Journal of Pharmaceutical Sciences xxx (2016) 1–8

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Rapid-Onset Sildenafil Sublingual Drug Delivery Systems: *In Vitro* Evaluation and *In Vivo* Pharmacokinetic Studies in Rabbits

Ming-Thau Sheu [1], Chien-Ming Hsieh [2], Ray-Neng Chen [3], Po-Yu Chou [1], Hsiu-O Ho [1,*]

[1] *School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan, ROC*
[2] *Department of Cosmetic Science, Providence University, Taichung City, Taiwan, ROC*
[3] *Department of Cosmetic Science and Management, Mackay Medicine, Nursing and Management College, Taipei, Taiwan, ROC*

ARTICLE INFO

Article history:
Received 15 December 2015
Accepted 14 January 2016

Keywords:
sildenafil
erectile dysfunction
sublingual tablets
sublingual spray
bioavailability

ABSTRACT

The aim of the present study was to prepare sublingual delivery systems for sildenafil and evaluate its relative bioavailability after sublingual administration in rabbits to attain a rapid onset of action with good efficacy at lower doses. For sublingual application, sildenafil and its citrate were formulated in 2 different dosage forms: the first was a sublingual spray consisting of sildenafil in 2 microemulsion systems, oleic acid or propylene glycol (PG), and the second was sublingual tablets prepared with various granulated sublingual sprays adsorbed onto a silicate adsorbant (Florite® R), binders (Cyclocel® or EMDEX®), and disintegrants (Ac-Di-Sol® or Kollidon® CL). Results showed that sublingual absorption of sildenafil spray prepared with PG was fairly rapid. At a 0.5-mg dose, the mean onset of action was 1.3 ± 0.6 min and lasted for about 1.5 h according to the pharmacokinetic studies. *In vivo* studies also showed that for sublingual tablets formulated with sildenafil in PG adsorbed onto Florite® R at a 1:1 weight ratio then mixed with Cycloel® and Ac-Di-Sol®, the onset action was fast at 1.9 ± 0.4 min and lasted for about 1 h at 0.5 mg. These findings suggest the potential for the sublingual delivery of sildenafil instead of the conventional oral administration.

Introduction

Sildenafil, administered as the commercially available Viagra formulation, was the first oral therapy to have a significant success for men with erectile dysfunction (ED).[1,2] However, there are numerous drawbacks with the oral delivery of sildenafil citrate: a long onset (i.e., it should be taken 1 h before sexual intercourse), lower bioavailability, and a considerable first-pass effect (70% of the oral dose). A high-fat meal will delay the onset of action of sildenafil.[3,4] In addition, the oral administration of sildenafil is also accompanied by undesirable dose-responsive side effects. At dosages of >50 mg, the incidences of side effects, such as abnormal vision problems, dyspepsia, nasal congestion, blinding headaches, diarrhea, rashes, syncope, priapism, cardiac risk, and urinary tract infections, increase.[5] Thus, there is a need and desire to develop drug delivery systems that promote the bioavailability of sildenafil at lower doses while minimizing its side effects. In general, the advantage of a drug delivery system is that it can deliver the active pharmaceutical ingredient (API) in an efficient manner without altering its chemical nature or biological activity.

Nasal and transdermal delivery systems have been examined as alternative dosage forms.[6-8] Among these, intranasal sildenafil citrate formulated as a microemulsion (ME) composed of oleic acid (OA)/Labrasol/Transcutol/H_2O (8.33%:33.33%:16.67%:41.67%) represents a safe and viable approach to achieving rapid-onset systemic drug levels and higher bioavailability by bypassing liver metabolism for the management of ED.[3] Furthermore, transdermal permeation of a sildenafil citrate-loaded self-nanoemulsifying drug delivery system and nanoemulsions was proven to improve the therapeutic performance of sildenafil citrate via the oral route. These formulations encompassed an oil blend of Caproyl 90® and Maisine 35-1®, Cremophor RH40® as a surfactant, and propylene glycol (PG) as a cosurfactant.[9] However, the drug possesses challenging physicochemical properties for nasal and transdermal delivery system formulations including its amphoteric nature, pH-dependent characteristics, scanty membrane permeability, and poor solubility in both aqueous and oily phases. The disadvantage of intranasal drug delivery is that a limited number of drugs can be delivered via the nasal mucosa. Additionally, patients with diseased or unhealthy nasal mucosa will likely have impaired

Conflict of interest: The authors report that no conflict of interest exists. The authors alone were responsible for the content and writing of the article.

* *Correspondence to:* Hsiu-O Ho (Telephone/Fax: 886-2-23371942).
E-mail address: hsiuoho@tmu.edu.tw (H.-O. Ho).

http://dx.doi.org/10.1016/j.xphs.2016.01.015
0022-3549/

drug absorption.[10] Administering medications using transdermal delivery systems also has disadvantages, including the potential for skin reactions ranging from allergic contact dermatitis to irritant contact dermatitis. Another drawback of using medication patches is the potential for the loss of adhesive properties, which may lead to decreased drug delivery.[11]

On the other hand, sublingual delivery is well documented in the literature.[12-15] The main use for the sublingual route of drug administration is to provide a rapid onset of action of potent drugs. Some researchers believe that sublingual administration would allow men to get results at a lower dosage than when a tablet is swallowed whole. It can also avoid first-pass metabolism by the liver and is not affected by food. Another reason for the appeal of sublingual sildenafil is the convenience of not having to take it with water. In contrast, sublingual delivery does not have the disadvantage of nasal and transdermal delivery systems. An invention by El-Rashidy et al. provided a composition suitable for sublingual or buccal tablets for the relatively slow release of sildenafil.[5] The composition essentially consists of sildenafil, an osmotic agent, a swellable hydrophilic carrier, and a water-dispersible polymer. Preferably, the osmotic agent is mannitol, the hydrophilic carrier is microcrystalline cellulose, and the water-dispersible polymer is a gum or a cellulose derivative. The invention focused on a controlled-release sublingual tablet for sildenafil released in a water solution over a time period in the range of more than about 25~300 min. However, such a time frame might not be practical in the case of certain diseases or conditions such as ED. One study, which was conducted at the Urology Division of Ospedale De Lellis in Italy, was a comparison of 6 men taking Viagra as intended (swallowed whole) for 3 months, followed by 3 months of taking Viagra that had been crushed into a powder and placed in the mouth under the tongue. The result was that the time it took for the drug to be effective was basically cut in half: 62.8 min for Viagra swallowed whole vs. 29.3 min for crushed Viagra placed under the tongue.[16] All patients declared that they preferred the sublingual way because of its faster onset. Almost all studies of sildenafil in drug delivery systems were interested in improving the problem of late onset. However, there is currently no commercially available dosage form for the sublingual delivery of sildenafil. Thus, it would be valuable to develop a sublingual sildenafil delivery system to increase its bioavailability, decrease the administrated dose, and attain a rapid onset of action.

The important characteristics of tablet formulations used for sublingual delivery are short disintegration and dissolution times.[17] However, to achieve optimal sublingual delivery, properties of the active compound and other properties of the formulation have to be considered. The parent compound has to be soluble, stable, and easily permeable through the mucosal barrier at the administration site. Furthermore, the dosage form has to be rapidly dissolved at the administration site.[18] To demonstrate the feasibility of delivering a drug via the sublingual route, suitable *in vivo* models must be used to assess the delivery potential in clinical studies. A rabbit model for investigating sublingual drug absorption was established yielding results consistent with clinical data reported in the literature. The sublingual mucosa of both the rabbit and human is nonkeratinized, and delivery to the rabbit sublingual cavity presents an opportunity to correlate intraoral absorption in man.[19]

This study aimed to develop a new sublingual formula for sildenafil consisting of a sublingual spray and sublingual tablets and to study their relative bioavailability levels compared to conventional oral tablets after sublingual administration to rabbits.

Materials

Standard sildenafil citrate was purchased from Trans American Chemicals (San Diego, CA) and sildenafil was from ARYL S.A. (Buenos Aires, Argentina). The following chemicals were obtained and used as received: Florite® R (Tokuyama, Yamagata, Japan), adsorbant, is the calcium silicate. Cyclocel® (Wei Ming, Taipei, Taiwan), directly compressible material, is the mannitol thermal adhesion granulation. EMDEX® (JRS Pharma, Rosenberg, Germany), binder, is dextrate NF. Ac-Di-Sol® (FMC Biopolymer, Philadelphia, PA), superdisintegrant agent, is croscarmellose sodium. Kollidon® CL (BASF, Ludwigshafeh, Germany), superdisintegrant, is the crospovidone. Polyethylene glycol 600 (PEG 600) and PG were purchased from Riedel-de Haën (Seelze, Germany). All other reagents used were reagent grade or better.

Methods

High-Performance Liquid Chromatographic Assay Methods for In Vitro *and Plasma Samples*

An HPLC system equipped with a pump (Jasco PU-2089 quaternary gradient pump; Tokyo, Japan) and an autosampler (Jasco AS-2055 intelligent sampler) was used. The eluent was detected with a Jasco UV-2070 UV/Vis detector at 230 nm. The column was a reversed-phase C18 column (Inertsil 6, ODS-3, 4.6 × 150 mm; Vercopak, Taipei, Taiwan) maintained at 40°C. For dissolution and plasma samples, the mobile phase was a mixture of acetonitrile and 30-mM KH_2PO_4 (pH 6.0) at 50:50 (v/v) at a flow rate of 1.0 mL/min. Retention times were 6.2 min for sildenafil and 7.4 min for the analytical internal standard of butyl paraben.[20] The method was validated as showing acceptable intraday and interday accuracy and precision (data not shown).

Preparation and Characterization of the Sildenafil Sublingual Spray

Preparation of the Sildenafil Sublingual Spray

To prepare the sildenafil sublingual spray, components of 5 vehicles as indicated in Table 1 were examined. ME $T_{80}P^{B}_{600}$ and ME $T_{80}PG^{B}$ were ME systems prepared using a phase diagram. The pseudoternary phase diagrams of an oil (OA), surfactant (Tween 80), and cosurfactant (PEG 600 or PG) were developed using a water titration method. After identification of the ME region in the phase diagrams, the ME systems were selected at desired component ratios (Table 1). An excess amount of sildenafil or its citrate was added into about 1.0 mL of each vehicle in microcentrifuge tubes; the mixtures were heated to 40°C in a water bath and thoroughly vortex-mixed to ensure that the sildenafil or its citrate had fully dispersed in the vehicle. The mixtures were incubated in a water bath at 37.0 ± 0.5°C for 24 h to reach equilibrium. Then, the mixtures were filtered through a Millipore membrane filter (0.45 μm, Billerica, MA), and a sublingual spray containing sildenafil or its citrate salt was produced from the clear supernatant.

Table 1
Formulations of Sublingual Sildenafil Spray

Formulations	Drug	Vehicles	Sildenafil (mg)
ME $T_{80}P^{B}_{600}$	Sildenafil	H_2O/OA/T_{80}/PEG 600 (5:50:36:9)	4.7
ME $T_{80}PG^{B}$	Sildenafil	H_2O/OA/T_{80}/PG (5:45:40:10)	4.1
OA^{B}	Sildenafil	OA	10.0
PG^{B}	Sildenafil	PG	0.5
PG^{C}	Sildenafil citrate	PG	0.7

B, sildenafil; C, sildenafil citrate; P_{600}, PEG 600; T_{80}, Tween 80.

Characterization of the Sildenafil Sublingual Spray

According to our previous work,[21] the stability of sildenafil sublingual spray-incorporating MEs was studied via their clarity and phase separation. The solubilization capacities of the sublingual spray for sildenafil were investigated by HPLC as described.

Preparation and Characterization of Sildenafil Sublingual Tablets

Preparation of Sildenafil Sublingual Tablets

Sildenafil sublingual tablets containing compositions of various granulated sildenafil sublingual sprays adsorbed onto Florite® R, a binder (Cyclocel® or EMDEX®), and a disintegrant (Ac-Di-Sol® or Kollidon® CL) were prepared, and the formulations are listed in Table 2. Tablets were made with direct compression of the mixtures with 1 ton on a tablet press (Carver Laboratory Press, Wabash, IN).

Hardness Test

A hardness tester (Pharma Test, Hainbwg, Germany) was used to determine the tablet hardness. Three tablets were randomly chosen from each formulation of sublingual tablets, and the average value was determined.

Drug Dissolution

Drug release from sublingual tablets was evaluated according to a modified USP XXXII paddle method (dissolution tester: TDT-08L; Electrolab, India). The paddle rotation rate was 50 rpm, and the dissolution medium was 500 mL of simulated saliva fluid (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8.00 g NaCl per liter of distilled water, adjusted to pH 6.76 with phosphoric acid)[22] at a temperature of 37 ± 0.5°C. The medium (5 mL) was automatically withdrawn at predetermined intervals (0, 2, 4, 6, 8, 10, 30, and 60 min) and replaced with fresh medium of the same volume. The drug content was analyzed by HPLC as described previously. Dissolution profiles expressed as the cumulative release (%) versus time were plotted for comparison. The value of $T_{50\%}$ was calculated as the time required for 50% of the drug to dissolve from each individual release profile, and averages were reported. Each *in vitro* dissolution test was performed in triplicate.

Disintegration Time

The time in which a sublingual tablet disintegrated into powder in the aforementioned dissolution studies was taken as a disintegration time of the tablet.[22-24]

Pharmacokinetic Studies

Animal Experiments

All experiments were performed under an institutionally approved protocol for the use of animals in research (Taipei Medical University, Taipei, Taiwan). New Zealand white rabbits (3.0~4.0 kg) were used for sildenafil sublingual and intravenous (IV) administration with a washout period of 2 weeks. Rabbits were weighed and restrained before the experiment. For IV administration, an IV infusion of a sildenafil citrate injection (5.6 mg/mL in normal saline) was delivered through the marginal ear vein of a rabbit over 20 s. For per os (PO) administration, commercially available Viagra® was given at a dose equivalent to 100 and 50 mg sildenafil, respectively. For sublingual administration, 100 μL of a spray formulation saturated with sildenafil or its citrate was administered into the 1-cm position of the sublingual zone with a micropipette via a polyethylene tube (PT260). The tablet formulation was placed sublingually using small tweezers. The rabbit's head was held in an upright position for 30 s postadministration to minimize swallowing. Blood sampling (1 mL) began before dosing and at 2, 5, 10, 20, 30, 45, 60, 75, 90, 120, and 240 min after dosing via a marginal ear vein of the rabbit. Blood samples were prevented from coagulating with heparin and centrifuged at 3000 rpm for 15 min. Plasma was separated and stored at −30°C until being analyzed.

Plasma Treatment

Plasma samples (100 μL) were supplemented with 10 μL of the internal standard of butyl paraben (40 μM) in a phosphate-buffered solution (500-mM KH_2PO_4, pH 6.0) and then were precipitated with the addition of 200-μL acetonitrile. The mixture was vortex-mixed for 30 s and centrifuged at 10^4 rpm and 4°C for 5 min. An aliquot of the supernatant solution (170 μL) was analyzed by HPLC. Under these analytical conditions, the quantitation limit for sildenafil was found to be 10 nM.

Table 2
Formulations of Sublingual Sildenafil Tablets

Formulations	Vehicle					Adsorbant	Binder		Disintegrant		Total Weight (mg/Tablet)
	ME $T_{80}P^{B}_{600}$	ME $T_{80}PG^{B}$	OA^{B}	PG^{B}	PG^{C}	Florite® R	Cyclocel®	EMDEX®	Ac-Di-Sol®	Kollidon® CL	
ME $T_{80}P^{B}_{600}$ CA	100					50	30		27		207
ME $T_{80}P^{B}_{600}$ EA	100					50		30	27		207
ME $T_{80}P^{B}_{600}$ CK	100					50	30			18	198
ME $T_{80}P^{B}_{600}$ EK	100					50		30		18	198
ME $T_{80}PG^{B}$ CA		100				50	30		27		207
ME $T_{80}PG^{B}$ EA		100				50		30	27		207
ME $T_{80}PG^{B}$ CK		100				50	30			18	198
ME $T_{80}PG^{B}$ EK		100				50		30		18	198
OA^{B} CA			100			100	40		36		276
OA^{B} EA			100			100		40	36		276
OA^{B} CK			100			100	40			24	264
OA^{B} EK			100			100		40		24	264
PG^{B} CA				100		100	40		36		276
PG^{B} EA				100		100		40	36		276
PG^{B} CK				100		100	40			24	264
PG^{B} EK				100		100		40		24	264
PG^{C} CA					100	100	40		36		276
PG^{C} EA					100	100		40	36		276
PG^{C} CK					100	100	40			24	264
PG^{C} EK					100	100		40		24	264

ME $T_{80}P_{600}$, microemulsion formulation H_2O/OA/Tween 80/PEG 600 (5/50/36/9); ME $T_{80}PG$, microemulsion formulation H_2O/OA/Tween 80/PG(5/45/40/10)C, Cyclocel®; E, EMDEX®; A, Ac-Di-Sol®; K, Kollidon® CL; B, sildenafil base; C, sildenafil citrate.

Calculations and Statistical Analysis

Mathematical methods can be used to evaluate the similarity of drug dissolution profiles. Equations 1 and 2 are mathematical models used to compare dissolution profiles.

$$f1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \quad (1)$$

$$f2 = 50 \times \log\left\{ \left[1 + 1 \Big/ n \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where R_t is the percentage of dissolved product for a reference batch at time point t, T_t is the percentage of dissolved product for the test batch, and n is the number of time point. The factor, *f*1, is the average % difference over all time points in the amount of test brand dissolved as compared to the reference brand. The *f*1 value is 0 when the test and the reference profiles are identical and increases proportionally with the dissimilarity between the 2 profiles. The *f*2 value is between 0 and 100. The value is 100 when the test and the reference profiles are identical and approach zero as the dissimilarity increases.

The area under the curve ($AUC_{0\text{-}t}$) was determined by the linear trapezoidal method. T_{max}, C_{max}, and T_{onset} values of sublingual administration were read directly from the concentration-time profile. The $T_{1/2}$ was calculated by fitting the data of the terminal portion of the pharmacokinetic profile by a log-linear regression equation. The absolute bioavailability [$F\% = (AUC_{0\text{-t,sublingual}} \times Dose_{IV})/(AUC_{0\text{-t,IV}} \times Dose_{sublingual}) \times 100$] of sublingual administration from the spray or tablet was calculated. Statistical analysis was performed by Student t-test to calculate the significance ($p < 0.05$).

Results and Discussion

High-Performance Liquid Chromatographic Assay Methods for In Vitro *and Plasma Samples*

The results of intra- and inter-day validations for assaying sildenafil showed good precision and high accuracy. The linearity of the calibration curve of sildenafil was well correlated ($R^2 > 0.9999$) within a range of 10-10000 nM for intra- and inter-day assay. The equations of calibration curve for intra- and inter-day were $y = 0.0003\ x + 0.0016$ and $y = 0.0003\ x + 0.0014$, respectively. All data showed the excellent reproducibility of the sample analysis.

Formulations and Characterization of the Sublingual Spray and Tablets

In our previous work, the OA-based ME system using Tween 80 as the surfactant and ethanol as the cosurfactant at a ratio of 1:4 for intranasal delivery of sildenafil was demonstrated to have a fast enough onset to meet clinical needs.[21] Therefore, a ME system, OA, and PG were selected to develop the sublingual delivery of sildenafil and its citrate in this study. Based on preliminary screening (data not shown), the ME $T_{80}P^{B}_{600}$ and ME $T_{80}PG^{B}$ ME systems were constructed using H_2O as the liquid phase and OA as the oil phase with Tween 80 (T_{80}) as the surfactant and P_{600} or PG as the cosurfactant at ratios of 5:50:36:9 and 5:45:40:10, respectively, and sildenafil base was used as the model drug (Table 1). Sildenafil contents in various sublingual sprays were examined, and results are also summarized in Table 1. Results demonstrated that solubility levels of sildenafil in ME $T_{80}P^{B}_{600}$, ME $T_{80}PG^{B}$, OA^{B}, PG^{B}, and PG^{C} were 4.7, 4.1, 10.0, 0.5, and 0.7 mg, respectively. Among these, the solubility of sildenafil in OA (10.0 mg/mL) was the highest, including ME $T_{80}P^{B}_{600}$, ME $T_{80}PG^{B}$, and PG. This might be attributed to the association between a weak basic drug of sildenafil (pKa 8.7) and the acidic nature of OA.

Sublingual tablets were characterized in terms of the disintegration time, hardness, and dissolution half time ($T_{50\%}$). Influences of vehicles, binders, and disintegrants on the characteristics of sildenafil sublingual tablets were examined, and results are given in Table 3. Results showed that disintegration times and $T_{50\%}$ values for all 20 formulations varied from 0 to >60 min and 2.0 to 48.6 min, respectively. Comparisons of the influence of the vehicle on the characteristics of sildenafil sublingual tablets showed that formulations prepared with OA or PG disintegrated faster than those with ME systems. Similarly, the value of $T_{50\%}$ was shorter and the drug was obviously released faster from the OA and PG formulations. The delayed disintegration time of sublingual tablets prepared with ME systems as the vehicle could be the main reason for the lower dissolution rates of those formulations. A comparison between Cyclocel® and EMDEX® as the binder showed that the drug release rate and disintegration insignificantly changed in a fixed vehicle and disintegrant. For example, disintegration times of the PG^{B}CA and PG^{B}EA formulations were 6 and 4 min, and $T_{50\%}$ values were 3.6 and 3.5 min, respectively. For the PG^{B}CK and PG^{B}EK formulations, disintegration times were 1 and 2 min, respectively, and $T_{50\%}$ values were both 2.3 min. A comparison between Ac-Di-Sol® and Kollidon® CL as disintegrants on the characteristics of sildenafil sublingual tablets showed that most formulations prepared with Kollidon® CL disintegrated, and drug was released faster than those with Ac-Di-Sol® in the fixed vehicle and binder. For example, disintegration times of the PG^{B}CA and PG^{B}CK formulations were 6 and 1 min, and $T_{50\%}$ values were 3.6 and 2.3 min, respectively. Disintegration times for the ME $T_{80}PG^{B}$CA and ME $T_{80}PG^{B}$CK formulations were >60 and 2 min, and $T_{50\%}$ values were 48.6 and 7.7 min, respectively. Overall, it indicated that the selected vehicles had strong influences on disintegration time and drug dissolution of the sublingual tablets.

In a comparison of sildenafil and its citrate as the API on characteristics of the sublingual tablets, the dissolution test revealed that sildenafil and its citrate both dissolved almost instantly from sublingual tablets prepared with PG as the vehicle, and the range of disintegration times and $T_{50\%}$ values was 0~7 and 2.0~4.8 min,

Table 3
Disintegration Time, Hardness, and Dissolution Half Time ($T_{50\%}$) of Sildenafil Sublingual Tablets Prepared by Various Vehicles, Binders (EMDEX® or Cyclocel®), and Disintegrants (Ac-Di-Sol® or Kollidon® CL) (Mean ± SD, n = 3)

Formulations	Disintegration Time (min)	Hardness (kP)	$T_{50\%}$ (min)
ME $T_{80}P^{B}_{600}$ CA	>60	1.93 ± 0.12	46.3 ± 2.4
ME $T_{80}P^{B}_{600}$ CK	>60	1.07 ± 0.12	21.3 ± 2.00
ME $T_{80}P^{B}_{600}$ EA	≒53	1.93 ± 0.31	–
ME $T_{80}P^{B}_{600}$ EK	≒10	1.07 ± 0.15	18.3 ± 5.9
ME $T_{80}PG^{B}$ CA	>60	1.37 ± 0.06	48.6 ± 5.8
ME $T_{80}PG^{B}$ CK	≒2	0.83 ± 0.15	7.7 ± 1.3
ME $T_{80}PG^{B}$ EA	>60	1.33 ± 0.15	42.8 ± 23.4
ME $T_{80}PG^{B}$ EK	≒2	0.70 ± 0.00	9.00 ± 1.8
OA^{B} CA	≒8	9.97 ± 0.12	8.3 ± 2.6
OA^{B} CK	≒2	3.43 ± 0.60	16.0 ± 2.5
OA^{B} EA	≒2	9.20 ± 0.26	12.3 ± 3.3
OA^{B} EK	≒2	2.93 ± 1.37	11.2 ± 2.4
PG^{B} CA	≒6	2.63 ± 0.14	3.6 ± 0.5
PG^{B} CK	≒1	2.27 ± 1.10	2.3 ± 0.6
PG^{B} EA	≒4	1.97 ± 0.07	3.5 ± 0.5
PG^{B} EK	≒2	0.93 ± 0.06	2.3 ± 0.5
PG^{C} CA	≒7	5.03 ± 0.31	4.8 ± 1.4
PG^{C} CK	0	1.87 ± 0.91	2.0 ± 0.0
PG^{C} EA	≒4	4.93 ± 0.78	3.6 ± 1.0
PG^{C} EK	0	1.60 ± 0.95	2.0 ± 0.0

–, Dissolution had not reached 50% at the dissolution time.

Table 4
Results of the Difference ($f1$) and Similarity ($f2$) Factors for Dissolution Profiles Comparison of Sildenafil Sublingual Tablets Prepared With Various Vehicles, Binders (EMDEX® or Cyclocel®), and Disintegrants (Ac-Di-Sol® or Kollidon® CL)

Comparison	$f1$	$f2$	Description
ME $T_{80}P^{B}_{600}$ CA & ME $T_{80}P^{B}_{600}$ EA	58.10	41.90	Difference
ME $T_{80}P^{B}_{600}$ CK & ME $T_{80}P^{B}_{600}$ EK	15.91	61.77	Similarity
ME $T_{80}P^{B}_{600}$ CA & ME $T_{80}P^{B}_{600}$ CK	138.80	29.62	Difference
ME $T_{80}PG^{B}$ CA & ME $T_{80}PG^{B}$ EA	17.27	70.19	Similarity
ME $T_{80}PG^{B}$ CK & ME $T_{80}PG^{B}$ EK	5.73	70.26	Similarity
ME $T_{80}PG^{B}$ CA & ME $T_{80}PG^{B}$ CK	252.87	18.37	Difference
OA^{B} CA & OA^{B} EA	15.32	52.52	Similarity
OA^{B} CK & OA^{B} EK	11.54	65.29	Similarity
OA^{B} CA & OA^{B} CK	20.34	44.82	Difference
PG^{B} CA & PG^{B} EA	5.81	67.86	Similarity
PG^{B} CK & PG^{B} EK	3.10	77.52	Similarity
PG^{B} CA & PG^{B} CK	15.98	46.51	Difference
PG^{C} CA & PG^{C} EA	7.77	59.37	Similarity
PG^{C} CK & PG^{C} EK	7.02	62.07	Similarity
PG^{C} CA & PG^{C} CK	19.42	38.25	Difference

T_{80}, Tween 80; P_{600}, PEG 600; PG, propylene glycol; ^{B}, sildenafil; ^{C}, sildenafil citrate; C, Cyclocel®; E, EMDEX®; K, Kollidon® CL.

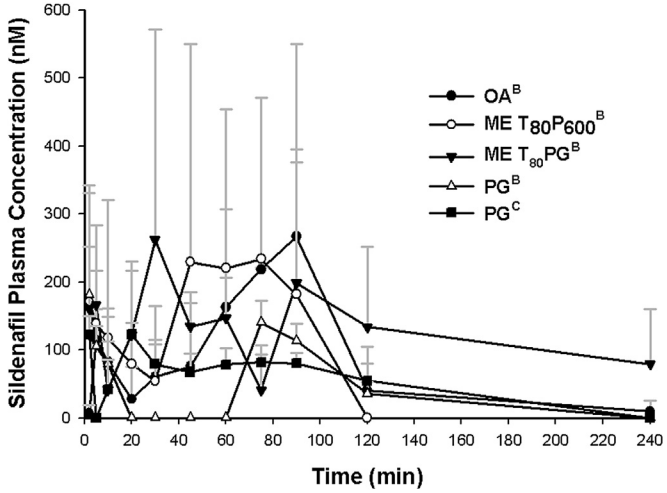

Figure 1. Plasma sildenafil concentration profiles of sublingual spray formulations composed of various vehicles in rabbits. P_{600}, PEG 600; PG, propylene glycol; T_{80}, Tween 80; B, sildenafil; C, sildenafil citrate.

respectively. However, sildenafil and its citrate released from sublingual tablets prepared with PG as the vehicle showed no significant differences in disintegration times or $T_{50\%}$ values. Many researchers have shown that tablets formulated with PG as the liquid vehicle were one of the most promising methods for promoting dissolution rates of poorly water-soluble drugs.[25-27] PG molecules contain 2 terminal hydroxyl groups; thus, there is also a probability of solubilization of the drug in the vehicle. The solubility of a drug not only determines the dissolution behavior of an API in the formulation, but it also affects the absorption and therapeutic efficacy of the drug.

The dissolution profiles of sildenafil from sublingual tablets prepared with different vehicles were compared using the difference ($f1$) and similarity factors ($f2$), and results are given in Table 4. Dissolution profile analysis is an important tool to evaluate formulation development and finished products. Dissolution profiles of sublingual tablets prepared with Cyclocel® as binder are not similar with EMDEX® at the ME $T_{80}P^{B}_{600}$ as vehicle because the calculated factors do not meet the acceptance criteria ($50 \leq f2 \leq 100$; $0 \leq f1 \leq 15$). However, the similarity factor $f2$ value was greater than 50, $f1$ was equal or less than 15; therefore, the dissolution profiles of sublingual tablets prepared with Cyclocel® as binder are similar with EMDEX® at the ME $T_{80}PG^{B}$, OA^{B}, PG^{B}, and PG^{C} vehicle used. A comparison between Ac-Di-Sol® and Kollidon® CL as disintegrants on the dissolution profile of all sildenafil sublingual tablets showed difference based on mathematical model because the calculated factors do not meet the acceptance criteria.

A number of disintegrants, known as superdisintegrants markedly improve tablet disintegration, but their efficiency depends on the method of manufacture and physicochemical characteristics of the tablet formulation. These factors have been analyzed in different articles. In the last years, the role of this kind of disintegrant in tablets prepared by direct compression had been studied. Velasco et al. studied the effect of the addition of 3 disintegrants on the tabletability of calcium-phosphate–based materials for direct compression.[28] The comparison of the disintegration times showed that the lowest values were found for Ac-Di-Sol® and Explotab®; on the opposite, Esma Espreng® was less effective as disintegrant. These 2 superdisintegrants also show better disintegrating properties than different starches.[29]

On account of the important characteristics of sublingual tablet used for delivery is fast dissolution. Drug release was satisfactory for $PG^{B}CA$, $PG^{C}CA$, and $PG^{C}EA$, because at least 80% of sildenafil was dissolved in the medium within 15 min of the test. Propylene glycol as the vehicle can increase sildenafil release from sublingual tablets; it is the oral mucosal permeation enhancers. Ac-Di-Sol® has good bioadhesive properties for a vehicle for buccal delivery. In tablet formulations, Ac-Di-Sol® is used in oral pharmaceutical formulations as a disintegrant and may be used in the direct-compression process. The Ac-Di-Sol® seemed to be a better disintegrant of choice to prepare sildenafil sublingual tablets in the studies. Cyclocel® is widely used in pharmaceutical formulations. Cyclocel® may be used in direct-compression tablet applications and is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and “mouth feel.” Cyclocel® is also used as a diluent in rapidly dispersing oral

Table 5
Mean Pharmacokinetic Parameters for Intravenous Injection of Sildenafil Citrate, Oral Administration of Viagra®, and Sublingual Spray of Sildenafil in Rabbits (Mean ± SD, n = 3)

Formulations	Dose (mg)	T_{onset} (min)	Duration (min)	T_{max} (min)	C_{max} (nM)	K_{el} (h^{-1})	$T_{1/2}$ (h)	$AUC_{0\text{-inf}}$ (nM h)	F (%)
IV	5.6	–	200.0	2	1589.8	0.04	0.32	1550.5	100.0
Viagra® (PO)	100.0	5.5 ± 2.7	236.5	67.5 ± 2.1	9027.2 ± 2464.0	0.02 ± 0.00	0.66 ± 0.11	16,400.9 ± 3482.7	53.4 ± 13.9
Viagra® (PO)	50.0	5.5 ± 5.3	198.5	86.3 ± 25.9	3596.4 ± 998.1	0.02 ± 0.00	0.50 ± 0.10	5502.2 ± 523.5	39.7 ± 3.8
OA^{B}	10.0	3.3 ± 2.9	10.0	90.0 ± 35.1	266.7 ± 195.9	0.08 ± 0.08	0.25 ± 0.16	372.5 ± 155.3	10.7 ± 5.6*
$MET_{80}P^{B}_{600}$	3.4	3.7 ± 3.5	79.3	38.3 ± 33.3	351.3 ± 122.1	0.13 ± 0.05	0.10 ± 0.02	330.9 ± 236.2	30.1 ± 24.1
$MET_{80}PG^{B}$	3.5	5.6 ± 3.4	57.9	99.3 ± 68.1	228.2 ± 191.2	0.03 ± 0.04	4.59 ± 6.29	572.7 ± 184.2	60.5 ± 19.5
PG^{B}	0.5	1.3 ± 0.6	93.2	16.3 ± 24.8	192.8 ± 57.9	0.03 ± 0.00	0.37 ± 0.03	145.9 ± 33.5	78.7 ± 18.6*
PG^{C}	0.7	1.8 ± 0.3	22.0	17.3 ± 14.2	133.2 ± 18.3	0.03 ± 0.00	0.36 ± 0.04	202.0 ± 28.4	78.6 ± 11.0*

* Significant at $p < 0.05$.

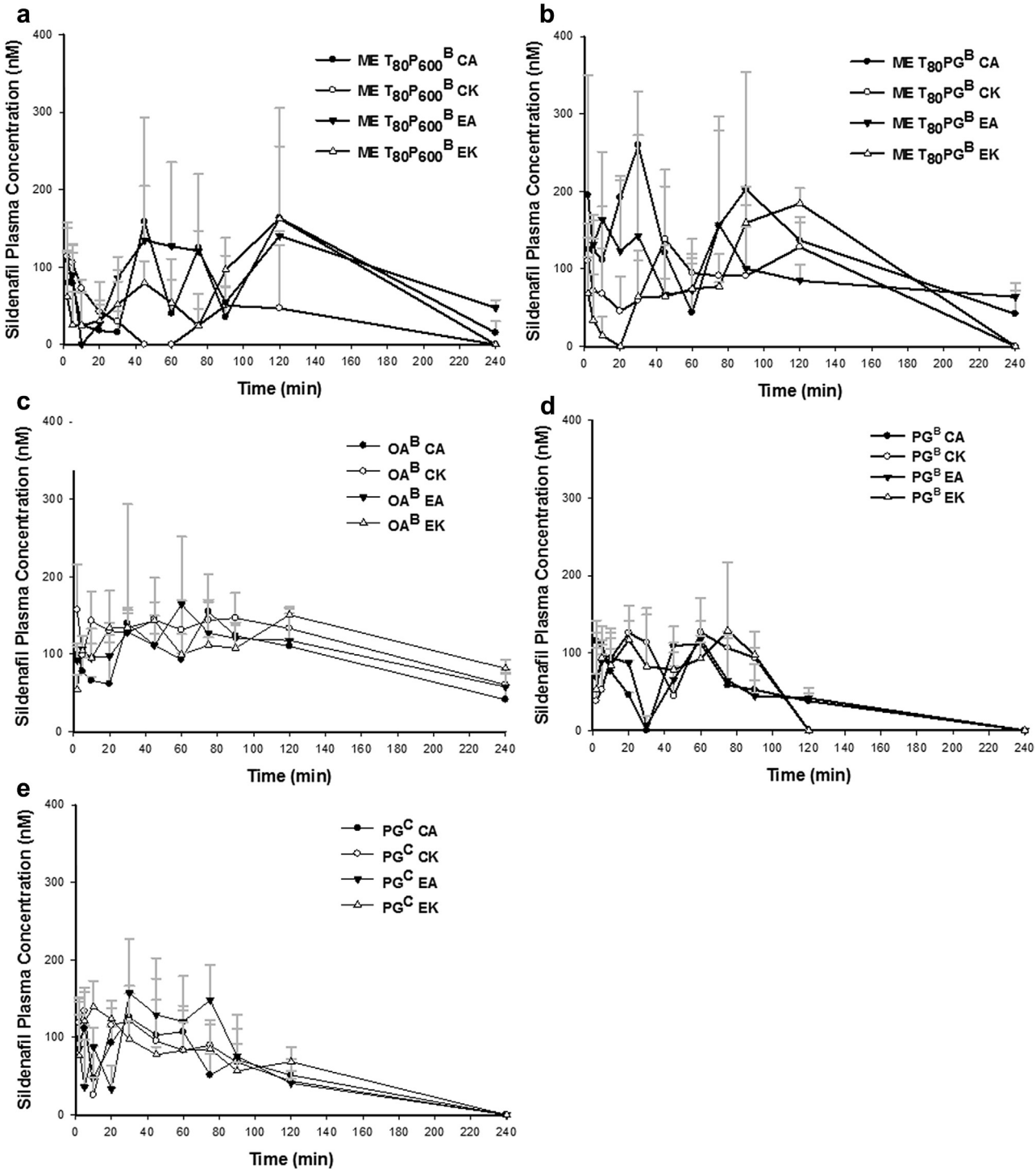

Figure 2. Plasma sildenafil concentration profiles of sublingual tablet formulations composed of various vehicles [(a) ME $T_{80}P^{B}_{600}$; (b) ME $T_{80}PG^{B}$; (c) OA^{B}; (d) PG^{B}; and (e) PG^{C}], binders (EMDEX® or Cyclocel®), and disintegrants (Ac-Di-Sol® or Kollidon® CL) in rabbits. T_{80}, Tween 80; P_{600}, PEG 600; ^{B}, sildenafil; ^{C}, sildenafil citrate; C, Cyclocel®; E, EMDEX®; A, Ac-Di-Sol®; K, Kollidon® CL.

dosage forms. Therefore, Cyclocel® can provide sweet taste and increase dissolution in the sildenafil sublingual tablets. Besides that, EMDEX® is generally used in directly compressible chewable tablets because of its sweet taste. However, drug dissolution profiles may be distinct due to differences in formulations and manufacturing processes, but the difference must not comprise product bioavailability.

Sublingual Pharmacokinetics of Sildenafil

Sildenafil Sublingual Spray

Sublingual spray as summarized in Table 5 was selected to examine the influence of various vehicles on the sublingual absorption of sildenafil. The resultant plasma profiles and corresponding pharmacokinetic parameters are illustrated in Figure 1 and

Table 6
Mean Pharmacokinetic Parameters for Intravenous Injection of Sildenafil Citrate, Oral Administration of Viagra®, and Sublingual Tablets of Sildenafil in Rabbits (Mean ± SD, n = 3)

Formulations	Dose (mg)	T_{onset} (min)	Duration (min)	T_{max} (min)	C_{max} (nM)	K_{el} (h^{-1})	$T_{1/2}$ (h)	$AUC_{0\text{-}inf}$ (nM h)	F (%)
IV	5.6	–	200.0	2	1589.8	0.04	0.32	1550.5	100.0
Viagra® (PO)	100.0	5.5 ± 2.7	236.5	67.5 ± 2.1	9027.2 ± 2464.0	0.02 ± 0.00	0.66 ± 0.11	16,400.9 ± 3482.7	53.4 ± 13.9
Viagra® (PO)	50.0	5.5 ± 5.3	198.5	86.3 ± 25.9	3596.4 ± 998.1	0.02 ± 0.00	0.50 ± 0.10	5502.2 ± 523.5	39.7 ± 3.8
ME $T_{80}P^{B}_{600}$ CA	4.7	2.0 ± 0.0	77.5	40.7 ± 36.7	221.7 ± 92.6	0.02 ± 0.02	0.66 ± 0.36	239.4 ± 44.4	26.67 ± 4.90*
ME $T_{80}P^{B}_{600}$ CK	4.7	5.0 ± 0.0	4.0	31.3 ± 50.8	142.3 ± 14.8	0.14 ± 0.10	0.15 ± 0.15	117.7 ± 126.8	12.25 ± 8.03*
ME $T_{80}P^{B}_{600}$ EA	4.7	3.0 ± 1.7	76.5	100.9 ± 36.6	181.4 ± 60.4	0.01 ± 0.00	1.43 ± 0.33	388.1 ± 38.9	31.96 ± 2.46
ME $T_{80}P^{B}_{600}$ EK	4.7	45.7 ± 44.0	117.9	60.7 ± 59.0	185.3 ± 119.8	0.04 ± 0.01	0.32 ± 0.08	301.7 ± 170.7	24.54 ± 12.02*
ME $T_{80}PG^{B}$ CA	4.1	2.0 ± 0.0	160.0	40.7 ± 36.7	284.9 ± 84.8	0.02 ± 0.02	0.94 ± 0.58	397.4 ± 69.4	59.86 ± 2.79
ME $T_{80}PG^{B}$ CK	4.1	3.0 ± 1.7	141.8	75.0 ± 26.0	157.3 ± 53.6	0.04 ± 0.01	0.33 ± 0.05	311.3 ± 13.2	63.36 ± 8.46
ME $T_{80}PG^{B}$ EA	4.1	2.0 ± 0.0	93.0	25.7 ± 21.8	204.2 ± 129.5	0.01 ± 0.00	2.19 ± 1.01	352.3 ± 38.9	57.13 ± 3.20
ME $T_{80}PG^{B}$ EK	4.1	29.3 ± 44.8	146.4	120.0 ± 0.0	184.5 ± 119.4	0.04 ± 0.00	0.28 ± 0.00	364.5 ± 36.7	57.85 ± 5.80
OA^{B} CA	10.0	11.4 ± 16.2	123.8	65.0 ± 17.3	158.0 ± 10.9	0.01 ± 0.02	1.79 ± 1.39	447.7 ± 63.0	14.24 ± 5.04*
OA^{B} CK	10.0	2.0 ± 0.0	171.8	40.7 ± 36.7	167.1 ± 6.3	0.01 ± 0.00	1.78 ± 0.36	438.3 ± 125.7	12.48 ± 3.58*
OA^{B} EA	10.0	3.0 ± 1.7	152.9	80.0 ± 45.8	210.5 ± 56.6	0.01 ± 0.00	1.71 ± 0.20	439.3 ± 68.6	13.41 ± 1.42*
OA^{B} EK	10.0	6.7 ± 2.9	201.6	85.0 ± 37.8	168.0 ± 28.2	0.01 ± 0.01	1.88 ± 1.39	493.7 ± 127.1	14.06 ± 3.62*
PG^{B} CA	0.5	1.9 ± 0.4	62.0	67.5 ± 36.9	115.6 ± 26.5	0.03 ± 0.0	0.39 ± 0.03	166.2 ± 8.5	90.24 ± 4.63*
PG^{B} CK	0.5	12.3 ± 4.9	79.9	36.7 ± 20.8	126.6 ± 44.4	0.10 ± 0.10	0.19 ± 0.18	165.8 ± 9.9	90.09 ± 5.43*
PG^{B} EA	0.5	3.0 ± 1.7	64.5	2.3 ± 0.6	117.6 ± 23.3	0.03 ± 0.00	0.39 ± 0.05	166.8 ± 23.2	91.24 ± 12.60*
PG^{B} EK	0.5	5.3 ± 3.6	84.5	41.7 ± 29.3	116.8 ± 44.3	0.13 ± 0.03	0.09 ± 0.02	167.1 ± 7.0	90.73 ± 4.07*
PG^{C} CA	0.7	3.5 ± 2.2	57.4	35.0 ± 8.7	125.7 ± 40.5	0.03 ± 0.00	0.37 ± 0.00	235.0 ± 5.2	83.74 ± 11.12*
PG^{C} CK	0.7	2.6 ± 2.1	40.0	12.33 ± 15.4	133.8 ± 30.3	0.03 ± 0.01	0.36 ± 0.07	233.8 ± 20.9	81.06 ± 15.47*
PG^{C} EA	0.7	2.9 ± 1.8	83.4	40.0 ± 8.7	157.1 ± 69.9	0.03 ± 0.00	0.39 ± 0.02	208.3 ± 39.8	90.95 ± 8.13*
PG^{C} EK	0.7	3.4 ± 1.7	24.4	11.0 ± 9.0	139.1 ± 33.7	0.03 ± 0.00	0.35 ± 0.05	237.9 ± 9.4	95.95 ± 3.66*

* Significant at $p < 0.05$.

Table 5, respectively. T_{onset} indicates the time to achieve a minimal effective concentration (100 nM) as proposed by Sharabi et al.[30] The duration indicates the period of time in which the plasma concentration of drug was higher than the minimal effective concentration. T_{max} indicates the time to achieve the highest plasma concentration. C_{max}, K_{el}, $T_{1/2}$, AUC, and F (%) were defined as usual. Results showed the C_{max} did not exceed the toxic concentration,[31] and the time to achieve a minimal effective concentration (100 nM) was smaller than oral administration for all sublingual sprays of sildenafil in the study, which indicated that the prepared systems were effective or exhibited no serious toxicity with sublingual administration. The absolute bioavailability of sildenafil sublingual spray was larger than that by oral administration except for the OA^{B} formulation. Results of comparisons of the vehicle on the pharmacokinetic parameters after sublingual administration of sildenafil spray are given in Table 5, which clearly indicates that the use of PG as the vehicle to formulate spray to carry a low dose (0.5 mg) of sildenafil base (Formulation PG^{B}) for sublingual delivery led to higher bioavailability (78.7%), a shorter onset time (1.3 min), and a longer duration (93.2 min) than those for OA and the ME systems. For those ME systems using PG as the cosurfactant (ME $T_{80}PG^{B}$), the T_{onset} value was not rapid enough (5.6 min), but its average absolute bioavailability was about 60.5% because PG enhanced the penetration of sildenafil into the rabbit sublingual mucosa.

Sublingual Tablets

Figure 2 displays sildenafil plasma concentration-time profiles in rabbits after sublingual administration of sildenafil tablets prepared with different vehicles, binders, and disintegrants. Mean pharmacokinetic parameters for intravenous injections of sildenafil citrate, oral administration of Viagra®, and sublingual tablets of sildenafil in rabbits are given in Table 6. Results showed that the C_{max} did not exceed the toxic concentration for any sublingual tablets of sildenafil in the study, which indicates that the prepared systems exhibited no serious toxicity with sublingual administration.

Comparisons of the influence of the vehicles on plasma profiles after sublingual administration of sildenafil tablets, as shown by Figure 2a (ME $T_{80}P^{B}_{600}$), 2B (ME $T_{80}PG^{B}$), 2C (OA^{B}), 2D (PG^{B}), and 2E (PG^{C}) at the same scale, indicate that the use of both PG^{B} and PG^{C} as the vehicle led to higher bioavailability and shorter onset times than those for ME $T_{80}P^{B}_{600}$, ME $T_{80}PG^{B}$, and OA (Table 6). Results also showed that it was easy to achieve rapid onset, but it was difficult to achieve high bioavailability after the sublingual administration of sildenafil tablets. For formulations using ME $T_{80}P^{B}_{600}$ as the vehicle, the T_{onset} of ME $T_{80}P^{B}_{600}$CA was the fastest at about 2 min, the duration was maintained for about 77.5 min, but the absolute bioavailability was only 26.67% at 4.7 mg. When using ME $T_{80}PG^{B}$ as the vehicle, the onset of time for ME $T_{80}PG^{B}$CA was the fastest at about 2 min, its duration was maintained for about 160.0 min, and the absolute bioavailability was 59.86% at 4.1 mg. When OA^{B} was used as the vehicle, the onset of time for OA^{B}CK was the fastest at about 2 min, the duration was maintained for about 171.8 min, but the absolute bioavailability was only 12.48% at the high dose (10 mg). In the group with PG^{B} as the vehicle, the PG^{B}CA formulation presented optimal results. It had the fastest onset (1.9 min), the duration was 62.0 min, and it had high bioavailability (90.24%) at the low dose (0.5 mg). When PG^{C} was used as the vehicle, the fastest T_{onset} was detected at about 2.6 min, the duration was only 40.0 min, and the absolute bioavailability achieved 81.06% with the PG^{C}CK formulation. Overall, results clearly indicated that the use of PG as the vehicle to formulate tablets to carry a low dose (0.5 mg) of sildenafil base for sublingual delivery led to higher bioavailability than those for OA and the ME systems.

Influences of the binders (Cyclocel® and EMDEX®) on the plasma profiles after the sublingual administration of sildenafil tablets prepared with the same vehicle and disintegrant were compared. T_{onset} values of the PG^{B}CA and PG^{B}EA formulations were about 1.9 and 3.0 min, durations were 62.0 and 64.5 min, and absolute bioavailability levels were 90.24% and 91.24%, respectively. These results indicated that most of the sublingual tablets prepared with different binders showed insignificant differences for T_{onset}, duration, and absolute bioavailability with the same vehicle.

In comparisons of the effects of Ac-Di-Sol® and Kollidon® CL as disintegrants with the same vehicle and binder, T_{onset} values of the

PG^BCA and PG^BCK formulations were about 1.9 and 12.3 min, durations were 62.0 and 79.9 min, and absolute bioavailability levels were 90.24% and 90.09%, respectively. T_{onset} values of the PG^BEA and PG^BEK formulations were about 3.0 and 5.3 min, durations were 64.5.0 and 84.5 min, and absolute bioavailability levels were 91.24% and 90.73%, respectively. When Kollidon® CL was used as the disintegrant, although its T_{onset} was not rapid enough, its duration was long and absolute bioavailability was similar when Ac-Di-Sol® was used. These results indicated that sublingual tablets prepared with different disintegrants showed no significant difference in absolute bioavailability with the same vehicle. Based on these comparisons, influences of the binder, disintegrant, and vehicle on the sublingual absorption of sildenafil were almost consistent with results of the drug release studies. The vehicle used plays a critical role in the *in vitro* evaluation and *in vivo* pharmacokinetic studies in rabbits.

The optimal formulation of PG^BCA (0.5 mg) for sildenafil tablets delivered via sublingual administration was compared with the PO of Viagra® at a dose of 50 mg. The absolute bioavailability of Viagra® was 39.7%, the T_{onset} was about 5.5 min, and the duration was maintained for longer than 3 h; however, the C_{max} was 3596.4 nM, which was above the toxic concentration. Compared to Viagra®, the absolute bioavailability for PG^BCA was 90.24%, the T_{onset} was 1.9 min, the duration was 62 min, and most importantly, its C_{max} did not exceed the toxic concentration. This result demonstrates that the absolute bioavailability of PG^BCA after sublingual administration was larger than that of Viagra®, the onset was rapid enough, and the duration and the concentration achieved a level suitable to overcome ED without exceeding the toxic level.

Conclusions

The sildenafil sublingual spray (PG^B) prepared with the vehicle, PG, provided a fast enough onset and high bioavailability. Sublingual tablets (PG^BCA) in a composition containing granulated PG^B adsorbed onto Florite® R, with Cyclocel® as the binder and Ac-Di-Sol® as the disintegrant, represent a safe and viable approach to achieve rapid-onset systemic drug levels and higher bioavailability through bypassing liver metabolism for the management of erectile dysfunction. The sublingual systems could also be useful for substances other than sildenafil where a rapid onset unrelated to meals is desirable.

Acknowledgments

The financial support by the National Science Council, Taiwan, ROC (NSC96-2320-B-038-010-MY3) is gratefully acknowledged.

References

1. Doggrell S. Do vardenafil and tadalafil have advantages over sildenafil in the treatment of erectile dysfunction? *Int J Impot Res*. 2007;19(3):281-295.
2. Eardley I, Donatucci C, Corbin J, et al. Pharmacotherapy for erectile dysfunction. *J Sex Med*. 2010;7(1 Part 2):524-540.
3. Elshafeey AH, Bendas ER, Mohamed OH. Intranasal microemulsion of sildenafil citrate: in vitro evaluation and in vivo pharmacokinetic study in rabbits. *AAPS PharmSciTech*. 2009;10(2):361-367.
4. Nichols DJ, Muirhead GJ, Harness JA. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol*. 2002;53(Suppl 1):5S-12S.
5. El-Rashidy R. *Controlled Release of Sildenafil Delivered by Sublingual or Buccal Administration*. WO 00/5477. 2002.
6. Kotyla T, Kuob F, Moolchandani V, Wilson T, Nicolosi R. Increased bioavailability of a transdermal application of a nano-sized emulsion preparation. *Int J Pharm*. 2008;347(1-2):144-148.
7. Shakeel F, Ramadan W. Transdermal delivery of anticancer drug caffeine from water-in-oil nanoemulsions. *Colloids Surf B Biointerfaces*. 2010;75(1):356-362.
8. Valiveti S, Agu RU, Hammel DC, et al. Intranasal absorption of delta(9)-tetrahydrocannabinol and WIN55,212-2 mesylate in rats. *Eur J Pharm Biopharm*. 2007;65(2):247-252.
9. Elnaggar YSR, El-Massik MA, Abdallah OY. Sildenafil citrate nanoemulsion vs. self-nanoemulsifying delivery systems: rational development and transdermal permeation. *Int J Nanotechnol*. 2011;8(Nos. 8/9):749-763.
10. Xie Y, Lu W, Cao S, Jiang X, Yin M, Tang W. Preparation of bupleurum nasal spray and evaluation on its safety and efficacy. *Chem Pham Bull (Tokyo)*. 2006;54(1):48-53.
11. Gaikwad AK. Transdermal drug delivery system: formulation aspects and evaluation. *Compr J Pharm Sci*. 2013;1(1):1-10.
12. Amancha KP, Giron W, Li HS, Goskonda V. *Sildenafil Sublingual Spray Formulation*. US2015/0133459 A1. 2015.
13. Deveci S, Peskircioglu L, Aygün C, Tekin MI, Dirim A, Özkardes H. Sublingual sildenafil in the treatment of erectile dysfunction: faster onset of action with less dose. *Int J Urol*. 2004;11(11):989-992.
14. Goswami T, Jasti B, Li X. Sublingual drug delivery. *Crit Rev Ther Drug Carrier Syst*. 2008;25(5):449-484.
15. Huang X, Xiong C, Zhou J, Shen J. Effect of sublingual medication of sildenafil citrate/apomorphine on sexual behavior of male rats. *Andrologia*. 2009;41(2):71-75.
16. De Siati M, Saugo M, Franzolin N. The start of pharmacological activity after sublingual administration of sildenafil citrate in 30 patients affected by erectile dysfunction. *Arch Ital Urol Androl*. 2003;75(1):18-20.
17. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: development, technologies, taste-masking and clinical studies. *Crit Rev Ther Drug Carrier Syst*. 2004;21(6):433-475.
18. Bredenberg S, Duberg M, Lennernas B, et al. In vitro and in vivo evaluation of a new sublingual tablet system for rapid oromucosal absorption using fentanyl citrate as the active substance. *Eur J Pharm Sci*. 2003;20(3):327-334.
19. Dali MM, Moench PA, Mathias NR, Stetsko PI, Heran CL, Smith RL. A rabbit model for sublingual drug delivery: comparison with human pharmacokinetic studies of propranolol, verapamil and captopril. *J Pharm Sci*. 2006;95(1):37-44.
20. Sheu MT, Wu AB, Yeh GC, Hsia A, Ho HO. Development of a liquid chromatographic method for bioanalytical applications with sildenafil. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2003;791(1-2):255-262.
21. Lu HT, Chen RN, Sheu MT, Chang CC, Chou PY, Ho HO. Rapid-onset sildenafil nasal spray carried by microemulsion systems: in vitro evaluation and in vivo pharmacokinetic studies in rabbits. *Xenobiotica*. 2011;41(7):567-577.
22. Late SG, Yu YY, Banga AK. Effects of disintegration-promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets. *Int J Pharm*. 2009;365(1-2):4-11.
23. Harrika B, Veerareddy VN. Formulation and evaluation of fast disintegrating rizatriptan benzoate sublingual tablets. *Malay J Pharm Sci*. 2012;10(1):45-60.
24. Trambadiya DA, Bhadani MN, Shah KV. Formulation and evaluation of fast disintegrating metoprolol succinate sublingual tablets. *Pharma Science Monitor*. 2013;4(2):3975-3988.
25. Nokhodchi A, Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. *J Pharm Pharm Sci*. 2005;8(1):18-25.
26. Singh SK, Srinivasan KK, Gowthamarajan K, Prakash D, Gaikwad NB, Singare DS. Influence of formulation parameters on dissolution rate enhancement of glyburide using liquisolid technique. *Drug Dev Ind Pharm*. 2012;38(8):961-970
27. Spireas S, Sadu S. Enhancement of Prednisolone dissolution properties using liquisolid compacts. *Int J Pharm*. 1998;166(2):177-188.
28. Velasco MV, Muñoz-Ruiz A, Monedero MC, Castellanos MR. Effect of the addition of three disintegrants on the tabletability of calcium-phosphate based materials. *Eur J Pharm Biopharm*. 1994;40(5):344-347.
29. Visavarungroj N, Remon JP. Crosslinked starch as a disintegrating agent. *Int J Pharm*. 1990;62(2-3):125-131.
30. Sharabi FM, Daabees TT, El-Metwally MA, Senbel AM. Comparative effects of sildenafil, phentolamine, yohimbine and L-arginine on the rabbit corpus cavernosum. *Fundam Clin Pharmacol*. 2004;18(2):187-194.
31. Walker DK, Ackland MJ, James GC, et al. Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog and man. *Xenobiotica*. 1999;29(3):297-310.