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# Formulation and Evaluation of Transdermal Gel of Sildenafil Citrate

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Subject: Formulation Science

## Abstract:

The present study was undertaken to formulate and evaluate transdermal gel of Sildenafil citrate. Sildenafil citrate is a drug of choice used in the treatment of premature ejaculation disorder. Transdermal gel has gained more and more importance because the gel based formulations are better percutaneously absorbed than creams and ointment bases. Therefore, transdermal gel of Sildenafil citrate was prepared using different polymers such as carbopol 934P containing permeation enhancer PEG 400 at different proportions. The study encompasses compatibility studies using FTIR spectra, drug content, viscosity, spreadability, and pH determination. Further the optimized formulation F2 was evaluated by *in vitro* and *ex vivo* diffusion study. Optimized formulation batch F2 subjected to stability as well as *ex vivo* study. The preliminary compatibility studies conducted revealed that there was no interaction between Sildenafil citrate and excipients. *In vitro* drug release study was carried out with Franz diffusion cell using cellophane membrane in pH 7.4 phosphate buffers as diffusion medium. Formulation batch F2 containing carbopol 934P and PEG 400 permeation enhancer showed 99.20 % drug release at 180 min and 7.98 g.cm /sec spreadability. Result showed that formulation batch F2 showed better drug release at 3 h. Formulation batch F2 was used further for stability and *ex vivo* study. A maximum percentage drug diffused of Sildenafil citrate from carbopol gel formulation batch F2 was found 80.94 % at 240 min through goat skin in *ex vivo* drug diffusion study. Stability studies conducted under accelerated condition were shown satisfactory results. It was concluded that carbopol gel containing Sildenafil citrate showed good consistency, spreadability, homogeneity and stability. So, transdermal gel had wider prospect for transdermal preparations.

***Key words***: Sildenafil citrate, Carbopol 934P, PEG 400, Transdermal gel of Sildenafil citrate.

## Introduction:

Premature ejaculation is one of the most common forms of sexual dysfunction and is thought to affect up to 30 % of men. Both the term “premature ejaculation” (PE) and the term “rapid ejaculation” (RE) are used to describe this condition. 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.” [1,2]

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.[5,6]

**Classification of penetration enhancers [7]**

1. Terpenes: E.g. Nerodilol, Menthol, 1,8 Cineol, Limonene, Carvone etc.

2. Pyrrolidones: E.g. N-Methyl-2-Pyrrolidone, Azone etc.

3. Fatty acids and esters: E.g. Oleic acid, Linoleic acid, Lauric acid, Capric acid etc.

4. Sulfoxides and similar compounds: E.g. Dimethyl sulfoxide, N,N-Dimethyl Formamide

5. Alcohols, Glycols, and Glycerides: E.g. Ethanol, Propylene glycol, Octyl alcohol etc.

6. Miscellaneous enhancers: E.g. Phospholipids, Cyclodextrins, Amino acid derivatives, Enzymes etc.

**Selection of drug candidate for transdermal delivery [8]**

The transdermal route of administration cannot be employed for a large number of drugs. Judicious choice of the drug substance is the most important decision in the successful development of a transdermal system. The drug candidate should have following ideas characteristics:

**Adequate skin permeability**
- Drugs with low molecular weight
- Drugs with low melting point
- Drugs with moderate oil and water solubility
- Potent drugs

**Adequate skin acceptability**
- Non-irritating drugs
- Non-metabolizing drugs

**Adequate clinical need**
- Need to prolong administration
- Need to reduce side effects on target tissues
- Need to increase patient compliance

**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.

**Transdermal gel forming substances [7, 8]**

Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

1. Natural polymers
   A) Proteins: Collagen, Gelatin
   B) Polysaccharides: Agar, Tragacanth, Guar Gum, Xanthan Gum, Gellan Gum, Pectin
2. Semisynthetic polymers
   Cellulosic derivatives: Carboxymethyl cellulose, Methyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose
3. Synthetic polymers
   A) Carbomer: Carbopol 940, Carbopol 934P
   B) Poloxamer
   C) Polyacrylamide
   D) Polyvinyl alcohol
   E) Polyethylene and its co-polymers
4. Inorganic substances
   A) Aluminium hydroxide
   B) Besitonite

## Materials and methods:

Sildenafil Citrate (Zydus cadila Healthcare Limited, Ahmedabad), Denim Perfume (Sunrise Remedies Pvt. Ltd. Santej, Ahmedabad), Carbopol 934P (Coral Pharmachem, Ahmedabad) were obtained as a gift sample. Polyethylene glycol 400 and sodium chloride were purchased from S.D Fine Chemicals Ltd, Boisar, India. All the chemicals were used as received without any further treatment and purification.

**1. PREFORMULTAION STUDIES [8]**

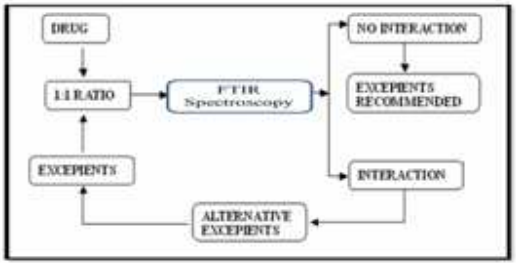
Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such that the appropriate physical and chemical data is available to aid the selection of new chemical entities that enter the development process. During this evaluation, possible interaction with various inert ingredients intended for use in final dosage form was also considered in the present study. The following data must be considered.

**A) Drug - Excipient Compatibility Study**

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate

administration, to promote the consistent release and bioavailability of the drug and protect it from degradation. API and excipients were been thoroughly mixed in predetermined ratio given in below table and passed through the 40# sieve. The blend was filled in transparent glass vials and were closed with gray coloured rubber stoppers and further sealed with aluminum seal and charged in to stress condition at above condition. Similarly API should also be kept at all condition as for the samples. Samples were withdrawn for analysis within two day of sampling date as per the compatibility study plan. Physical observation should be done at every week up to 1 month and FTIR studies and DSC Studies were carried out to determine the compatibility of excipients with the drug

- **Fourier transform Infrared Spectroscopy**




- **Drug-Excipient Compatibility Studies by DSC**

DSC thermograms of pure drug (Ropinirole Hydrochloride) and its physical mixture with polymers (Pullulan, HPMC, PVA) were carried out to investigate any possible interaction between the drug and the utilized polymer (Pullulan, HPMC, PVA). The selected heating rate is from 50°C to 300°C at an increase of 20°C per minute using Differential Scanning Calorimeter (shimadzu corporation, Japan).

## 2. Analytical Method Development

### 2.1. Determination of $\lambda_{max}$

The $\lambda_{max}$ of Sildenafil Citrate was determined prior to developing the standard curves. In this study 100 µg/mL solutions of Sildenafil Citrate were prepared in phosphate buffer pH 7.4 scanned for maximum 200 to 400 nm wavelength range.

### 2.2. Calibration curve of Sildenafil Citrate

Calibration curve for Sildenafil Citrate was developed in phosphate buffer pH 7.4.

### 2.3. Preparation 7.4 pH Phosphate Buffer

0.2 M potassium dihydrogen phosphate was prepared and 250 mL of this solution was mixed with 195.5 mL of 0.2 M NaOH and volume was made up to 1000 mL with distilled water. The pH of the buffer was adjusted to 7.4.

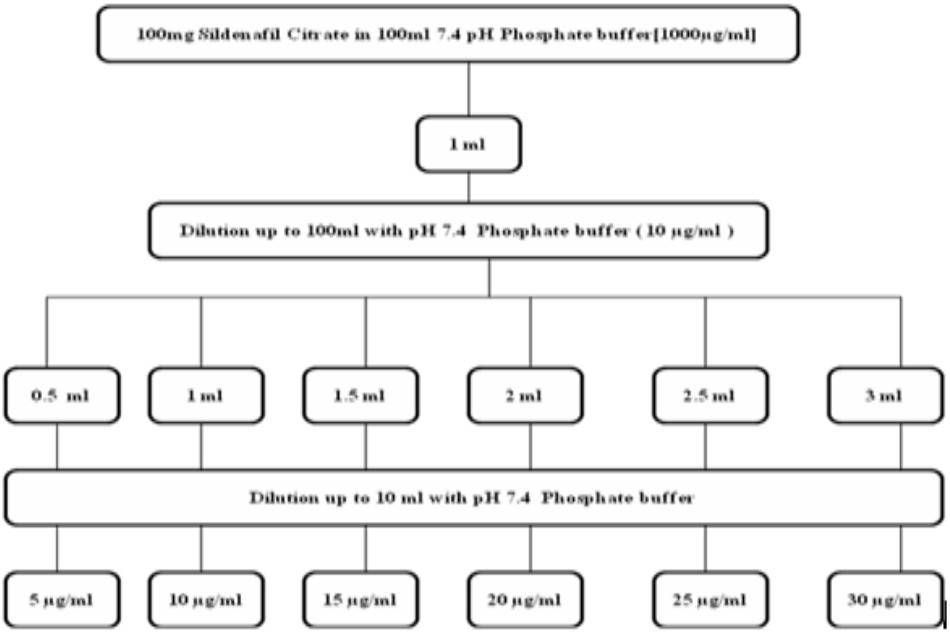



**Figure 1: Flowchart for preparation standard stock solution for calibration curve**

**3. Preliminary trial batches for formulation of transdermal gel of Sildenafil Citrate**

**Table 1: Preliminary trial batches for optimization of polymer concentration using Carbopol 934P**

| Ingredients | P1 | P2 | P3 | P4 | P5 |
|---|---|---|---|---|---|
| Sildenafil Citrate (g) | 2.9 | 2.9 | 2.9 | 2.9 | 2.9 |
| Carbopol 934P (g) | 0.5 | 0.8 | 1.0 | 1.2 | 1.5 |
| Ethanol (mL) | 1 | 1 | 1 | 1 | 1 |
| NaCl 0.5 M Solution (mL) | 1 | 1 | 1 | 1 | 1 |
| Triethanolamine (mL) | QS | QS | QS | QS | QS |
| DENIM Perfume (mL) | 1 | 1 | 1 | 1 | 1 |
| Dist. Water(mL) | 97 | 97 | 97 | 97 | 97 |

**Table 2: Formulation of carbopol (1.0 g) transdermal gel with permeation enhancer**

| Ingredients | F1 | F2 | F3 |
|---|---|---|---|
| Sildenafil Citrate (g) | 2.9 | 2.9 | 2.9 |
| Carbopol 934P (g) | 1.0 | 1.0 | 1.0 |
| PEG 400 (mL) | 16 | 20 | 24 |
| Ethanol (mL) | 1 | 1 | 1 |
| NaCl 0.5 M Solution (mL) | 1 | 1 | 1 |
| Triethanolamine (mL) | QS | QS | QS |
| DENIM Perfume (mL) | 1 | 1 | 1 |
| Dist. Water (mL) | 97 | 97 | 97 |

**4. Evaluation parameters of Transdermal gel of Sildenafil Citrate**

**A. pH Measurement [17]**

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. [74]

**B. Viscosity Measurement [17,18]**

Brookfield digital viscometer was used to measure the viscosity of prepared gel formulations. The spindle no. 6 was rotated at 10 rpm. The reading, near to 100 % torque was noted. Samples were measured at 30 ± 1 °C. [44]

**C. Spreadability [19]**

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application. The therapeutic efficacy of a formulation also depends upon its spreading value It was determined by wooden block and glass slide apparatus. Weights of about 2 g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides. [74]

Spreadability was then calculated by using the formula:

$$S = \frac{M.L}{T} \quad ..(1)$$

Where,

S = Spreadability

M = Weight tide to the upper slide

L = Length of a glass slide

T = Time taken to separate the slide completely from each other.

**D. Homogeneity [21]**

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

**E. Drug content [22]**

A specific quantity (1 g) of developed gel was taken and dissolved in 100mL of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2 h on mechanical shaker in order to get complete solubility of drug. The solution was filtered through 0.45 µm membrane filter and estimated spectrophotometrically at 293 nm using phosphate buffer (pH 7.4) as blank.

**F. *In-vitro* Drug Diffusion Study [23]**

*In-vitro* drug release studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 mL. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell.

The formulated gels were weight up to 1 g and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 RPM; the temperature was maintained at 37 ± 0.50 °C.

The samples of 1 mL were withdrawn at time interval of 15, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min., analyzed for drug content spectrophotometrically at 293 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug diffused from gels were plotted against time.

**G. Mechanism of Drug Release [24, 25, 26]**

Various models were tested for explaining the kinetics of drug release.

To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Hixon-Crowell model and Korsmeyer-Peppas release model.

- **Zero order release rate kinetics**

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_0.t \quad ..(2)$$

Where 'F' is the drug release, '$K_0$' is the release rate constant and't' is the release time.

The plot of percentage drug release versus time is linear.

- **First order release rate kinetics**

The release rate date are fitted to the following equation

$$\text{Log } (100 - F) = K\,t \quad ..(3)$$

A plot of log % drug release versus time is linear.

- **Higuchi release model**

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$F = K\,t^{1/2} \quad \ldots\ldots\ldots (4)$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of percentage drug release versus square root of time is linear.

- **Hixon-Crowell model**

To study the Hixon-Crowell release kinetics, the release rate data were fitted to the following equation,

$$W_0^{1/3} - W_t^{1/3} = k\,t \quad \ldots\ldots\ldots (5)$$

Where, '$W_o$' is the original mass/weight of drug, '$W_t$' is the mass/weight at 't' time, 'k' is Hixon-Crowell constant.

In this model ($W_o^{1/3} - W_t^{1/3}$) versus time is linear.

- **Korsmeyer and Peppas release model:**

The release rate data were fitted to the following equation,

$$M_t / M_\infty = k.t^n \quad \ldots\ldots\ldots (6)$$

Where, $M_t / M_\infty$ is the fraction of drug released,

'K' is the release constant,

't' is the release time.

'n' is diffusion exponent, if n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non-fickian diffusion (swellable and cylinder Matrix).

In this model, a plot of log ($M_t/M_\infty$) versus log (time) is linear. The dissolution data of Formulation of transdermal gels were fitted to Zero-order, First-order, Higuchi, Hixon- Crowell, and Korsmeyer-Peppas model to study the kinetics of drug release.

**H. *Ex-vivo* drug release study of optimized batch** [69]

Franz diffusion cell was used in study for *ex-vivo* diffusion of drug. The cell consists of two chambers, the donor and the receptor. The donor compartment is open at the top and is exposed to the atmosphere. The receptor compartment is surrounded by a water jacket for maintaining the temperature at 37 °C ± 2 °C and is provided with a sampling port. The diffusion medium was pH 7.4 phosphate buffer, which was stirred with magnetic beads (operated by a magnetic stirrer).

A Goat skin as a membrane was placed between the two chambers. The diffusion media was stirred to prevent the formation of concentrated drug solution just beneath the membrane. Samples from the receptor compartment were taken at various intervals of time over a period of 6 hours and the concentration of the drug was determined by UV Spectrophotometric method using the standard curve. Amount of drug diffused at various time intervals was calculated and plotted against time.

**Figure 2 : Diffusion study of optimized batch by Franz diffusion cell**

**I. Stability Study**

In any rational design and evaluation of dosage forms for drugs, stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of the drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

The international conference on Harmonization (ICH) guidelines titled 'stability testing of New Drug substance and product's (Q1A) describes the stability test requirements for drug registration applications in the European union, Japan and the USA.

Stability studies as per ICH guidelines,

**Long-Term Testing:** 25 °C ± 2 °C / 60 % RH ± 5 % for 12 months.

**Accelerated Testing:** 40 °C ± 2 °C / 75 % RH ± 5 % for 6 months.

Stability studies were carried out at 40 °C ± 2 °C / 75 ± 5 % RH for the selected formulation for one month.

**Method**

The selected formulation was packaged in air tight plastic container or aluminium container. They were then stored at 40 °C / 75 % RH, for one month and evaluated for their physical appearance and drug diffused at specific interval of time per ICH guidelines.

## Results & Discussion:

**A) Drug-Excipient Compatibility Studies by FT-IR**

**a) Fourior Transform Infrared Spectroscopy**

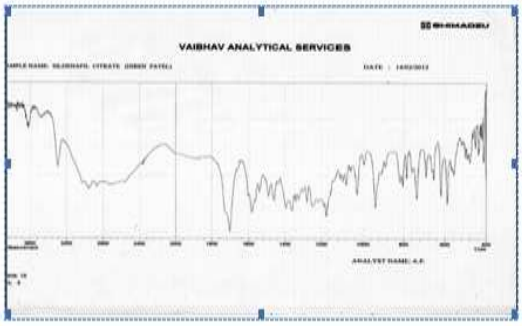



Figure 3 : FT-IR spectra of Sildenafil Citrate

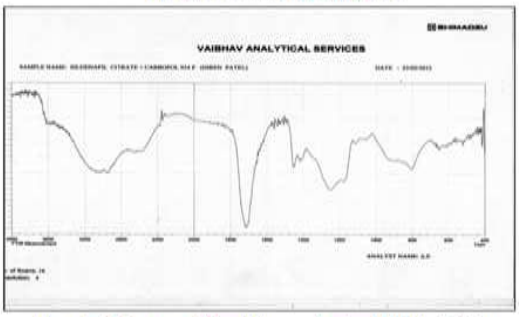



Figure 4 : FT-IR spectra of Sildenafil Citrate and carbopol 934P Physical Mixture

Pure drug Sildenafil Citrate spectra showed sharp characteristic peaks at 1050 $cm^{-1}$(S=O Streching), 3100 $cm^{-1}$(C-H stretching), 1600 $cm^{-1}$(N-H streching), 1700 $cm^{-1}$(C=O Streching). All the above characteristic peaks of drug appear in the spectra of all other spectra of drug with polymer mixtures and formulations of mouth dissolving film at the same wave number, indicating no modification or interaction between the drug and the excipients.

From this it can be concluded that the drug has maintained its identity without losing its characteristic properties. It will not show any adverse effect in action of the formulation and helps to study desired parameters in the present study.

**b) Drug-Excipients Compatibility Studies by Differential Scanning Calorimetry Study**

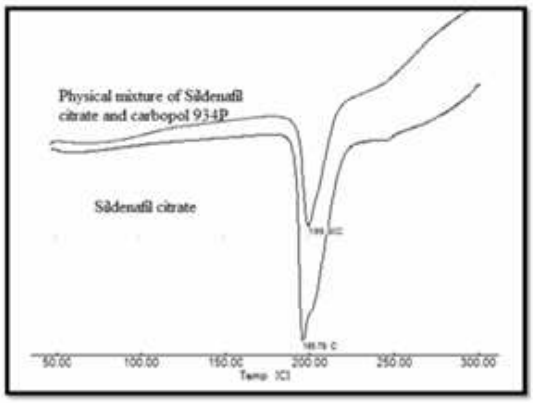



**Figure 5 : DSC Spectra of Sildenafil Citrate and physical mixture of Sildenafil Citrate with carbopol 934P**

Samples were analyzed by using DSC shimadzu corporation, Japan. The samples were placed into a pieced aluminium sample container. The studies were performed under static air atmosphere in the temperature range of 50 °C-300 °C at a heating rate of 20 °C per min. The peak temperatures were determined after calibration with a standard.

The DSC thermograph of Sildenafil Citrate exhibits endothermic peak at 195.79 °C corresponding to its melting point. Drug with carbopol 934P exhibits peak at 199.8 °C. Drug with HPMC K100M exhibits peak at 198.8 °C. So, results indicate that weak interaction occurs between drug and polymer.

**B) Calibration curve of Sildenafil Citrate in Phosphate buffer pH 7.4**

**Table 3 : Calibration curve of Sildenafil Citrate in 7.4 pH phosphate buffer at 293 nm**

| Concentration (µg/ml) | Absorbance | | | Average |
|---|---|---|---|---|
| | I | II | III | |
| **0** | 0.000 | 0.000 | 0.000 | 0.000 ± 0.000 |
| **5** | 0.143 | 0.144 | 0.142 | 0.143 ± 0.001 |
| **10** | 0.271 | 0.271 | 0.271 | 0.271 ± 0.000 |
| **15** | 0.416 | 0.415 | 0.415 | 0.415 ± 0.001 |
| **20** | 0.538 | 0.541 | 0.540 | 0.540 ± 0.002 |
| **25** | 0.667 | 0.665 | 0.668 | 0.667 ± 0.002 |
| **30** | 0.827 | 0.827 | 0.828 | 0.827 ± 0.001 |

**Note:** Values are mean value of 3 observation (N=3), and values in parenthesis are standard deviation (± SD)

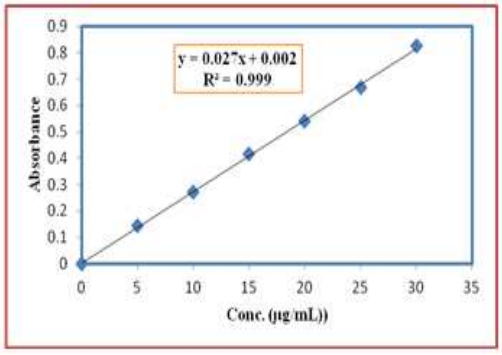



**Figure 6 : Calibration curve of Sildenafil Citrate in phosphate buffer pH 7.4**

**Table 4 : Optical characteristic and precision of the proposed method**

| | |
|---|---|
| $\lambda_{max}$ (nm) | 293.00 |
| Correlation coefficient($r^2$) | 0.999 |
| Slope(a) | 0.027 |
| Intercept(b) | 0.002 |
| Regression equation(y) | 0.027(x) + 0.002 |

**C. Preliminary trial batches for optimization of carbopol polymer concentration**

**1. Evaluation of carbopol transdermal gel of Sildenafil Citrate**

Formulation batches of carbopol transdermal gel of Sildenafil Citrate P1 to P5 were evaluated for viscosity and *in vitro* drug release measurement.

**Table 5: Viscosity measurements of preliminary trial batches P1 to P5**

| Batch No. | Viscosity (cps) |
|---|---|
| P1 | 205361 ± 1.10 |
| P2 | 233168 ± 0.73 |
| P3 | 278072 ± 0.85 |
| P4 | 324713 ± 0.92 |
| P5 | 351789 ± 0.58 |

**Note:** Values are mean value of 3 observation (N=3) and values in parenthesis are standard deviation (± SD)

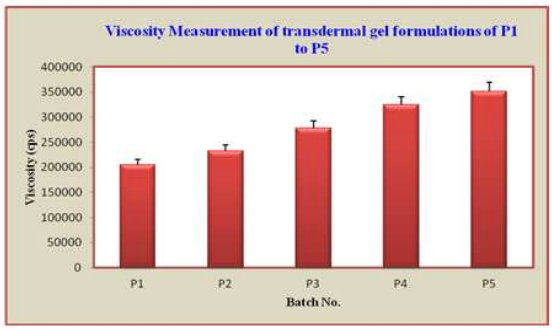



**Figure 7: Evaluation of viscosity measurements of transdermal gel formulation batches P1 to P5**

The viscosity of the transdermal gel formulations generally reflects its consistency. The results of viscosity measurement of Sildenafil Citrate transdermal gel containing different concentration (0.5, 0.8, 1.0, 1.2 and 1.5 g) of carbopol showed in Table 18 The viscosity of P1, P2, P3, P4 and P5 gel formulations can be ranked according to their viscosity values as follows: (351789 ± 1.10) > (324713 ± 0.73) > (278072 ± 0.85) > (233168 ± 0.92) > (205361 ± 0.58) cps. A result showed that as the concentration of polymer increases, viscosity of gel formulations also increases. But at the high concentration of polymer may affect the *in vitro* drug release and spreadability of gel formulations.

**Table 6 : *In-vitro* drug release study of preliminary trial batches P1 to P5**

| Time (min) | *In-vitro* drug release (%) CDR Batch No. | | | | |
|---|---|---|---|---|---|
| | **P1** | **P2** | **P3** | **P4** | **P5** |
| 0 | 00.00 ± 0.00 | 00.00 ± 0.00 | 00.00 ± 0.00 | 00.00 ± 0.00 | 00.00 ± 0.00 |
| 15 | 22.00 ± 0.88 | 21.10 ± 1.07 | 18.10 ± 0.34 | 17.29± 0.77 | 16.23± 0.84 |
| 30 | 37.10 ± 2.07 | 35.23 ± 0.91 | 29.28 ± 2.26 | 28.37 ± 0.83 | 27.54 ± 0.44 |
| 60 | 45.58 ± 0.51 | 40.49 ± 1.62 | 38.12 ± 1.39 | 36.21 ± 0.92 | 35.10 ± 0.65 |
| 90 | 55.22 ± 0.91 | 50.53 ± 0.62 | 45.65 ± 1.41 | 42.58 ± 0.14 | 43.63 ± 0.80 |
| 120 | 65.13 ± 0.48 | 61.89 ± 0.34 | 58.41 ± 0.78 | 56.10 ± 0.52 | 55.98 ± 1.92 |
| 150 | 77.85 ± 0.81 | 73.88 ± 0.29 | 70.82 ± 0.24 | 68.67 ± 1.19 | 67.01 ± 0.28 |
| 180 | 89.90 ± 1.42 | 85.00 ± 0.71 | 82.10 ± 0.73 | 76.10 ± 1.31 | 74.85 ± 0.76 |
| 210 | 99.24 ± 0.98 | 95.12 ± 0.69 | 93.70 ± 0.21 | 88.93 ± 0.38 | 85.95 ± 0.17 |

**Note:** Values are mean value of 3 observation (N=3), and values in parenthesis are standard deviation (± SD)

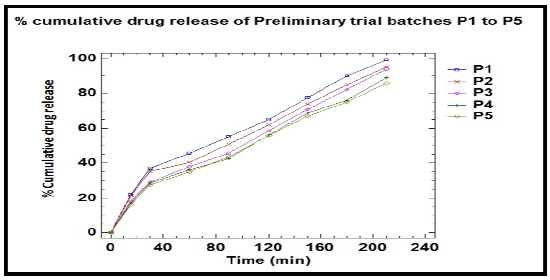



**Figure 8: *In-vitro* drug release study of formulation batches P1 to P5**

The total amount of drug released for a fixed period of 4 hour was found to decrease with increase carbopol concentration. The *In vitro* drug release of P1, P2, P3, P4 and P5 gel formulations can be ranked according to their drug release values as follows: (99.24 ± 0.98 %) > (95.12 ± 0.69 %) > (93.70 ± 0.21 %) > (88.93 ± 0.38 %) > (85.95 ± 0.17 %). A result showed that as the concentration of carbopol polymer increases, *in-vitro* drug release of gel formulations decreases. Even though a good drug release was observed with 0.5 g carbopol concentration, as it was too soft and less viscous in

nature, and an optimum polymer concentration of 1 g which showed good consistency was selected for further study on drug release.

**D.Evaluation parameters of carbopol transdermal gel formulations batches F1 to F3**

**A) pH measurement**

**Table 7: pH measurements of formulation batches of F1 to F3**

| Batch No. | pH |
|---|---|
| **F1** | 7.00 ± 0.03 |
| **F2** | 6.89 ± 0.04 |
| **F3** | 6.96 ± 0.03 |

**Note:** Values are mean value of 3 observation (N=3) and values in parenthesis are ± SD

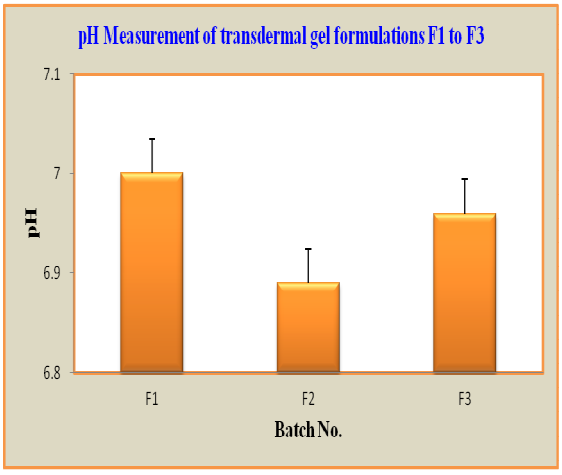



**Figure 9: pH measurements of formulation batches of F1 to F3**

The pH values of all formulated gel formulations ranges from 6.89 to 7.00 which lies in the normal pH range. The pH values lies in the normal pH range which is compatible to normal pH range of skin.

**B) Viscosity measurement**

**Table 8: Viscosity measurements of formulation batches of F1 to F3**

| Batch No. | Viscosity (cps) |
|---|---|
| F1 | 289853 ± 0.72 |
| F2 | 287988 ± 1.22 |
| F3 | 287441 ± 0.33 |

**Note:** Values are mean value of 3 observation (N=3) and values in parenthesis are standard deviation (± SD)

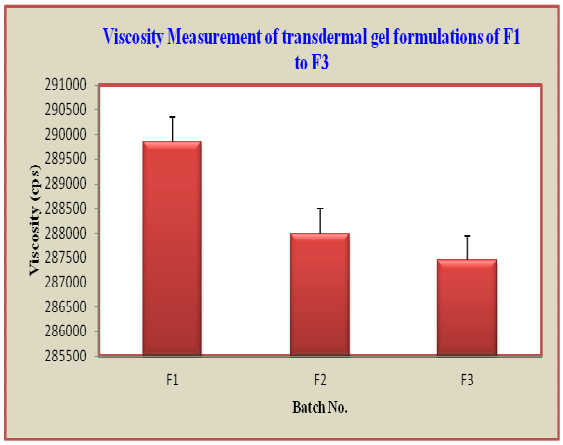



**Figure 10: Viscosity measurements of formulation batches of F1 to F3**

The viscosity of the transdermal gel formulations generally reflects its consistency. The results of viscosity measurement of Sildenafil Citrate transdermal gels containing fixed concentration of carbopol polymer (1 g) and different concentration of permeation enhancer (16, 20, 24 mL) of PEG 400 The viscosity of F1, F2 and F3 gel formulations can be ranked according to their viscosity values as follows: (289853 ± 0.72) > (287988 ± 1.22) > (287441 ± 0.33) cps. Results showed that as the concentration of permeation enhancer increases, viscosity of gel formulations slightly decreases or no change in viscosity.

**C) Spread ability measurement**

**Table 9: Spread ability measurements of formulation batches of F1 to F3**

| Batch No. | Spread ability (gm.cm/sec) |
|---|---|
| **F1** | 7.74 ± 0.50 |
| **F2** | 7.98 ± 0.71 |
| **F3** | 8.19 ± 0.37 |

**Note:** Values are mean value of 3 observation (N=3) and values in parenthesis are standard deviation (± SD)

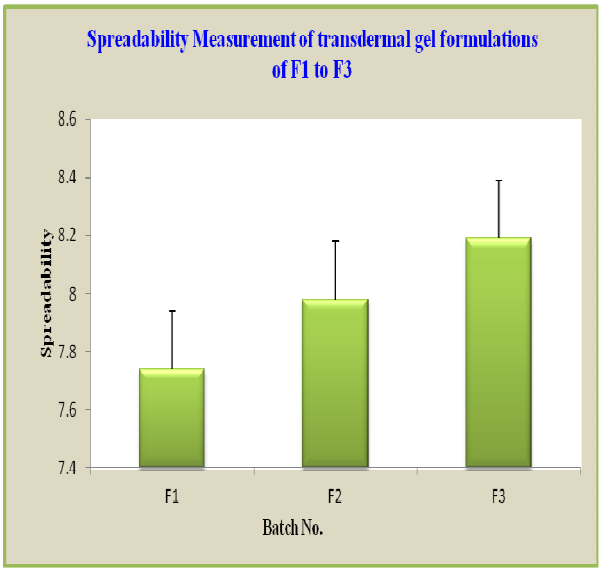



**Figure 11: Spread ability measurements of formulation batches of F1 to F3**

The result showed that as the conc. of permeation enhancer increases, the spreadability of transdermal gel formulations also increases. Spreadability of batch was F3 < F2 < F1. But there was not observed significant changes in spreadability between F1 to F3 formulation batches. All batches shows better spreadability.

**D) Homogeneity**

**Table 10: Homogeneity of formulation batches of F1 to F3**

| Batch No. | Homogeneity |
|---|---|
| F1 | Homogenous |
| F2 | Homogenous |
| F3 | Homogenous |

All formulated transdermal gel showed good homogeneity with absence of lumps. The formulated preparations were slightly opaque in nature.

**E) Percentage drug content measurement**

**Table 11: Percentage drug content measurements of formulation batches of F1 to F3**

| Batch No. | % Drug Content |
|---|---|
| **F1** | 99.62 ± 0.34 |
| **F2** | 99.83 ± 0.83 |
| **F3** | 99.72 ± 0.72 |

**Note:** Values are mean value of 3 observation (N=3) and values in parenthesis are standard deviation (± SD)

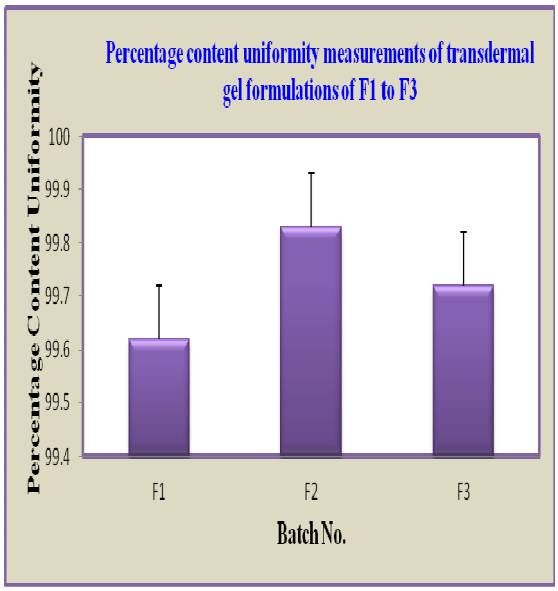



**Figure 12: Percentage content uniformity measurement of formulation batches of F1 to F3**

Drug content defines the uniform distribution of drug in the formulation. Percentage drug content was measured for all transdermal gel formulations. Results of transdermal gel formulations listed in the Table 24. The results revealed that the drug content was almost uniform in all the transdermal gels with low SD values. We can conclude that uniform drug loading of Sildenafil Citrate was found in gel formulation.

**F) *In-vitro* Drug release Measurement**

**Table 12: *In-vitro* drug release study of formulation batches of F1 to F3**

| Time (min) | *In-vitro* drug release (%) CDR | | |
|---|---|---|---|
| | Batch No. | | |
| | F1 | F2 | F3 |
| 0 | 0.00 ± 0.00 | 0.00 ± 0.00 | 00.00 ± 0.00 |
| 15 | 32.30 ± 0.84 | 38.4 ± 0.64 | 38.60 ± 0.91 |
| 30 | 40.59 ± 0.44 | 49.23 ± 0.15 | 50.11 ± 0.55 |
| 60 | 49.71 ± 0.65 | 55.41± 0.27 | 55.63 ± 0.62 |
| 90 | 56.23 ± 0.98 | 62.10 ± 1.33 | 62.60 ± 0.58 |
| 120 | 68.59 ± 1.92 | 72.23 ± 1.03 | 73.14 ± 1.14 |
| 150 | 82.29± 0.73 | 85.70 ± 0.73 | 86.38 ± 0.79 |
| 180 | 91.33 ± 0.76 | 99.20 ± 0.95 | 99.28 ± 0.85 |
| 210 | 98.10 ± 0.34 | - | - |

**Note:** Values are mean value of 3 observation (N=3) and values in parenthesis are standard deviation (± SD)

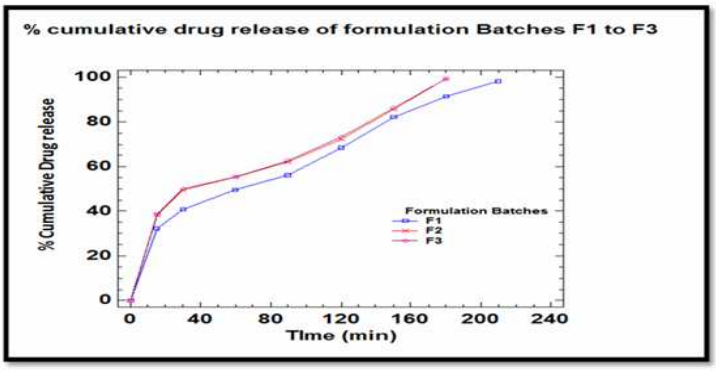
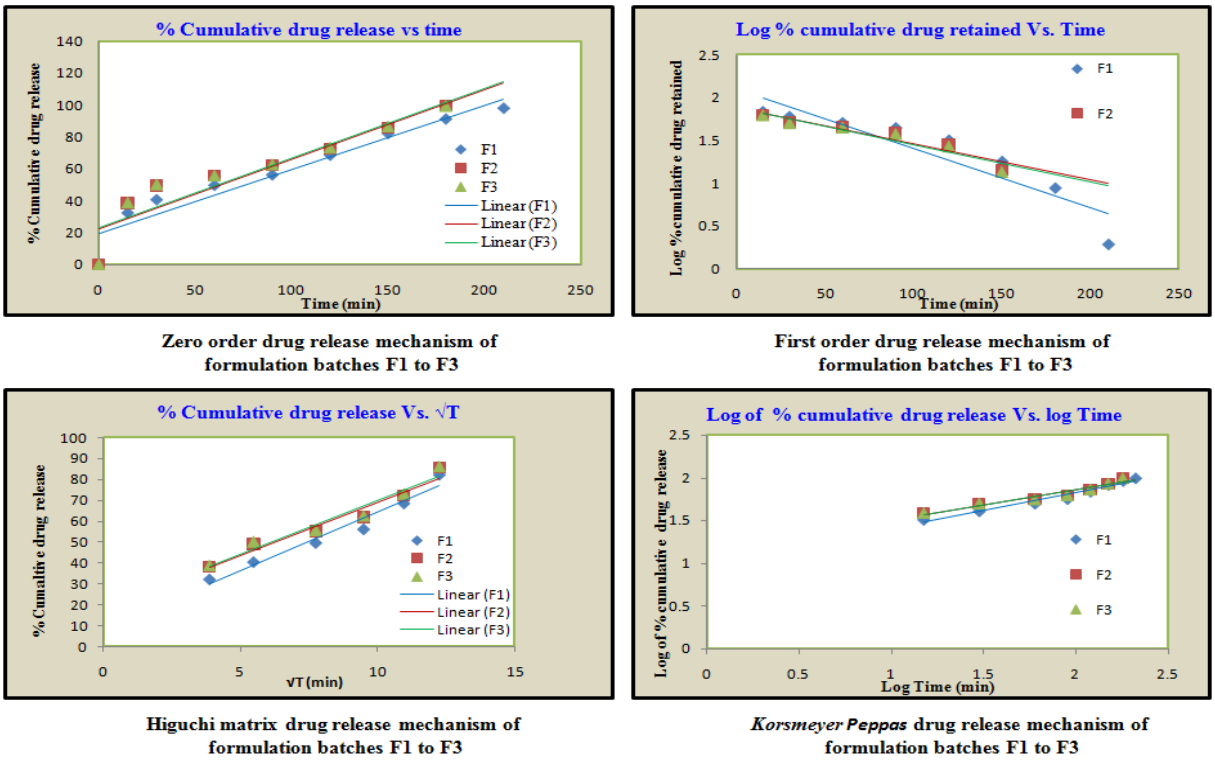



**Figure 13: *In-vitro* drug release study of formulation batches of F1 to F3**

The total amount of drug released for a fixed period of 3 h was found to increase with increase permeation enhancer PEG 400 concentration. The *in vitro* drug release of F3, F2 and F1 gel formulations can be ranked at 3 h according to their drug release values as follows: (99.28 ± 0.85 %) > (99.27 ± 0.95 %) > (91.33 ± 0.76 %). A result showed that as the concentration of permeation enhancer increases, the *in-vitro* drug release of gel formulations increases. Table 25 revealed that PEG 400 release was maximum (93.70 %) over a period of 3 h at 20 mL permeation enhancer concentration level. Further increase in PEG 400 concentration to 24 mL level showed no further increase in drug release.

**G) Pharmacokinetic drug release study**




**Zero order drug release mechanism of formulation batches F1 to F3**

**First order drug release mechanism of formulation batches F1 to F3**

**Higuchi matrix drug release mechanism of formulation batches F1 to F3**

***Korsmeyer Peppas* drug release mechanism of formulation batches F1 to F3**

**Figure 14: Pharmacokinetic drug release mechanism of formulation batches F1 to F3**

**Table 13: Regression co-efficient ($r^2$) of different kinetic models and diffusion exponent (n) of *Korsmeyer Peppas* model**

| Formulation | Regression | | | Korsemeyer | |
|---|---|---|---|---|---|
| | Zero order | First Order | Higuchi | N | Regression |
| F1 | 0.93 | 0.89 | 0.99 | 0.42 | 0.96 |
| F2 | 0.87 | 0.94 | 0.98 | 0.35 | 0.94 |
| F3 | 0.87 | 0.94 | 0.98 | 0.35 | 0.94 |

The *in-vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations. Higuchi's and Korsmeyer model in order to determine the mechanism of the drug release. The results of linear regression analysis data including regression coefficient are summarized in Table 26.

When the regression coefficient 'r' value of zero order and first order plots were compared, it was observed that the 'r' values of zero order plots were in the range of 0.87 to 0.93 whereas the 'r' values of first order plots were in the range of 0.89 to 0.94 indicating drug release from all the formulation was not found to follow first order kinetics.

Figure 24 showed the percent drug released versus square root of time plots. It was observed that the 'r' values for the Higuchi's plots were found to be in the range of 0.98 to 0.99 for the formulation studied indicated the release of drug from these

formulations was governed by diffusion controlled process.

The Peppas model is widely used to confirm whether the release mechanism is Fickian diffusion, non-Fickian diffusion or zero order. 'n' value could be used to characterize different release mechanisms.

When Korsmeyer et al equation was fitted to dissolution data values, the exponent 'n' was found to be in the range of 0.35 to 0.42 indicating the drug release by Fickian diffusion.

### H) Stability Study

**Table 14 : Comparison of *in-vitro* drug release study of formulation batch F2 carbopol transdermal gel after 1 month stability study(40 °C ± 2 °C / 75 % ± 5 % RH)**

| ***In-vitro* drug release of formulation batch F2 (%) CDR** | | |
|---|---|---|
| **Time (min)** | **(Initial)** | **After 1 month stability study at (40 °C ± 2 °C / 75 % ± 5 % RH)** |
| 0 | 0.00 ± 0.00 | 0.00 ± 0.00 |
| 15 | 38.4 ± 0.64 | 36.93 ± 0.12 |
| 30 | 49.23 ± 0.15 | 48.53 ± 0.38 |
| 60 | 55.41± 0.27 | 53.84 ± 0.62 |
| 90 | 62.10 ± 1.33 | 61.79 ± 0.78 |
| 120 | 72.23 ± 1.03 | 71.64 ± 1.22 |
| 150 | 85.70 ± 0.73 | 85.25 ± 0.85 |
| 180 | 99.20 ± 0.95 | 99.04 ± 0.53 |

**Note:** Values are mean value of 3 observation (N=3) and values in parenthesis are standard deviation (± SD)

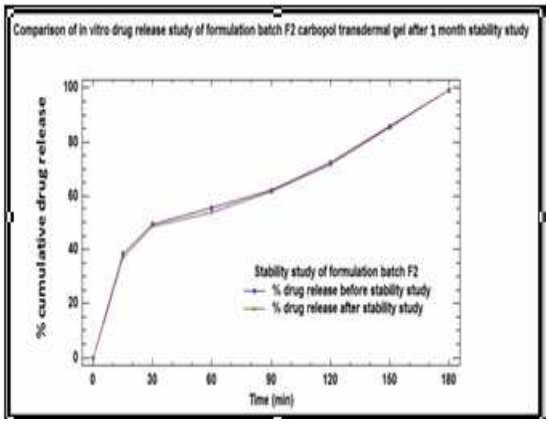



**Figure 15 : Comparison of *In vitro* drug release study of formulation batch F2 carbopol transdermal gel after 1 month stability study**

The selected formulations were subjected to the accelerated stability at 40 ± 2 °C / 75 ± 5 % RH for 1 month and evaluated for their *in-vitro* drug release study. There were no significant variations in the *in-vitro* drug release study. So, the formulated transdermal gel of Sildenafil Citrate is stable at 40 ± 2 °C / 75 ± 5 % RH.

### I) *Ex-vivo* study

**Table 15: *Ex- vivo* study of optimized formulation batch F2**

| ***Ex-vivo* diffusion study of formulation batch F2** | |
|---|---|
| **Time (min)** | **Percentage cumulative drug diffused of formulation batch F2 (± S.D.)** |
| 0 | 0.00 ± 0.00 |
| 15 | 09.23 ± 0.21 |
| 30 | 19.12 ± 0.58 |
| 60 | 27.59 ± 0.42 |
| 90 | 36.47 ± 0.56 |
| 120 | 43.29 ± 0.20 |
| 150 | 52.35 ± 1.10 |
| 180 | 62.58 ± 1.28 |
| 210 | 71.34 ± 0.84 |
| 240 | 80.94 ± 0.14 |

**Note:** Values are mean value of 3 observation (N=3) and values in parenthesis are standard deviation (± SD)

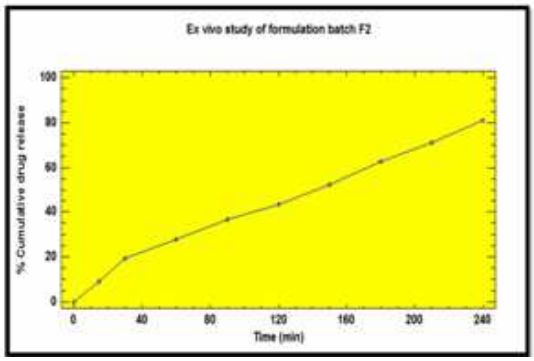



**Figure 16: Ex-vivo study of optimized formulation batch F2 carbopol transdermal gel**

*Ex-vivo* study of carbopol transdermal gel formulation batch F2 was performed by using Franz diffusion cell. A result showed that 80.94 ± 0.14 % drug releases occur at 240 min. So, we can conclude that the carbopol gel (1 g) containing 20 mL permeation was the optimized batch for the formulation of transdermal gel of Sildenafil Citrate.

After evaluation of all transdermal gel, we finally conclude that formulation batch F2 containing 1 g carbopol and 20 mL permeation enhancer have better spreadability, homogeneity, viscosity and percentage drug release. So, formulation batch F2 was the final optimized batch for formulation of transdermal gel of Sildenafil Citrate.

**Photograph of formulated transdermal gel of Sildenafil Citrate**

**Figure 17: Photograph of formulated transdermal gel of Sildenafil Citrate**

## Conclusion:

Sildenafil citrate is the drug of choice in the treatment of premature ejaculation. 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. In preliminary study HPMC 100KM and carbopol 934P were evaluated for their efficiency to form a transdermal gel.

Different parameters studied were carried out for transdermal gel formulations. Between two polymers, carbopol was found to be suitable candidate as it gives better consistency, viscosity, spreadability, pH, homogeneity, and *in-vitro* drug diffusion. Carbopol concentration was optimized by trial and error method. Permeation enhancer was used for increasing the permeability and *in-vitro* drug diffusion of Sildenafil citrate.

Results showed that in-vitro drug diffusion increase after addition of permeation enhancer in transdermal gel formulation. So, it was concluded that carbopol transdermal gel with permeation enhancer is effective in the treatment of Premature Ejaculation.

Further transdermal gel of Sildenafil citrate can also be prepared by using different gel forming polymer and natural permeation enhancer to produce economical enhancer.

**"Cite This Article"**

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**References:**

1. Harrison T R., Harrison's Principles of Internal Medicine, 16th Edn, McGraw Hill Publishing Company; 1976; 271-274.
2. Metz, M. E., Pryor, J. L., Nesvacil, L. J., Abuzzahab, F., and Koznar, J., "Premature ejaculation: A Psychophysiological review." J. Sex Marital Therapy. 1997, 10, 23-30.
3. Drug Card for Sildenafil Citrate. http://www.drugbank.com
4. Drug Card for Sildenafil Citrate. www.rxlist.com
5. Chien, Y. W., Novel Drug Delivery systems. 2nd Edn, Marcel Dekker Inc. New York: 1992; 499.
6. Jain, N. K, Controlled and Novel drug delivery system. 1st Edn, CBS Publications, New Delhi: 1997; 110-115
7. Ryan, D. G. and Peterson, T. A., "Myths about transdermal drug delivery." Drug Del. Tech. **2003**, 3(4), 1-7.
8. Vivek kumar , R., "Formulation and evaluation of MIMOSA PUDICA GEL" Int. J. Pharmacy and Pharm. Sci. **2011**, 3(1), 2011, 55-57.
9. Wade, A. and Paul, J. W., Hand Book of Pharmaceutical Excipients. 2nd edition. The Pharmaceutical Press and the American Pharmacists Association, New York, 1994.
10. Kaplan, H. S., "The New Sex Therapy: Active Treatment of Sexual Dysfunctions." Brunner/Maazel, New York, 1974.
11. Washington, D. C., Diagnostic and Statistical Manual of Mental Disorders, 4th Edn, Text Revision. American Psychiatric Association, **2000**.
12. Masters, W. H., Johnson, V. E., "Human Sexual Inadequacy."J. Am. Coll. Cardio. **1970**.1011-1014.
13. Halcox, J. P., Nour, K. R., Zalos, G., "The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia." J. Am. Coll. Cardiol. **2002**, 40, 1232-1240.
14. Mahmud, A., Hennessy, M., Feely, J., "Effect of sildenafil on blood pressure and arterial wave reflection in treated hypertensive men." J. Hum. Hyperten. **2001**,

15, 707-713.
15. Jarow, J. P., Burnett, A. l., Geringer, A. M., "Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment." J. Urol. **1999**, 162, 722-725.
16. Sivakranth, M., Abdul, S. A. and Rajasekhar, S., "Formulation and Evaluation of Oral Fast Dissolving Tablets Of Sildenafil Citrate." Int. J. Pharm. Pharm. Sci. **2011**, 3(2), 112-21.
17. Gupta, V., "Formulation and evaluation of naproxen gel containing tulsi oil as penetration enhancer" Int. J. Pharm. Clinical Res. **2009**, 1(3), 153-155.
18. Valenta, C., Nowak, M. and Hadgraft, J., "Influence of phloretin and 6-ketocholestanol on the permeation of progesterone through porcine skin." Int. J. Pharm. **2001**, 217, 79–86.
19. Cordero, J.A., Alarcon, L., Escribano, E., Obach, R. and Domenech, J. "A Comparative study of the transdermal penetration of a series of Nonsteroidal anti-inflammatory drugs." J. Pharm. Sci. **1997**, 86(4), 503-508.
20. Dave, B. S., Patel, M. M., Gohel, M. C. and Bajaj, S. B., "Studies on effect of l-limonene and other formulation ingredients on permeation of diclofenac sodium through rat skin." Int. J. Pharm. Excip. **2003**, 50-54.
21. Barhate, S. et al. "Development of Meloxicam Sodium Transdermal Gel" Int. J. Pharma. Res. Deve. **2011**, 2, 1-7.
22. Patel, J., Patel, B., Banwait, H., Parmar, K. and Patel, M., "Formulation And Evaluation of Topical Aceclofenac Gel Using Different Gelling Agent." Int. J. Drug Dev. Res. **2011**, 3, 9275-9344.
23. Gohel, M. C., Jani, G. K., Amin, A., Bajaj, S. and Dave, B. S., "Application of simplex lattice design for the development of transdermal gels of diclofenac Sodium." J. Pharm. Sci. **2000**, 62(2), 108-14.
24. Martin, A., Bustamante, P. and Chun, A.H.C., Physical Pharmacy, 4th Edn, B. I. Waverly Pvt. Ltd., New Delhi: 1999; 139-168.
25. Higuchi, W. I., "Diffusional models useful in biopharmaceutics-drug release rate processes." J. Pharm. Sci. **1967**, 56(3), 315-24.
26. Peppas, N.A. and Ritger, P. L., "A simple equation for description of solute release II. Fickian and anomalous release from swellable devices." J. Control Release. **1987**, 5(1), 37-42.