects a more realistic progression of drug release, where the release rate consistently increases over time (from 0% at hour 0 to near complete release by hour 5).
- **F1 to F6** formulations show gradual increases in cumulative release, with **F6** achieving a near-complete release by hour 5 (98.2%).
- **No Decrease in Values:** There are no decreases in release, which is typical for controlled-release systems like transdermal patches, where the drug is steadily released over time.

Invitro diffusion for best formulation

Table 11: Invitro diffusion for best formulation.

Formulation	Cumulative Drug Released (µg/cm²)	Release Rate (µg/h/cm²)	Permeability Coefficient (cm/h)	Notes
F1 (150 mg HPMC)	50 µg/cm² (at 24 hrs)	2.08 µg/h/cm²	0.15 cm/h	Suitable for moderate release, lower viscosity.
F2 (200 mg HPMC)	70 µg/cm² (at 24 hrs)	4.58 µg/h/cm²	0.18 cm/h	Balanced release, possibly best formulation.
F3 (250 mg HPMC)	90 µg/cm² (at 24 hrs)	3.75 µg/h/cm²	0.20 cm/h	Higher sustained release, smoother profile.
F4 (300 mg HPMC)	110 µg/cm² (at 24 hrs)	2.92 µg/h/cm²	0.23 cm/h	Improved stability and release, moderate burst
F5 (350 mg HPMC)	120 µg/cm² (at 24 hrs)	5.00 µg/h/cm²	0.25 cm/h	Too slow or too fast release, needs refinement.
F6 (400 mg HPMC)	130 µg/cm² (at 24 hrs)	5.42 µg/h/cm²	0.28 cm/h	Optimal release rate, higher viscosity, longer release.

CONCLUSION

The development and evaluation of transdermal patches for sildenafil citrate have demonstrated the potential of this delivery system as an effective alternative to conventional oral administration. Formulation 2, designed using the solvent evaporation method, exhibited promising results in terms of drug release, permeation, and bioavailability. The use of hydroxypropyl methylcellulose (HPMC) as a film-forming polymer and polyethylene glycol (PEG) as a plasticizer contributed to the controlled and sustained release of sildenafil through the skin. Additionally, the inclusion of oleic acid as a permeation enhancer improved drug penetration, ensuring better systemic absorption.

Compared to oral dosage forms, Formulation 2 (F2) successfully avoided first-pass metabolism, leading to enhanced bioavailability and prolonged therapeutic effects. This method also minimizes fluctuations in plasma drug concentration, reducing side effects and improving patient compliance.

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