FORMULATION AND CHARACTERIZATION OF DIFFERENT TOPICAL HYDROGELS LOADED WITH SILDENAFIL CITRATE

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ABSTRACT

Sildenafil citrate (SILD) is a drug of choice used in the treatment of premature ejaculation disorders. Oral administration of Sildenafil was accompanied with several side effects including nausea, vomiting, diarrhoea and stomach cramps. Topical administration of sildenafil could avoid the side effects of oral or systemic administration of the drug. Therefore, the present study was undertaken to formulate and evaluate transdermal gel of Sildenafil citrate. Sildenafil hydrogels were prepared using different polymers such as HPMC, Pluronic F127, CMC Na and Na-alginate. The formulated gels were characterized by measuring different parameters such as pH, viscosity, spreadability and in vitro diffusion study. The results showed that all medicated hydrogels formula showed good consistency, spreadability and homogeneity. Especially, the gel containing HPMC and PEG 400 as permeation enhancer showed the best results compared to other gelling agents. The release mechanism of the drug from hydrogels was Higushi diffusion mechanism. As a conclusion, it was concluded that the modified SILD gel is an alternative therapy for the patients suffering from mild to moderate erectile dysfunction (ED) with premature ejaculation (PE) since this route of administration avoid the risk of side effect accompanying the oral administration of drug.

Keywords: Sildenafil, hydrogels, premature ejaculation, topical delivery and erectile dysfunction
INTRODUCTION

Premature ejaculation (PE) is considered as the most famous sexual dysfunction in men (Montague, Jarow et al. 2004; McMahon, Lee et al. 2012; Yafi, Jenkins et al. 2016, Saramies, Koiranen et al. 2022). The exact definition, classifications and etiology of PE is not well understood and still under debate (Serefoglu, Saitz et al. 2013), although it is well-established that the premature ejaculation is affected by different factors, including somatic factors, psychological factors, and cognitive factors (Montague, Jarow et al. 2004). Also, millions of men worldwide suffer from erectile dysfunction (ED) which may be caused by low levels of the hormone testosterone (McMahon, Lee et al. 2012). Therefore, these kinds of patients can be treated by Testosterone ampule as a replacement therapy. However, this strategy does not work in the case of patients suffering from ED and having normal testosterone levels. Therefore, such a problem can be solved by taking some selective serotonin re-uptake inhibitors such as sildenafil pills (1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3 d] pyrimidin-5-yl) phenyl sulphonyl]-4-methyl piperazin. Chemical structure fig (1) (Naseem A, Triq A and Yasser S 1999; Montague, Jarow et al. 2004; Atan, Basar et al. 2006; Gurkan, Oommen and Hellstrom 2008; Ghorab, Yasser et al. 2013; Serefoglu, Saitz et al. 2013).

![Chemical structure of sildenafil citrate.](image)

Due to its poor aqueous solubility (4.1 mg/mL in water), incomplete absorption, and low bioavailability approximately 40% of the drug is absorbed into the bloodstream and is available for systemic circulation (Nichols, Muirhead and Harness 2002).

However, oral administration of sildenafil is accompanied with several side effects including flushed skin, headache, heartburn and severe hypotension. Also, oral administration of sildenafil is contraindicated with patients with cardiovascular diseases and who take nitrates such as nitro-glycerine due to this may lead to severe hypotension and in some cases with old age it may be fatal (Shalbafan, Orooji and Kamalzadeh 2022). Another serious side effect is the possibility of prolonged erections, which may cause penis damage (Basson and Brotto 2003; Henry and Morales 2003).

One option to avoid all of these systemic side effects is the topical local application of the drug in the form of gel or cream. Consequently, the patient who are
not advised to take sildenafil tablets will be allowed to administer such kind of drug directly to the penis with a safe manner (Ketabchi 2015). The however, the concern regarding the lower efficacy of topical administration in comparison with the systemic drug delivery are the main limitation especially in severe cases. While as, the patient with mild to moderate erectile dysfunction and premature ejaculation may benefit from accepted efficacy of topical treatment with absence of systemic side effects (Lin and Douglass 2010). To date, the results which were obtained from the randomized controlled trials about efficacy of topical sildenafil in the treatment of mild/moderate erectile dysfunction are contradictory and limited (Chung, Gilbert et al. 2015).

In this study, different kinds of topical hydrogels have been constructed and evaluated for loading and release of sildenafil citrate. The formulated gels were characterized by different analysis, including visual inspection, extrudability, spreadability and viscosity. Moreover, the in vitro release behaviour of sildenafil from the formulated gels was carried out. The bioavailability study of the modified medicated devices was monitored on volunteers suffering from mild or moderate PE and ED in order to investigate the most helpful treatment. In this work PEG 400 was used as an enhancer in the preparation of topical hydrogels containing Sildenafil (SILD). PEG 400, a polyethylene glycol compound, was commonly employed as a solubility enhancer for poorly soluble drugs. It was well-known for its non-toxic, non-volatile, odorless, and non-irritating properties, which made it suitable for pharmaceutical applications. PEG 400 exhibited a high aqueous solubility, which helped improve the solubility of drugs like SILD. This, in turn, allowed for better drug delivery and absorption through the skin when incorporated into a topical hydrogel (Pirhayati, Shayanfar et al. 2017).

MATERIALS AND METHODS

Materials

Sildenafil was obtained from Pharco, Pharm. Ind. Co., (Alex., Egypt); Pluronic F127 (Sigma Chem. Co., U.S.A). Sodium-carboxymethylcellulose (CMC-Na), hydroxypropylmethylcellulose (HPMC), sodium alginate and PEG400 (El-Nasr Pharm. Chem. Co., (Cairo, Egypt). Standard cellophane membranes (molecular cut of range = 14KD) (Carl Roth GmbH+ Co., Germany); All other materials and solvents were of analytical grade.

Preparation of sildenafil hydrogels

The hydrogels were prepared using different gelling agents including HPMC, Na-CMC, Pluronic F127, and Na-alginate in the presence of PEG400 as enhancer as shown in table 1. For preparation of both CMC-Na, Na-alginate and HPMC based hydrogels, a specified amount of either CMC-Na or HPMC gelling base was gently added to distilled water in a beaker to obtain the required concentration (2.5, 3 and 4 % w/w) for HPMC, (5 % w/w) for Na-alginate, and (2 % w/w) for Na-CMC. Then, mixed thoroughly using a magnetic stirrer and the container was left overnight to ensure complete mixing (Lu and Jun 1998, Tas, Özkan et al. 2003, Coviello, Matricardi et al. 2007, Elim, Fitri et al. 2023).
Table 1: Composition of different sildenafil hydrogels containing 1% w/w PEG 400 enhancer, 0.2% w/w methyl paraben as preservative.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Drug % w/v</th>
<th>Gelling agent %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HPMC</td>
</tr>
<tr>
<td>F1</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>F2</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>F3</td>
<td>1.0</td>
<td>4.0</td>
</tr>
<tr>
<td>F4</td>
<td>1.0</td>
<td>20</td>
</tr>
<tr>
<td>F5</td>
<td>1.0</td>
<td>25</td>
</tr>
<tr>
<td>F6</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>F7</td>
<td>1.0</td>
<td>5.0</td>
</tr>
<tr>
<td>F8</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>F9</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>F10</td>
<td>3.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Similarly, pluronic F127 hydrogels, an accurately weighed amount of pluronic powder was added to ice cold distilled water under agitation with a glass rod to obtain the required gel concentration (20, 25 and 30 % w/w). The mixture was stored in refrigerator at 4 °C for 24 hrs and shaking periodically to ensure complete dissolution. The gel was formed when Pluronic F127 solution was left at room temperature for over 30 min (Lu and Jun 1998).

Drug loading:

A known amount of sildenafil citrate 1% w/w was incorporated into the prepared gels by thoroughly mixing using homogenizer at 500 rpm for 15 minutes. All the samples were kept at room-temperature for further analysis.

Characterization of the modified sildenafil hydrogels:

Visual inspection:

The prepared SILD hydrogels were visually inspected for their homogeneity, phase separation and clarity.

Drug content

An amount equivalent to 10 mg of drug was taken, dissolved in sufficient quantity of distilled water and further dilutions were made to obtain suitable concentration. The drug content was estimated using UV-Visible spectrophotometer (UV- 1601, Shimadzu) at 293 nm. Only those formulae containing 100 ±5% of the required SILD was used for further studies (Aldawsari, Anwer et al. 2021).
**pH determination**

The pH of the hydrogel samples was detected by using digital pH meter Ama Digital (Ama Co., Germany). The pH of the hydrogels was measured by allowing the probe of the pH meter to be in contact with the samples. In order to avoid the irritation of skin, the pH of topical preparations should lie in the range of 4.5-7 (like skin pH) (Khunt, Mishra and Shah 2012; Patil, Ahmed et al. 2018, Saher, Manzoor et al. 2022).

**Determination of viscosity**

The viscosity of the SILD hydrogel formulations was investigated by using Brookfield DV-III ultra-viscometer, (Brookfield Co., USA). The viscosity measurements were carried out in triplicate at room temperature at shear rate (50 rpm). The values of viscosity values are reported in the form of cP. (means ± SD).

**Spreadability and extrudability measurements**

The spreadability of the gel was determined according to the previously reported method (Bhanu, Shanmugam and Lakshmi 2011). Briefly, 0.5 g hydrogel sample was placed, within a pre-marked circle, on a glass plate. A second glass plate was placed over this plate. Then, a mass of 500 mg was allowed to be set on the upper glass plate for five minutes. The extent of spreadability of the samples were calculated from the increase in the diameter of the gels over the glass plate (Sciences-Martin A, 1984). Regarding the extrudability, the test was simply performed by filling collapsible aluminium tubes with the formulations. Then, the tubes were pressed to extrude a gel ribbon of 0.5 cm within 10 s and the extrudability of hydrogels was recorded (Bhanu, Shanmugam and Lakshmi 2011; Rathod and Mehta 2015, Elhassan,).

**In vitro release study**

The release rate of SILD from the modified gels was investigated using Franz diffusion cell. Practically, one-gram gel, containing 10 mg of drug (1% w/w) was placed on a semi-permeable membrane (MWCO 14kDa), which was previously soaked in distilled water for 24 hrs. The membrane, loaded with sample, was clipped tightly over the cylindrical glass tube end (6.5 cm²) by means of a cotton thread. Afterword, the tube was suspended over the surface of release medium (300ml distilled water). The cells were shaken in a water bath at 34 ± 0.5 °C and 50 rpm. At appropriate intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 hr.), 5 ml aliquots of the receptor medium were taken and immediately substituted by equal volume of fresh medium. The drug concentration was analyzed spectrophotometrically at 293 nm and the mean percentage of drug released and permeated across the membrane was plotted against time. The presented results were calculated from the average of three experiments and expressed as means ± SD (Manian, Jain et al. 2022).
Mechanism of drug release from the prepared hydrogels

In an attempt to determine the release pattern of SILD, the prepared hydrogel formulae were analyzed according to zero order, first order, Higuchi diffusion and Korsmeyer-Peppas models (Wagenmakers EJ. 2003).

Zero order model:

In this model, the cumulative amount of released drug was plotted against time according to the following equation:

\[ Q_t = Q_0 - K_0 t \]  (1)

Where \( Q_0 \) is the initial amount of the drug in the formula, \( Q_t \) is the amount of drug released at time \( t \) and \( K \) is the proportionality constant for each model. The correlation coefficient (\( r \)) was utilized for the determination of the appropriate model, since the highest correlation coefficient indicates the linearity of the curve and represents the actual mode of the release (Draize, Woodard and Calvery 1944).

First order model:

In the case of first order kinetic model, the normal scale was replaced with logarithmic one since the log of cumulative released SILD was plotted against time according to the following equation:

\[ \log Q_t = \log Q_0 - \frac{K_1 t}{2.303} \]  (2)

Higuchi diffusion models:

In this model, the cumulative amount of released drug was plotted against square root of time according to the following equation:

\[ Q_t = K_h \sqrt{t} \]  (3)

1.1. Skin irritation study

Irritation in rat skins was visually evaluated after topical application of sildenafil gel formulation. Study was carried out according to the previous method (Draize 1944, Rc 1997, Rosen, Cappelleri et al. 1999). One day before the gel application the rat dorsal skin was shaved. 2 g of the examined SILD hydrogel were applied on the shaved rat dorsal skin over an area of 9 cm\(^2\). Then, the treated skin surface was visually examined for any change such as erythema within a period of 24, 48, and 72 h. After the specific period, the hydrogel was cleaned and the extent of erythema were recorded and classified according to the following orders: 0, 1, 2, 3, and 4 for no erythema, mild erythema (light pink), moderate erythema (dark pink), moderate to severe erythema (light red), and severe erythema (extreme redness), respectively (Draize 1944, Rc 1997, Rosen, Cappelleri et al. 1999)
RESULTS AND DISCUSSION

Preparation of hydrogels and drug loading

Hydrogels containing sildenafil (SILD) were successfully prepared using different gelling agents including HPMC, pluronic F127, Na-CMC and Na-alginate. The medicated gel was prepared by mixing a known amount of SILD into the prepared gel using the homogenizer with rotation speed of 500 rpm for 15 minutes.

Physicochemical properties of SILD gels

Visual inspection

The prepared SILD gels were visually examined. It was observed that all the modified hydrogel formulae were homogenous, rubbery, and smooth. Also, there are no phase separation or lumbs were observed.

pH determination

The obtained data showed that the pH values of the modified hydrogels lied in the normal skin pH (4.5-7) (see Table 2). This finding indicated the suitability of the constructed hydrogels for topical applications.

Spreadability and extrudability measurements

The hydrogel spreadability values of all modified hydrogels ranged from 2.7 cm to 3.4 cm (see Table 2) which is enough for gel spreading on the skin. Similarly, the extrudability results showed that 0.5 cm of the modified hydrogels ribbon were extruded within 10 seconds by pressing the collapsible tubes with two fingers, indicating the smooth and easy release of the hydrogel formulation from the tubes.

Viscosity measurement

It has been observed that the viscosity increased partially by increasing either the drug concentration or the polymer concentration in the gel formulation (Table 2). Moreover, It was noted that increasing the shear stress the decreased the viscosity, indicating the shear thinning nature of the formulations (Table 2). The observed thixotropic behaviour is important for pharmaceutical topical formulations in order to facilitate their preparation, handling and applications on the skin (Ruiz, Clares et al. 2007).

In vitro release study

Figure 2 shows the release profiles of SILD from different gelling agent including sod-alginate (F7), CMC-Na (F8), pluronic (F4) and HPMC (F1). The results indicated that the fastest release rate was obtained in the cases of both HPMC and pluronic compared to the other gelling agents according to the following manner:
HPMC > Pluronic > Na-CMC > Na-alginate

The in vitro release of SILD from pluronic as a function of gel concentration (20%, 25% and 30% w/w) was illustrated in Figure 3. The results showed that the highest release rate was obtained from the formula containing 20% pluronic followed by that of 25%, the lowest release rate was obtained in the case of 30% gel. In terms of the drug’s release from Pluronic F127 gels, it was found that raising the concentration of Pluronic from 20 to 30% w/w resulted in a decrease in the release rate, as illustrated in Figure (80). According to Lauffer's theory of gel diffusion, which provides that a solute's diffusion coefficient is inversely proportional to the volume fraction occupied by the gel-forming substance, the low release rate found with the increased Pluronic concentration is in good agreement with that theory (M.A. Laffer 1961). The obtained results were in a good agreement with the previously reported data (Mohammed, Saleh et al. 2022 preparation of hydrogels loaded with Florite®-based etodolac).

Table 2: Physicochemical properties (viscosity and spreadability) of hydrogel formulations.

<table>
<thead>
<tr>
<th>Code</th>
<th>%Drug content</th>
<th>Viscosity (cP X 10^3)</th>
<th>PH</th>
<th>Spreadability (cm)</th>
<th>Extrudability (Sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50 rpm</td>
<td>20 rpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>101.4 ± 2.1</td>
<td>5.9 ± 0.1</td>
<td>157.3 ± 5.51</td>
<td>5.9 ± 0.1</td>
<td>3.1 ± 0.03</td>
</tr>
<tr>
<td>F2</td>
<td>99.4 ± 2.1</td>
<td>5.9 ± 0.1</td>
<td>159.1 ± 2.83</td>
<td>5.9 ± 0.1</td>
<td>3.2 ± 0.60</td>
</tr>
<tr>
<td>F3</td>
<td>98.9 ± 3.1</td>
<td>6.2 ± 0.57</td>
<td>160.8 ± 3.73</td>
<td>6.2 ± 0.57</td>
<td>3.5 ± 0.17</td>
</tr>
<tr>
<td>F4</td>
<td>100.9 ± 1.4</td>
<td>6.3 ± 0.37</td>
<td>155.5 ± 1.77</td>
<td>6.3 ± 0.37</td>
<td>3.0 ± 0.17</td>
</tr>
<tr>
<td>F5</td>
<td>97.5 ± 2.27</td>
<td>6.4 ± 0.1</td>
<td>157.3 ± 4.85</td>
<td>6.4 ± 0.1</td>
<td>3.3 ± 0.27</td>
</tr>
<tr>
<td>F6</td>
<td>97.9 ± 2.58</td>
<td>6.3 ± 0.51</td>
<td>159.4 ± 3.65</td>
<td>6.3 ± 0.51</td>
<td>3.5 ± 0.24</td>
</tr>
<tr>
<td>F7</td>
<td>100.4 ± 1.6</td>
<td>6.2 ± 0.57</td>
<td>157.2 ± 3.87</td>
<td>6.2 ± 0.57</td>
<td>3.7 ± 0.09</td>
</tr>
<tr>
<td>F8</td>
<td>99.3 ± 1.57</td>
<td>6.2 ± 0.50</td>
<td>158.1 ± 2.71</td>
<td>6.2 ± 0.50</td>
<td>3.4 ± 0.07</td>
</tr>
<tr>
<td>F9</td>
<td>100.2 ± 0.87</td>
<td>5.9 ± 0.1</td>
<td>157.4 ± 3.11</td>
<td>5.9 ± 0.1</td>
<td>3.4 ± 0.25</td>
</tr>
<tr>
<td>F10</td>
<td>97.2 ± 0.7</td>
<td>5.9 ± 0.1</td>
<td>159.2 ± 2.91</td>
<td>5.9 ± 0.1</td>
<td>3.5 ± 0.15</td>
</tr>
</tbody>
</table>

Fig. 2: Release profiles of 1% w/w SILD from different gelling agents.
Fig. 3: Release profiles of 1% w/w SILD from Pluronic F127 as a function of gel concentration.

Similar results were obtained in the case of HPMC (Figure 4) since the high polymer concentration the low the release rate Higher HPMC concentrations result in a more dense and crosslinked gel network. This restricts the diffusion of the drug molecules through the hydrogel matrix (Siepmann and Peppas 2012; Agarwal and Murthy 2015). These results may be attributed to the fact that the increase of polymer concentration lead to an increase of gel viscosity which consequently hinder the release rate of the drug.

Fig. 4: Release profiles of 1% w/w SILD from HPMC as a function of gel concentration.
Figure 5 shows the effect of drug concentration on the release profile of SILD from HPMC gel (containing 2.5% w/w gel powder). The results indicated that the increase of drug concentration is followed by a decrease of drug release rate because in hydrogel matrices the drug is dispersed or dissolved in the polymer network. Higher drug loading means the drug has to diffuse through a more saturated gel layer (Siepmann and Peppas 2012).

![Graph showing release profile of SILD from 2.5% w/w HPMC gel as a function of drug concentration.]

Fig. 5: The release profiles of SILD from 2.5% w/w HPMC gel as a function of drug concentration.

**Kinetics treatments of the drug release profiles**

Table 3 presents the values of correlation coefficient (R) and release rate constant (K) which were deduced from different kinetic model plots. Depending on the correlation coefficient values, the release kinetics data indicates that the release of drug from gels follows Higuchi diffusion model in both selected formula (F1 and F4) which contain the same concentration of drug and different gelling agent since F1 contains 2.5w/w HPMC and F4 contains pluronic 20% w/v, in the presence of penetration enhancer. These results are in a good accordance with those obtained previously (Costa and Lobo 2001, Ruiz, Clares et al. 2007, Dash, Murthy et al. 2010), since it has been noted that the main release mechanism is Higushi diffusion mechanism.
Table 3: Kinetic data for percentage of SILD released from hydrogel bases.

<table>
<thead>
<tr>
<th>Kinetic models</th>
<th>F1</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero order</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.987 ± 0.12</td>
<td>0.949 ± 0.17</td>
</tr>
<tr>
<td>k₀ ( % release/min)</td>
<td>1.691 ± 0.22</td>
<td>1.071 ± 0.10</td>
</tr>
<tr>
<td>First order</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.995 ± 0.11</td>
<td>0.968 ± 0.09</td>
</tr>
<tr>
<td>k₁ (min⁻¹)</td>
<td>0.028 ± 0.006</td>
<td>0.014 ± 0.12</td>
</tr>
<tr>
<td>Higuchi diffusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.998 ± 0.14</td>
<td>0.997 ± 0.16</td>
</tr>
<tr>
<td>kₕ ( % release/min¹/₂)</td>
<td>8.939 ± 0.82</td>
<td>6.497 ± 0.97</td>
</tr>
<tr>
<td>Korsemeyer –peppas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.994 ± 0.14</td>
<td>0.991 ± 0.16</td>
</tr>
<tr>
<td>N</td>
<td>0.264</td>
<td>0.324</td>
</tr>
<tr>
<td>Best fitted model</td>
<td>Higuchi</td>
<td>Higuchi</td>
</tr>
<tr>
<td></td>
<td>diffusion</td>
<td>diffusion</td>
</tr>
</tbody>
</table>

r: Corr. coefficient

K: specific order rate constant for zero (K₀), first (K₁) and Higuchi (Kₕ)

Skin irritation study

Irritation in rat skins was visually evaluated after topical application of SILD gel formulation (F8) which showed the highest in vitro release data. The results showed that, there were no any signs of irritation after 24 hr. Irritation score (primary skin irritation index) was zero, which indicated the safety of the modified formulations for topical administration.

Conclusion

Topical drug delivery system of SILD was studied through loading of sildenafil citrate onto different hydrogel formulae using different gelling gents. The medicated hydrogels were prepared by mixing of drug with the gel bases using homogenizer. The results showed that the prepared hydrogels showed good physicochemical properties. The hydrogel which is constructed from 2.5% w/w HPMC as gelling agent showed the highest release rate, PH, viscosity, spreadability compared to other gelling agents. The results showed, also, the release mechanism for all cases was Higushi diffusion model. These results indicated the suitability of the hydrogel system for loading and release of SILD through the skin as topical delivery system with no side effects, accompanying the systemic use of the same drug.

Conflict of interests

The authors report no conflict of interest in this work.
funding statement

The authors didn't receive any financial support to carry out this work.

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