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RESEARCH ARTICLE

Optimized sildenafil citrate fast orodissolvable film: a promising formula for overcoming the barriers hindering erectile dysfunction treatment

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Abstract

Sildenafil citrate, a drug used to treat erectile dysfunction, is available in tablet form but has three major problems. First, the drug displays poor aqueous solubility, which delays its onset of action. Second, the drug undergoes extensive first-pass metabolism, resulting in a low (40%) bioavailability. Third, the gastrointestinal effects of sildenafil citrate include dyspepsia and a burning sensation. The objective of this study was to prepare sildenafil citrate using a fast orodissolvable film (ODF) containing the drug in a solid dispersion (SD) to mitigate the abovementioned problems. The solubility of sildenafil citrate in β-cyclodextrin derivatives was estimated, and SDs were prepared and characterized. To develop an ODF that disintegrates rapidly and releases the maximum amount of sildenafil citrate, a 3^3 Box–Behnken experimental design was used to estimate the effects of different concentrations of film forming polymer (X_1), the film modifier (X_2), and the plasticizer (X_3) on the responses, i.e. the disintegration time (Y_1) and the amount of drug released (Y_2). Pharmacokinetic studies with the optimized (ODF) were conducted on human volunteers. SD prepared using hydroxybutyl-β-cyclodextrin enhanced the solubility of sildenafil citrate by more than eightfold. The Y_1 for the optimized ODF was 89 seconds, and the Y_2 was 86%; this formula also exhibited a rapid onset of action, and its bioavailability was enhanced by 2.25-fold compared with that of the marketed tablet. The ODF is a promising formulation for sildenafil citrate that results in higher solubility, a rapid onset of action, and enhanced systemic bioavailability.

Keywords

Box–Behnken design, erectile dysfunction, hydroxybutyl-β-cyclodextrin, orodissolvable film, sildenafil citrate

History

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Introduction

Sildenafil citrate is the most common drug used for the treatment of erectile dysfunction. This compound is nearly insoluble in water and undergoes extensive first-pass metabolism, which leads to its low oral bioavailability (40%) and an onset of action that is attained within 60 minutes Al-Ghazawi et al. 2010. The drug lasts for four hours, although a lower response is observed at this time point compared with that at two hours Walker et al. 1999. The major adverse effects of this drug include gastrointestinal effects, such as dyspepsia, burning sensation, and interactions with food; in particular, fatty foods hinder its absorption Nichols et al. 2002.

Cyclodextrins have recently been recognized as useful excipients and form a group of cyclic oligosaccharides containing a truncated cone or torus structure. These structures can accommodate several types of lipophilic species within their cavities, enhancing the solubility of the lipophilic molecules due to the hydrophilic exterior surface and nonpolar interior cavity Fernandes et al. 2002. Typical natural β-cyclodextrins contain seven units of glucose monomers Chen and Jiang 2011. Recently, several grades of synthetic β-cyclodextrins, such as hydroxypropyl-β-cyclodextrin and hydroxybutyl-β-cyclodextrin, have become available.

Several techniques have been used in research and manufacturing to improve oral bioavailability. The utilization of solid dispersion technology through the formation of an inclusion complex between the drug and some soluble carriers is the most common technique and results in improvements in the solubility and enhancements in the dissolution rate Dahima et al. 2010. Therefore, this technology should improve the bioavailability of drugs, such as sildenafil citrate.

Orodissolvable films (ODFs) are a relatively new oral dosing form; these postage stamp-sized strips of thin polymeric films are formulated to disintegrate or dissolve almost instantaneously when placed on the tongue Cilurzo et al. 2010, El-Setouhy and El-Malak 2010. A drug in an ODF is absorbed through the oral mucosa and thus enters the systemic circulation without undergoing first-pass hepatic metabolism Malke et al. 2010. This formulation is administered easily and provides fast pharmacological action, thereby improving patient compliance. Furthermore, ODFs can be

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formulated using solid dispersions, thereby increasing the solubility of the drug.

The Box–Behnken experimental design is one of the response surface models used to hit the target, reduce variability in the experiment, maximize/minimize a response that increases the production yield or decreases the amount of waste, and represent opportunities for extensive financial gain Karnachi and Khan 1996. As this model has an orthogonal design, the factor levels are evenly spaced and coded for low, medium, and high settings: −1, 0, and +1, respectively. Therefore, the process is optimized to obtain the levels of the independent variables that provide the optimum response values Rajput et al. 2011.

To mitigate the abovementioned problems associated with the commercially marketed product, this work aimed to prepare sildenafil citrate citrate as a fast ODF containing the drug in a solid dispersion (SD) with β-cyclodextrin derivatives through the utilization of Box–Behnken experimental design.

Experimental methods

Materials

Sildenafil citrate was generously donated by EIPICO (Cairo, Egypt). Propylene glycol was purchased from Fluka AG, Buchs SG (Switzerland). Hydroxypropyl cellulose (HPC) and guar gum were purchased from Aqualone, London (UK); cyclodextrin (β-CD, hydroxypropyl-β-CD, and hydroxybutyl-β-CD) was donated by Nihon Shokuhin Kako Co., Ltd. Tokyo (Japan). All other chemicals were of analytical grade.

Methodology

Phase solubility studies

The phase solubility was analyzed according to Highuchi and Connors 1965. Excess sildenafil citrate was dispersed into a 20 mL aqueous solution of a hydrophilic carrier (β-cyclodextrin, hydroxypropyl-β-cyclodextrin, and hydroxybutyl-β-cyclodextrin) at various concentrations (1–10 mM/L). The mixture was then stirred for 24 h at 37 °C ± 0.5 °C. After equilibrating, the samples were filtered through a 0.22 μm nylon disc filter, and the absorbance was read after suitable dilution at 291 nm (Shimadzu 1700 UV-Visible spectrophotometer). The apparent stability constant (K_s) was calculated according to the hypothesis of a 1:1 stoichiometric ratio of complexes using the following equation:

$$K_s = \text{Slope}/S_o(1-\text{Slope})$$

where S_o is the equilibrium solubility of sildenafil citrate in water.

Preparation of the solid dispersion

After the phase solubility analysis, hydroxybutyl-β-cyclodextrin was chosen for the solid dispersion with sildenafil citrate. The SDs were prepared using two different techniques: kneading and coevaporation. For the kneading method, the required amounts of hydroxybutyl-β-cyclodextrin and distilled water were mixed in a mortar until a homogeneous paste was obtained. Sildenafil citrate was then added portion-wise while triturating with small amounts of methanol and an appropriate amount of water. Subsequently, the pastes were dried at 40 °C. The obtained SD was crushed and passed through an 80-mesh screen before being stored in a dry place until use Veiga et al. 1996. For coevaporation, sildenafil citrate and hydroxybutyl-β-cyclodextrin were mixed at a 1:1 molar ratio, and methanol was added under constant stirring until dissolution. The solvent was then evaporated, and the resultant solid dispersion was crushed and passed through an 80-mesh screen sieve before being stored in a dry place until use Patel and Patel 2007.

Solubility analysis of the prepared solid dispersion

Excess SD was dispersed in 5 mL of distilled water to obtain a supersaturated solution. These dispersions were shaken for 24 h at 25 °C until equilibrated. Two milliliters of the supersaturated solution was filtered through a 0.22 μm nylon filter, and 1 ml of the filtrate was diluted with methanol. The absorbance was measured at 291 nm. Solubility studies were also performed with pure sildenafil citrate.

Box–Behnken experimental design

Preliminary studies revealed the formulation variables that significantly affect the characteristics of sildenafil citrate (ODF). These factors include the concentration of hydroxypropyl cellulose (HPC) used as the film-formation polymer (X_1), the concentration of guar gum (GG) used as the film modifier (X_2), and the concentration of propylene glycol (PG) used as the plasticizer (X_3). The level for each formulation variable was selected based on the aforementioned studies and is reported in Table 1. The responses (Y_1 and Y_2) and their constraints are presented in Table 2. The Box–Behnken model is shown in the following equation:

$$Y = b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_1^2+b_5X_1X_2+b_6X_1X_3 +b_7X_2^2+b_8X_2X_3+b_9X_3^2+E$$

where b_0 through b_9 are the regression coefficients, and E is the experimental error. The experimental design was optimized to calculate the levels of the different independent variables that provide the optimal dependent responses based on the regression equation generated using System Statistical software (SAS).

Film preparation

The films were prepared using a solvent casting method Aliaa and Arwa 2011; hydroxypropyl cellulose was used as the film-formation polymer (X_1) at different concentrations according to a Box–Behnken experimental design, whereas guar gum was used as the film modifier (X_2). Both the compounds were dispersed in 20 mL of distilled water with continuous stirring for 30 min and maintained in a refrigerator for 24 h to remove all of the air bubbles. Accurately weighed quantities of the sildenafil citrate solid dispersion, propylene glycol, which was used as the plasticizer (X_3), and 1% aspartame, which was used as a sweetener, were dissolved separately in 2.5 mL of 50% ethanol solution in another beaker. After completely hydrating the polymer with water, the drug solution was added and mixed thoroughly in the polymer solution; the volume was increased to 25 mL with distilled water. The final solutions were poured onto a glass

Table 1. Variables and their levels in the Box–Behnken design.

	Levels		
Independent variables	Low	Medium	High
X_1 = Film forming polymer (HPC) %	1	2	3
X_2 = Film modifier (GG) %	0.2	0.4	0.6
X_3 = Plasticizer (PG) %	1	1.5	2
	Constraints		
Dependent variables	Low	High	Goal
Y_1 = Disintegration time (seconds)	95	230	Minimize
Y_2 = *In vitro* dissolution (%)	16.76	79.22	Maximize

Table 2. Experimental runs and observed values of responses for BBD.

	Factors			Responses	
Run	X_1	X_2	X_3	Y_1	Y_2
F1	1	0.4	2	100	79.22
F2	3	0.4	2	180	28.5
F3	3	0.2	1.5	210	24.5
F4	1	0.2	1.5	150	45.32
F5	2	0.6	2	110	55.45
F6	2	0.2	1	162	41.96
F7	2	0.2	2	95	29.27
F8	1	0.6	1.5	170	61.74
F9	2	0.6	1	200	22.19
F10	3	0.4	1	165	18.18
F11	1	0.4	1	190	60.9
F12	3	0.6	1.5	230	16.76
F13	2	0.4	1.5	172	20.22
F14	2	0.4	1.5	150	22.84
F15	2	0.4	1.5	140	21.33

Petri dish and allowed to dry before being carefully removed and cut into strips. Each strip contained 50 mg of sildenafil citrate, measured 2×2.5 cm, and was stored in an air-tight container.

Determination of physicochemical parameters

The average weight each of 10 samples of each formulation was determined. The thickness of each of sample was measured using micrometer screw gauge at five locations, and the mean thicknesses were calculated. The folding endurance was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times which is considered satisfactory to reveal good film properties. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

In vitro *disintegration of films*

The *in vitro* disintegration time of the film strips was determined using the method described by Misra and Amin 2009. The film strip was placed in a glass Petri dish (6.5 cm in diameter) containing 25 mL of distilled water at 37 °C with swirling every 5 s. The disintegration time was recorded as the time at which the film began to break or disintegrate.

Release studies of sildenafil citrate from films

The release studies were conducted in a paddle dissolution apparatus. Each film strip was fixed to a glass slab at the bottom of the dissolution vessel before the dissolution test to prevent the film strips from floating. The dissolution medium was 250 mL of PBS at pH 6.8 and was maintained at 37 ± 0.5 °C and stirred at 50 rpm. Three-milliliter samples were withdrawn at 1, 5, 10, 15, 20, 25, 30, 45, and 60 min; the volume was replenished with fresh buffer at 37 ± 0.5 °C. The sildenafil citrate concentration in the filtered samples was analyzed using UV-Vis spectroscopy at 291 nm.

In vivo studies on human volunteers

To compare the pharmacokinetics of sildenafil citrate in the optimized orodispersible film (treatment A) with the conventional Viagra® tablet (Pfizer, Cairo, Egypt; treatment B), a single dose of sildenafil citrate (50 mg) was given to the volunteers using a double blind, randomized, cross-over design. Fasting subjects were administered a single 50-mg oral dose of sildenafil citrate orodispersible film or the reference product during each period of the study.

Subject population

Twelve healthy Egyptian male volunteers aged between 30 and 45 years (median weight = 72 ± 5.5 kg and median height = 177 ± 6.7 cm) were chosen. The health status of the volunteers was confirmed using a complete medical history and laboratory analyses performed at the beginning of the study. No medication was allowed during the study.

Sample collection

The study was conducted according to the Helsinki agreement protocol and the requirements of the ethical committee of the Faculty of Medicine at Beni Suef University in Egypt. The drug was administered during each period of the study with a one-week washout period. Blood samples (5 mL) were collected at the following time intervals: 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 18, and 24 h. The blood samples were centrifuged, and the plasma was collected and stored at −20 °C until assayed.

Chromatographic conditions

The pharmacokinetic parameters of sildenafil citrate were determined using a method based on that developed by Sheu et al. 2003 involving the extraction of sildenafil citrate with dichloromethane. The DCM was then allowed to evaporate under nitrogen, and the residue was dissolved in 0.2 mL of the mobile phase (acetonitrile and potassium dihydrogen phosphate [30 mM] 56:44, v/v). The column was an RPC18.

Pharmacokinetic analysis

The pharmacokinetic parameters were estimated using WinNonlin® (version 1.5, Scientific consulting, Inc., Cary, NC). C_{max} (ng/mL) and T_{max} (h) were the observed maximum drug concentration and the time needed to reach the maximum concentration, respectively. $AUC_{(0–24)}$ (ng·h/mL) was calculated using the relative bioavailability (AUC test/AUC standard × 100).

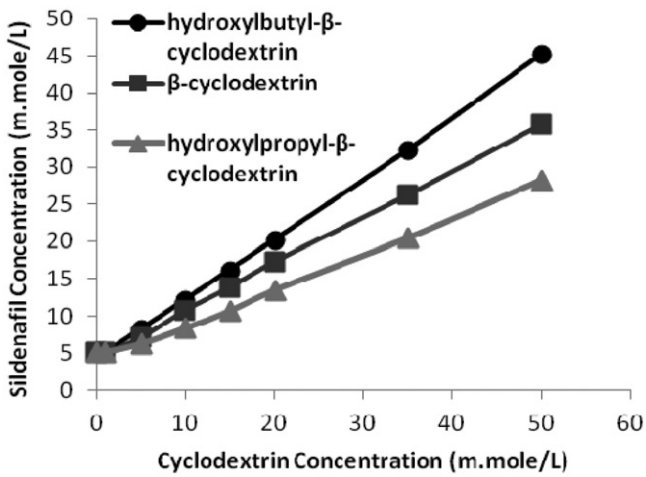

Figure 1. The phase solubility diagrams of sildenafil citrate with different concentrations of the three β-cyclodextrin carriers.

Statistical analysis

The statistical analyses were performed using a *t*-test for paired data with SPSS® 7.5 for Windows. The level of statistical significance was $p \leq 0.05$.

Results

Phase-solubility study and solubility analysis of the prepared solid dispersion

The phase-solubility analysis evaluated the affinity between the cyclodextrin and drug molecules in water. Figure 1 shows the phase-solubility curve of sildenafil citrate in the presence of CDs; an increase in the concentration of the CDs resulted in increases in the solubility of sildenafil citrate. The solubility of sildenafil citrate was increased nine-fold with 50 mM/L hydroxybutyl-β-cyclodextrin, sevenfold with 50 mM/L β-cyclodextrin, and fivefold with 50 mM/L hydroxypropyl-β-cyclodextrin.

The phase-solubility plots were type A for all three CDs, indicating that a 1:1 (sildenafil citrate:CD) inclusion complex was formed. The Ks values were 954 M^{-1} for hydroxybutyl-β-CD, 357 M^{-1} for β-CD, and 205 M^{-1} for hydroxypropyl-β-CD, indicating that a more suitable and stable complex was formed with hydroxybutyl-β-CD compared with the other two polymers.

The saturation solubility studies revealed that the aqueous solubility of pure sildenafil citrate was 3.38 ± 0.23 mg/mL and that this solubility increased with its dispersion in hydroxybutyl-β-CD to 9.54 ± 0.42 mg/mL in a SD prepared using the kneading method and to 24.33 ± 0.61 mg/ml in a SD prepared using coevaporation.

Box–Behnken experimental design

For the 3^3 Box–Behnken experimental design, 15 different formulae were prepared as shown in Table 2.

Estimation of the quantitative effects of the factors

Student's *t*-test was used to estimate the quantitative effects of the factors. The effects of X_1, X_2, and X_3 on Y_1 and Y_2 determined through ANOVA are presented in Table 3.

Table 3. Factor effects and associated *p* values for Y_1 and Y_2 responses.

	Response					
	Y_1			Y_2		
Factor	Factor effect	*F* ratio	*p* value	Factor effect	*F* ratio	*p* value
X_1	43.75	9.94	0.025*	−39.81	147.10	0.0001*
X_2	23.25	2.81	0.155	3.77	1.32	0.302
X_3	−58.0	17.47	0.009*	12.30	14.05	0.013*
X_1^2	53.0	6.73	0.049*	25.09	26.99	0.004*
$X_1 X_2$	0.0	0.00	1.000	−12.08	6.77	0.048*
$X_1 X_3$	52.5	7.16	0.044*	−4.0	0.74	0.428
X_2^2	19.0	0.87	0.395	6.13	1.61	0.260
$X_2 X_3$	−11.5	0.34	0.583	22.98	24.50	0.004*
X_3^2	−43.5	4.54	0.087	25.37	27.58	0.003*

* Significant effect of factors on individual responses.

Table 4. Regression Equations of the fitted models.

Response	Equation
Disintegration time (Y_1)	$245.25-162.88X_1-45.63X_2+121.0X_3+26.5X_1^2+0.0X_1X_2+52.5X_1X_3+237.5X_2^2-57.5X_2X_3-87.0X_3^2$
Cumulative % release (Y_2)	$248.46-52.02X_1-163.82X_2-177.89X_3+12.55X_1^2-30.2X_1X_2-4.0X_1X_3+76.68X_2^2+114.88X_2X_3+50.75X_3^2$

The analysis of the variance of Y_1 revealed that four effects had *p* values less than 0.05, whereas the analysis of the variance of Y_2 found six effects with *p* values less than 0.05. As shown in Table 4, the concentration of the film-forming polymer has a significant synergistic effect on the disintegration time and a significant antagonistic effect on the concentration of sildenafil citrate released from the film. However, the plasticizer concentration has a significant antagonistic effect on Y_1 and a significant synergistic effect on Y_2. Additionally, Y_1 and Y_2 were significantly affected by the synergistic effect of the quadratic term X_1^2, whereas Y_2 was significantly affected by the quadratic term X_3^2. The interaction effects X_1X_3 and X_2X_3 have significant synergistic effect on the disintegration time and the percentage of sildenafil citrate released, respectively. In contrast, the interaction effect X_1X_2 has a significant antagonistic effect on the percentage of sildenafil citrate released. In addition, the concentration of the film modifier (guar gum) and its quadratic term (X_2^2) exhibited no significant effect on either the disintegration time or the concentration of sildenafil citrate released.

Response surface and contour plots

The relationship between the factors and responses can be understood by plotting the response surface and contour for the estimated effects (Figure 2).

Based on the results shown in Figure 2(A), at a fixed percentage of X_2 (0.4%), an increase in X_1 to 3% and a decrease in X_3 to 1% decreases the disintegration time to 165 s. The use of a low level of X_1 (1%) and the increase in X_3 up to 2% decreases the Y_1 to 100 s. The contour plot (Figure 2B) suggests the exact percentages of X_1 and X_3 that

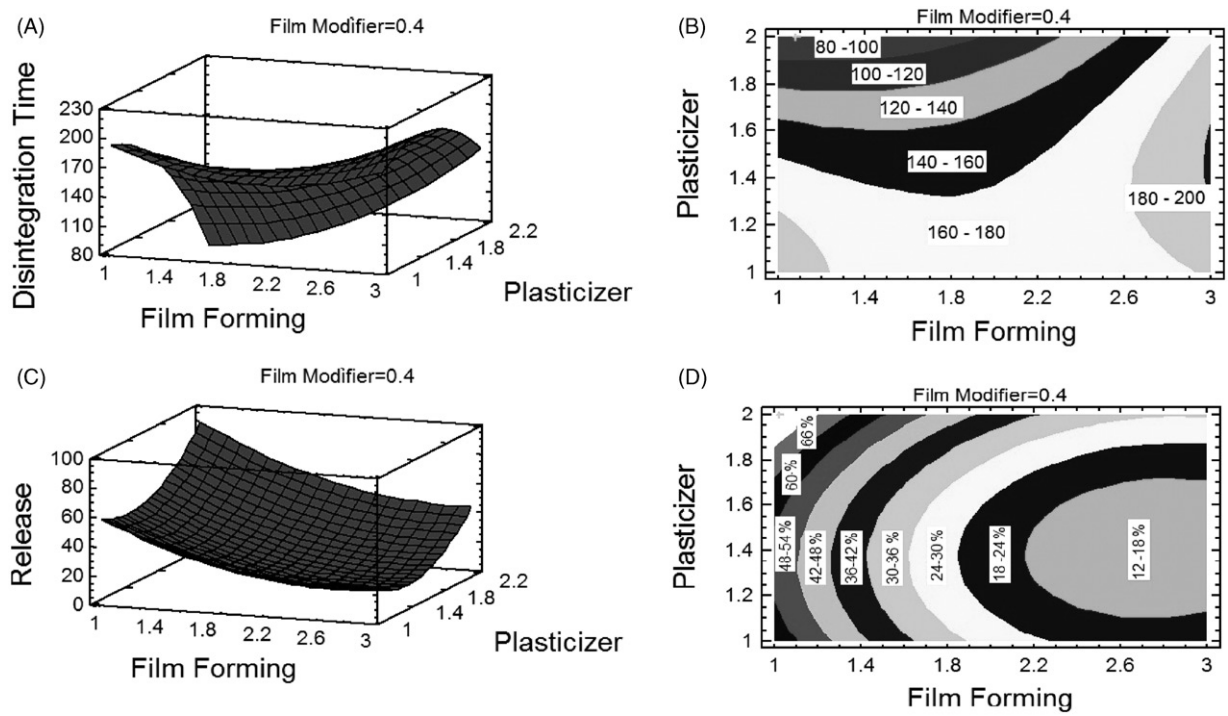

Figure 2. (A) Response surface plot (3D) showing the effect of X_1 and X_3 on Y_1. (B) contour plot showing relationship between various levels of two variables to attain fixed values of Y_1. (C) Response surface plot (3D) showing the effect of X_1, X_2, and X_3 on Y_2. (D) Contour plot showing relationship between various levels of two variables to attain fixed values of Y_2.

Table 5. Optimum desirability with observed values of the responses for the optimized sildenafil citrate ODFs formulation.

Factor	Optimum value	Response	Predicted value	Observed value
Film forming % (X_1)	1	Disintegration time (Y_1)	92.70	89.45
Film modifier % (X_2)	0.5	Cumulative % release (Y_2)	83.68	86.56
Plasticizer % (X_3)	2			

minimize the disintegration time for a fixed X_2 (0.4%). The use of a low level of X_1 and a high level of X_3 can produce a film that disintegrates within 80 to 100 s.

The effects of X_1 and X_3 on the cumulative percentage release (Y_2) are displayed in a response surface plot (Figure 2C). A at fixed level of X_2 (0.4%), an increase in X_1 to 3% and a decrease in X_3 to 1% decreases Y_2 to 18.18%. The use of a low level of X_1 (1%) and increasing X_3 to 2% increases Y_2 to 79.22%. Additionally, the contour plot (Figure 2D) suggests the exact percentages of X_1 and X_3 that produces a film that releases the maximum amount of drug within 30 min. The use of a low level of X_1 with a high X_3 can release the maximum amount of drug, as in the case of F1.

Optimized formulation

Table 4 reveals the calculated optimal combination of factor levels that attain the target by fulfilling the requirements for each response. To verify the validity of the design, the responses of the optimized formulations were evaluated (Table 5) to ensure the desired disintegration time and drug release profile of the sildenafil citrate ODF. All the fabricated film formulations prepared were smooth, almost transparent with good flexibility. It was observed that result of uniformity of weight; thickness and drug content were satisfactory with respect to variation of these parameters between films of same formulation.

In vivo *absorption studies*

The mean plasma concentration-time curves of the prepared optimized ODF and Viagra tablet are illustrated in Figure 3. The pharmacokinetic parameters were evaluated using WinNonLin® Professional software. The total drug absorbed over a period of 24 h is shown in Table 6; this measurement was determined using the differences in T_{max} between the two treatments. The AUCs were statistically significant ($p < 0.05$). Moreover, the relative bioavailability of the optimized sildenafil citrate ODF was 225% compared with Viagra® tablets as the reference standard.

Discussion

The phase-solubility analyses evaluated the affinity between the cyclodextrin and sildenafil citrate molecules in water. The solubility of sildenafil citrate increased as the CD concentrations increased because CDs have a nonpolar cavity interior that attract lipophilic drugs, such as sildenafil citrate, due to either dipolar or induced dipolar interactions, as well as Van der Waals hydrophobic interactions Fernandes et al. 2002. Additionally, the surfactant-like properties of CD carriers arise from the hydrophilicity of the exterior surface, which reduce the interfacial tension between the water and sildenafil citrate molecules Fernandes et al. 2002.

The stability constants (K_s) for the sildenafil citrate complexes indicate that the drug's binding potential with

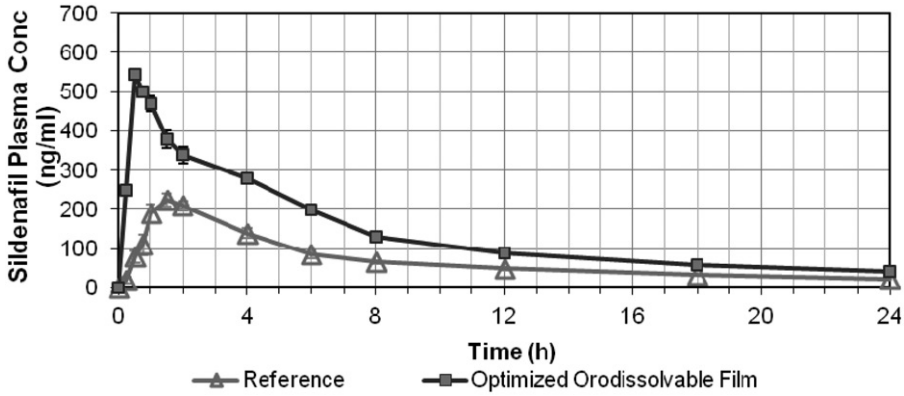

Figure 3. Plasma concentration of Sildenafil citrate following the administration of the reference (Viagra® tablets), and optimized ODF. Data represent the mean values of $n = 6 \pm$ S.D.

Table 6. Pharmacokinetic parameters ± S.D of sildenafil following the administration of a single oral dose (50 mg) of the market formulation (Viagra® tablets), and the selected optimized ODF formulation.

Pharmacokinetic parameter	Marked formula (Viagra® tablets)	Optimized sildenafil citrate ODF
C_{max} (ng/ml)	215 ± 20.25	545 ± 31.34
t_{max} (hr)	1.25 ± 0.11	0.4 ± 0.07
$AUC_{(0-24)}$ (ng h/ml)	1135 ± 165	2205 ± 206
$AUC_{(0-\infty)}$ (ng h/ml)	1190 ± 176	2415 ± 225
$t_{1/2}$ (h)	3.5 ± 0.32	3.6 ± 0.41
Kel (h^{-1})	0.27 ± 0.043	0.29 ± 0.023

hydroxybutyl-β-CD is higher than that with β-CD or hydroxypropyl-β-CD. This difference is likely due to the presence of alkyl chains on hydroxybutyl-β-CD, which increased the hydrophobicity around the cavity Omar et al. 2007. The stability constant for hydroxypropyl-β-CD was low because this polymer is more soluble in water and less hydrophobic than β-CD; therefore, it does not form stable complexes with the hydrophobic sildenafil citrate molecules.

The preparation of sildenafil citrate SD through coevaporation was more efficient than the kneading method; the solubility of sildenafil citrate increased approximately eightfold compared with that obtained in pure state due to its higher affinity toward inclusion in the hydrophobic CD cavity. This process was aided by heating and stirring during coevaporation, which provided sufficient energy for sildenafil citrate to interact in the correct orientation Liu and Zhu 2006. In contrast, the kneading method produced true inclusion complexes inefficiently due to the hindered sildenafil citrate-CD interactions in a semisolid medium; the solubility increased only threefold relative to that of the pure state.

A three-level, three-factor Box–Behnken experimental design was utilized to evaluate the effects of the concentrations of hydroxypropyl cellulose, which was used as the film-forming polymer (X_1), guar gum, which was used as the film modifier (X_2), and propylene glycol, which was used as the plasticizer (X_3), in order to minimize the disintegration time (Y_1) and maximize the amount of drug released (Y_2). Polymers impart the necessary mechanical properties to the oral film and influence the release of the active ingredient into the oral cavity. This design is suitable for exploring the quadratic response surfaces, constructing second-order polynomial models, and optimizing the process using a small number of experimental runs. The analysis of the variance in the disintegration time and the statistical significance of each effect indicated that the concentration of the film-forming material has a significant synergistic effect on the disintegration time and a significant antagonistic effect on the amount of drug released; the p values were 0.025 and 0.0001, respectively. These results may be attributed to the improvement in the swelling of the polymer upon contact with the dissolution medium, the hardening of the release path of the drug from the film, and the increase in the time required for disintegration obtained by increasing the concentration of the film-forming material Kianfar et al. 2012. However, the concentration of the plasticizer has a strong antagonistic effect on the disintegration time and a strong synergistic effect on the amount of drug released; the p values were 0.009 and 0.004, respectively. The plasticizer level affected the mechanical properties of the film by lowering the glass transition temperature (Tg) and influencing the disintegration and dissolution characteristics Repka and McGinity 2000. Furthermore, the plasticizer molecules inserted themselves between the polymer strands, thereby breaking the polymer–polymer interactions and increasing the molecular mobility of the polymer strands. Accordingly, increases in the concentration of the plasticizer increased resulted in decreases in the film stiffness and increases in the film ductility.

The pharmacokinetic study revealed that the administration of sildenafil citrate as a fast ODF can modify its pharmacokinetic profile, increasing its bioavailability by more than 2.25-fold relative to that of the marketed oral tablet. Compared with the marketed tablet, the T_{max} for the ODF containing a sildenafil citrate SD was significantly lower ($p < 0.05$) because sildenafil citrate is a lipophilic drug with poor aqueous solubility. The preparation of this drug as a SD enhanced its solubility and tissue permeability, thereby shortening its onset of action. The onset of action for the tablet begins after 1 h because the plasma level reaches 215 ng/mL at this point; this concentration was attained after 10 min using the ODF, as shown in Figure 3.

These results demonstrate that the ODF containing sildenafil citrate SD was easily absorbed, which indicates that the ODF circumvented the delayed onset observed with the tablet. Additionally, the pharmacokinetics of drugs delivered via ODF formulations are dictated by the properties of the ODF rather than the physicochemical properties of the drug molecules. When an ODF is administered orally, it is instantly wetted by saliva, which results in its rapid

disintegration and dissolution to release the drug Alka et al. 2012. In addition, the bioavailability of sildenafil citrate exhibited an increase of more than 2.2-fold; this increase could be attributed to the decreased amount of hepatic first-pass metabolism associated with orally administered tablets, which may improve the *in vivo* bioavailability.

Conclusions

A Box–Behnken experimental design was utilized to formulate sildenafil citrate as a fast ODF. This novel drug delivery system provided short disintegration times and a maximum amount of released drug. The bioavailability of sildenafil citrate was enhanced by more than 2.25-fold relative to that of the marketed tablet, and the onset of action was shortened to 10 min. The use of this ODF formula may lead to the elimination of the major drawbacks associated with the conventional tablet and allow patients to tolerate the drug without fear of gastrointestinal side effects.

Declaration of interest

The authors state no conflicts of interest. This work was supported by the Deanship of Scientific Research (DSR) of King Abdulaziz University of Jeddah (Grant No. 166-005-D1433).

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