



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Research Article


November 2016 Vol.:7, Issue:4

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Pharmaceutical Studies on the Availability of Sildenafil Citrate from Certain Topical Delivery Systems



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals



ISSN 2349-7203

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Submission: 5 November 2016
Accepted: 10 November 2016
Published: 25 November 2016

Keywords: Sildenafil, hydrogels, emulgels, kinetic, in-vitro release and stability study

ABSTRACT

Oral administration of sildenafil (SILD) was accompanied with several side effects including nausea, stomach cramps, headache and severe hypotension. 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 and emulgels were prepared. The formulated sildenafil gels were characterized by measuring different parameters such as pH, viscosity, spreadability and *in vitro* diffusion behavior. Also, the mechanism of drug release was investigated. The results showed that all medicated gels formula showed good consistency, spreadability, homogeneity and stability. In general, the hydrogel system showed higher release rate compared with emulgel. Especially, the gel formula containing 2% w/w HPMC showed the best results compared to other gelling agents. The release mechanism of the drug from both hydrogels and emulgels was Higushi diffusion mechanism. Moreover, the results of stability study indicated that all prepared gel system retain their original physicochemical properties and exhibited no irritation effect on the skin. These results indicated the possibility of using SILD via topical route of administration rather than the systemic one and, consequently, the patient can use it safely with no side effects.



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INTRODUCTION

Millions of men worldwide suffer from both Premature ejaculation (PE) and erectile dysfunction (ED) which may be caused by low levels of the hormone testosterone ^[1]. Testosterone replacement therapy can potentially help these men. Unfortunately, this strategy does not help men with ED and normal levels of testosterone. Therefore, some selective serotonin reuptake inhibitors have been used to treat these sexual problems such as all antidepressants. Also, the group of phosphodiesterase (PDEI) inhibitors such as sildenafil and tadalafil were widely used for the improvement of sexual dysfunction ^[2-5]. This enzyme promotes degradation of cGMP, which regulates blood flow in the penis. Consequently, inhibition of this enzyme leads to increase the blood supply to the penis and improve the erectile dysfunction ^[6]. However, oral administration of sildenafil is accompanied with several side effects including flushed skin, headache and severe hypotension. Also, oral administration of sildenafil is contraindicated with patients with cardiovascular diseases and who take nitrates such as nitroglycerine due to this may lead to severe hypotension and in some cases, with old age, it may be fatal. ^[7].

Alternatively, the topical administration of sildenafil has the advantage of lack of significant systemic absorption and thus systemic side effects ^[8]. So, men for whom the oral medications are unsafe, or cause too many side effects, would be able to deliver the drug directly to the penis in a controlled manner. However, questions about the lower efficacy of topical therapy compared to systemic are the main limitation, especially in severe cases. However, mild and moderate cases of erectile dysfunction and premature ejaculation may benefit from accepted efficacy of topical therapy with absence of systemic side effects ^[9]. Results from randomized controlled trials about efficacy of topical sildenafil in men with mild to moderate erectile dysfunction associated with premature ejaculation are limited and contradictory ^[10].

In this study, different kinds of transdermal delivery systems (hydrogels and emulgels) have been constructed and evaluated for loading and release of sildenafil citrate. The formulated systems were characterized by different analysis, including visual inspection, extrudability, spreadability and viscosity. Moreover, the *in vitro* release behavior of sildenafil from the formulated systems was carried out. Finally, the accelerated stability study was carried out under high-stress conditions.

MATERIALS AND METHODS

Materials

Sildenafil was kindly gifted by Pharco, Pharm. Ind. Co., (Alex., Egypt); Standard cellophane membranes (molecular weight cut off range = 14 kDa) were purchased from Carl Roth (Carl Roth GmbH+ Co., Germany); hydroxypropyl methylcellulose (HPMC), carbopol 940, PEG400, oleic acid and tween 80 were obtained from El-Nasr Pharm. Chem. Co. (Cairo, Egypt). All other materials and solvents were of analytical grade.

Preparation of SILD hydrogels:

The hydrogels were prepared using different gelling agents including HPMC and carbopol 940 in the presence of different penetration enhancers as shown in table 1. For hydrogel preparation, a specified amount of HPMC gelling base was gently added to water in a beaker to obtain the required concentration. Then, mixed thoroughly using a magnetic stirrer and the container was left overnight to ensure complete mixing.

Preparation of SILD emulgel:

For preparation of the emulsion, the oil phase of the emulsion was prepared by dissolving lipophilic emulsifying agent like span 20 in the oil while the aqueous phase was prepared by dissolving hydrophilic emulsifying agent like tween 20 in purified water. Preservatives like methyl parabens were dissolved in the aqueous phase. Penetration enhancers were mixed in oil phase. Both the oily and aqueous phases were separately heated to 70–80 °C, then the oily phase was added, portion wise, to the aqueous phase with continuous stirring and allowed to cool to room temperature. The gel phase in the formulations was prepared by either dispersing gelling agent (HPMC 2% w/w) in purified water with constant stirring. The previously obtained emulsion was incorporated into the gel in 1:1 ratio with gentle stirring to obtain a product of a cream like consistency which is called an emulgel.

Drug loading:

The medicated gels were prepared by thoroughly mixing a known amount of sildenafil citrate (SILD) (0.5, 1 and 1.5% w/w) into the prepared gel using homogenizer at 500 rpm for 15 minutes. All the samples were kept at room temperature for further analysis.

Table 1: Composition of SILD Hydrogel formulations containing 0.2% w/w methylparaben as preservative and quantity sufficient of perfume.

Formula code	HPMC (% w/w)	Carbopol 940 (% w/w)	Enhancers (% w/w)				
			Oleic acid	PEG 400	Ethano l	menthol	Tween 80
F1	2.0						
F2	3.0						
F3	4.0						
F4		1.0					
F5		2.0					
F6	2.0		1.0				
F7	2.0			1.0			
F8	2.0				1.0		
F9	2.0					1.0	
F10	2.0						1.0

Evaluation of the prepared SILD topical delivery systems:

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.

pH determination:

The pH values of hydrogel samples were monitored using digital pH meter. Practically, the pH of the hydrogels was monitored by allowing the probe of the pH meter to be in contact with the samples via direct immersion of the probe of pH meter in a beaker containing a suitable amount of the gel base. Noteworthy, to avoid the skin irritation, the pH of topical preparations should lie in the range of 4.5-7 (skin pH) ^[11].

Rheological characterization:

The rheological properties were studied by measuring the viscosity using Brookfield DV-III ultra viscometer, RV model (Brookfield Co., USA). All measurements were carried out at room temperature using spindle T-D 94 at 50 rpm. The values of viscosity are displayed in the form of centipoises. All values were given as means \pm standard deviation.

Spreadability and extrudability measurements

The spreadability of the gel was determined according to the following procedure. 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 was calculated from the increase in the diameter due to spreading of the gels over the glass plate ^[12]. Regarding the extrudability, the test was carried out by filling collapsible aluminum tubes with the formulations. Then, the tubes were pressed to extrude a gel ribbon of 0.5 cm within 10 (s) and the gel extrudability was monitored ^[13].

***In vitro* release study**

The *in vitro* release study carried out using Franz diffusion cell. Practically, one gram gel, containing 10 mg of drug (1% w/w) was placed on a semipermeable cellulosic cellophane membrane (MWCO 14kDa), which was previously soaked in distilled water. The membrane, loaded with sample, was clipped tightly over the cylindrical glass tube end (6.5 cm²) by means of a cotton thread. The top of the tube was covered with perforated aluminum foil. Afterward, the tube was suspended so that the membrane was 1 cm just below the surface of release medium (200ml distilled water). The cells were shacked in a thermostatically controlled water bath at 34 \pm

0.5 °C and 50 rpm. At appropriate intervals, 5 ml aliquots of the receptor medium were withdrawn and substituted by equal amount 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 independent experiments and expressed as means ± SD.

Mechanism of drug release from the prepared hydrogels

To investigate the release mechanism of SILD, the formulated hydrogel formulae were analyzed according to different kinetic release orders, including zero order, first order, Higuchi diffusion and Korsmeyer-Peppas models ^[14]. 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)
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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 ^[14]. 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 2. Regarding the Higushi diffusion model, the cumulative amount of released drug was plotted against square root of time according to the following equation 3. While as, in Korsmeyer-Peppas model, log Q_t was plotted against log t according to equation 4.

$\log Q_t = \log Q_0 - \frac{K_1 t}{2.303}$	(2)
$Q_t = K_h \sqrt{t}$	(3)
$\log Q_t = \log K + \frac{1}{2} \log t$	(4)

Skin irritation study

The ability of the chemical agents, included in the gel formulation, to cross the stratum cornea barrier and, subsequently, interact with viable cells of the epidermis and dermis may lead to skin

irritancy. Therefore, the skin irritation effect of the prepared gels was monitored according to the previously reported procedure ^[15]. Briefly, 2 g of the tested SILD gels were applied to the shaved dorsal skin of the rats and occluded with gauze and bandage. After one day, the gel formulation was removed and the extent of edema and erythema were recorded as following orders: 1, mild erythema; 2, moderate erythema and 3 severe erythema.

Accelerated stability study

The accelerated stability studies were carried out according to ICH guidelines by storing the selected SILD formulations, in a stability chamber, under stress conditions, including high degrees of temperature (40⁰C) and high degrees of humidity (75% RH) for three months. Afterward, the formulations were analyzed for the changes in the physicochemical properties such as homogeneity, drug content, pH and the in vitro release behavior and then compared with the previously stated ones ^[16-18].

RESULTS AND DISCUSSION

Preparation of hydrogels and drug loading

Hydrogels containing sildenafil (SILD) were successfully prepared using HPMC and cabopol 940 as gelling agents. 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. Similarly, the medicated emulgel was prepared using HPMC for comparison with the gels.

Physicochemical properties of SILD gels

pH determination

The pH values of the prepared gel formulations were in the range of 6.5 to 7.1 (see Table 2), which lies in the normal pH range of the skin (4.5-7). This finding indicated the suitability of the prepared gels for transdermal or topical applications

Spreadability and extrudability measurements

The spreadability values of all prepared gels varied between 2.5 cm – 3.5 cm (see Table 2) which is considered to be sufficient for spreading the gel on the skin. Similarly, the results of extrudability showed that all the prepared formulations were extruding 0.5 cm of the gel ribbon

within 10 seconds by pressing the collapsible tubes with two fingers. The obtained results indicated the smooth and easy release of the gel from the tubes.

Viscosity measurement

The results showed that the viscosity decreased by increasing the shear stress, indicating the shear thinning nature of the formulations. The observed shear thinning or thixotropic behavior is important for pharmaceutical topical formulations in order to facilitate their preparation, handling and applications on the skin. 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).

Table 2: Physicochemical properties (homogeneity, viscosity, pH, spreadability, and drug content) of different gel formulations. The results are represented as the mean \pm SD.

Formulation code	Homogeneity	Viscosity (cP X 10 ³)	pH	Spreadability (cm)	Drug content (%)
F1	homogenous	159.5 \pm 4.57	6.5 \pm 0.41	3.1 \pm 0.05	98.9 \pm 4.2
F2	homogenous	163.1 \pm 3.87	6.7 \pm 0.23	3.9 \pm 0.6	95.2 \pm 4.5
F3	homogenous	164.8 \pm 4.13	6.6 \pm 0.16	3.9 \pm 0.27	98.3 \pm 3.1
F4	homogenous	156.4 \pm 3.67	6.8 \pm 0.11	3.0 \pm 0.19	100.3 \pm 2.5
F5	homogenous	165.3 \pm 3.15	6.8 \pm 0.15	3.9 \pm 0.14	101.2 \pm 2.7
F6	homogenous	157.9 \pm 2.45	6.9 \pm 0.17	3.5 \pm 0.25	98.3 \pm 4.1
F7	homogenous	158.9 \pm 1.27	6.9 \pm 0.11	3.6 \pm 0.17	97.6 \pm 3.1
F8	homogenous	157.4 \pm 2.61	7.0 \pm 0.14	3.3 \pm 0.09	98.9 \pm 2.2
F9	homogenous	156.9 \pm 2.61	6.7 \pm 0.23	3.3 \pm 0.14	99.2 \pm 4.7
F10	homogenous	157.2 \pm 1.81	6.7 \pm 0.13	3.6 \pm 0.17	96.2 \pm 3.1

In vitro release study

Figure 1 shows the release profiles of SILD from different gelling agent including HPMC and carbopol 940. The results showed that SILD release in the case of hydrogel system constructed from HPMC is higher than that obtained in the case of carbopol as a gelling agent. Also, the *in*

in vitro release of SILD from HPMC as a function of gel concentration (2%, 2.5% and 3% w/w) was studied and illustrated in Figure 2.

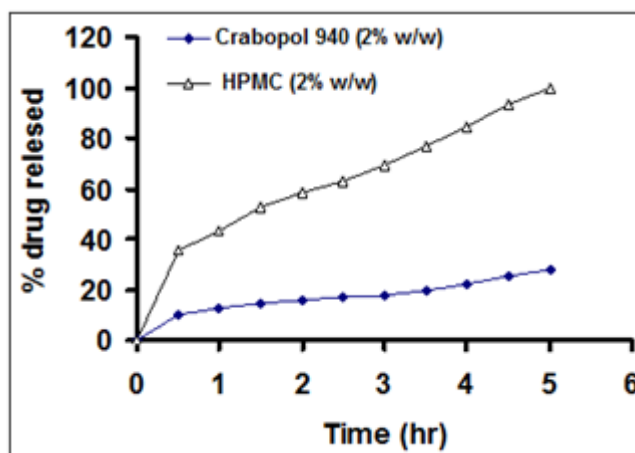


Figure 1: The release profiles of SILD from either 2% w/w HPMC gel or 2% w/w carbopol 940 gel.

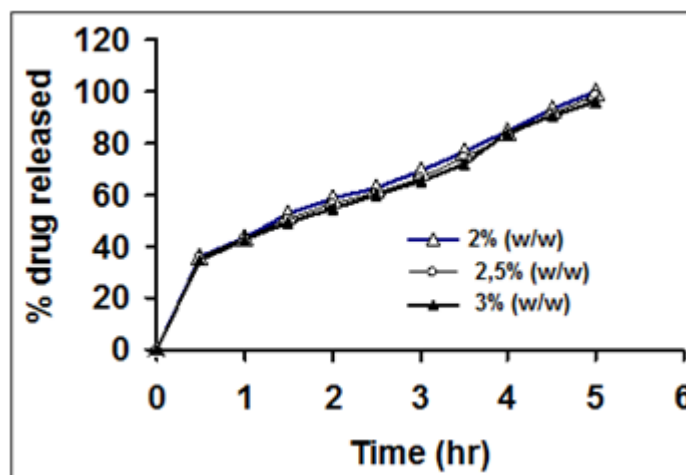


Figure 2: Release profiles of 1% w/w SILD from HPMC as a function of gel concentration.

The results showed that the highest release rate was obtained from the formula containing 2% w/w HPMC followed by that of 2.5% w/w and the lowest release rate was obtained in the case of 3% w/w gel. Moreover, the impact of different percutaneous enhancers (PEG400, ethanol, menthol, oleic acid and tween 80) on the release of SILD were investigated and the result was illustrated in Figure 3. The results indicated that there is no significant difference between the investigated enhancers. This finding is in a good agreement with the previously reported data.

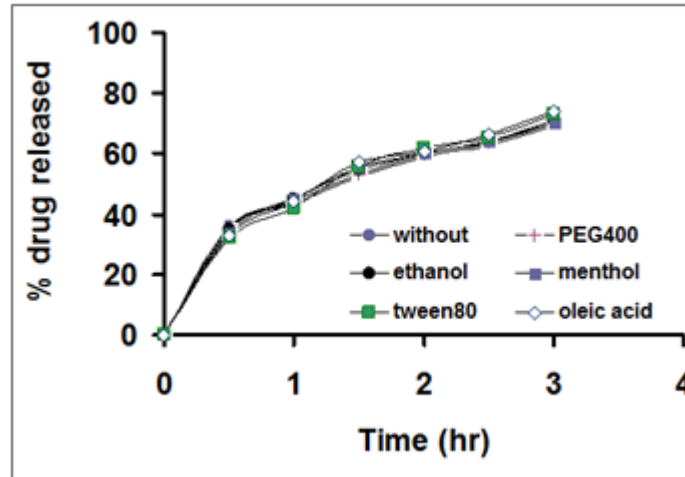


Figure 3: Effect of penetration enhancers on the release profile of SILD from HPMC gel base.

Figure 4. Shows the release profiles of SILD from HPMC hydrogel in comparison with HPMC emulgel at the same concentration of gelling agent (2% w/w). The results indicated that the release of drug in the case of hydrogel is higher than in the case of emulgel. This result may be due to the hydrophobic nature of emulgel which hinder the release of SILD to the aqueous medium.

Kinetics treatments of *in vitro* release data

The obtained values of correlation coefficient (r) and release rate constant (k) of each formulation for different kinetic models (zero order, first order, Higuchi and Korsmeyer-Peppas) are shown in Table 3.

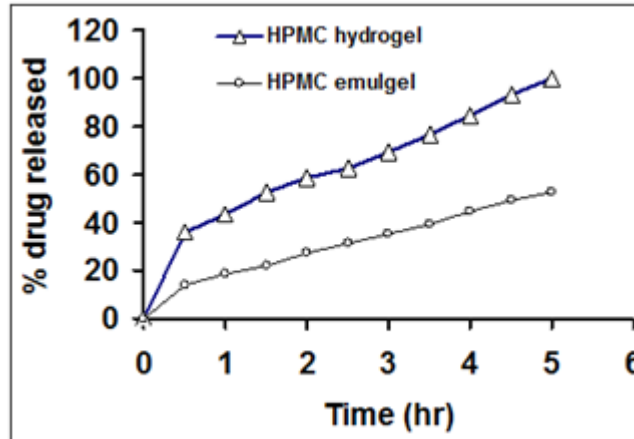


Figure 4: The release profiles of SILD from either 2% w/w HPMC gel or 2% w/w carbopol 940 gel.

Table 3: Kinetic data for percentage of SILD released from hydrogel bases.

Kinetic models		Different hydrogel formulae	
		(HPMC,gel)	(HPMCemulgel)
Zero order	R	0.977 ± 0.16	0.968 ± 0.14
	k_0 (%release/min)	1.691 ± 0.22	1.058 ± 0.12
First order	R	0.994 ± 0.14	0.957 ± 0.18
	k_1 (min ⁻¹)	0.028 ± 0.006	0.014 ± 0.12
Higuchi diffusion	R	0.996 ± 0.14	0.997 ± 0.14
	k_h (% release/min ^{1/2})	8.939 ± 0.82	6.497 ± 0.97
Korsmeyer-Peppas	R	0.990 ± 0.15	0.994 ± 0.15
	Slope	0.389 ± 0.14	0.421 ± 0.15
Best fitted model		Higuchi	Higuchi

r: Corr. coefficient

K: specific order rate constant for zero, first and Higuchi

Depending on the correlation coefficient values, the release kinetics data indicates that the release of SILD hydrogel or emulgel follows Higuchi diffusion model in both selected formula (HPMC

gel and HPMC emulgel) which contain the same concentration of drug and different gelling base. The obtained results are in a good agreement with the finding obtained previously reported data [19].

Skin irritation study

There were no any signs of irritation has been observed after 24 hr (zero of erythema score). These result indicated the safety of gel bases for topical drug delivery.

Stability study

The results of accelerated stability study showed that the formulated SILD gels or emulgels retain their original physicochemical characteristics such as the homogeneity, the drug content and the release behavior after three months.

CONCLUSION

In this study, we reported on the availability of sildenafil citrate from certain topical delivery systems. SILD hydrogels were prepared using two different gelling agents (HPMC and carbopol 940). The hydrogels were prepared by simple mixing of SILD, at different concentrations, with the gel bases using homogenizer rotated at high speed. Also, for comparison, SILD emulgel was prepared using HPMC as gelling. The results showed that the prepared gels showed good physicochemical properties. The hydrogel which is constructed from 2% w/v HPMC as gelling agent showed a higher release rate compared to carbopol at the same concentration. Also, the hydrogels showed a higher release rate compared to emulgel. Regarding the effect of percutaneous enhancer on the in vitro release rate of SILD, the results showed that there is no significant difference. Moreover, the release mechanism for all cases was Higushi diffusion model. The obtained gels showed no signs of irritation on skin indicating that the gels are safe for topical administration. The results of stability studies indicated that the modified gels were stable. Prospectively, the bioavailability studies of the modified gels on volunteers will be the subject of the next article.

Conflict of interests

The authors report no conflict of interest in this work.

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