Pulmonary arterial hypertension (PAH) is a life-threatening disease. It is characterized by elevations in the pulmonary arterial pressure and pulmonary vascular resistance, leading to right ventricular failure and premature death (1). Treatments of PAH include medications, oxygen, and lung transplant. The main medications for pulmonary arterial hypertension are:

- Sildenafil (Viagra)
- Tadalafil (Cialis)
- Sildenafil (Revatio)
- Bosentan (Tracleer)
- Ambrisentan (Letairis)
- Macitentan (Adempas)

These medications target the endothelial and smooth muscle cells of the pulmonary arteries to reduce vascular resistance and improve blood flow. Additionally, oxygen therapy is used to supplement oxygen levels and support the patient. In severe cases, lung transplant is considered. The combination of these treatments can significantly improve the quality of life for patients with PAH.
hypertension include: endothelin receptor antagonists, prostacyclin analogs and phos-
phodiesterase type 5 inhibitors (PDE5Is).

Sildenafil citrate (SILD), a selective inhibitor of cGMP specific phosphodiesterase 
type 5 (PDE5), was approved by the FDA for the treatment of PAH in 2005. It improves 
cardiocirculatory diseases and is useful for patients with congestive heart failure as well as 
secondary pulmonary hypertension. It relaxes the arterial wall, and hence decreases the 
pulmonary arterial resistance and pressure. This improves symptoms of right-sided 
heart failure by reducing the workload of the right ventricle of the heart. Since PDE5 is 
primarily distributed within the arterial wall smooth muscle of the lungs and penis, 
SILD acts selectively in both of these areas without inducing vasodilatation in other areas 
of the body, which is considered to be an advantage of SILD (2–3). SILD decreases myo-
cardial apoptosis, fibrosis, and hypertrophy by activating protein kinase G, inhibiting 
Rho kinase, and increasing Bcl-2 (4–5). Moreover, SILD was shown to prevent hypoxic 
pulmonary vasoconstriction without affecting systemic hemodynamics in healthy adults 
breathing 11% oxygen (6).

SILD is currently available on the market in the form of oral tablets and intravenous 
injections. Although the peroral route is considered by patients and clinicians to be the 
most convenient route for drug delivery, the oral bioavailability of SILD is only 40% and 
a high-fat meal delays its absorption (7–8). Parenteral administration overcomes this 
drawback and provides excellent bioavailability; however, it involves poor patient com-
pliance. These limitations have stimulated the development of alternative administra-
tion routes such as trans-buccal mucosal routes, which are now among the most popular 
routes for systemic drug delivery. Sublingual mucosa is characterized by high blood supply 
and hence rapid absorption and acceptable bioavailability of many drugs is achieved. 
Buccal mucosa is substantially less permeable than the sublingual area and hence does 
not provide rapid absorption and enhanced bioavailability observed with sublingual ad-
ministration (9).

In this study, orodispersible sublingual tablets (ODSTs) containing SILD, which is 
absorbed through the sublingual mucosa and enters directly into the systemic circula-
tion avoiding the first pass metabolism, were prepared in an attempt to enhance its bio-
availability and produce rapid onset of action for the treatment of PAH via a comfortable 
delivery system. Two techniques for improving oral disintegration, dissolution and bio-
availability were comparatively studied. The first technique employed was direct compre-
sion of solid dispersions (SDs) of SILD using poloxamer as a carrier and the second 
technique was freeze drying using various excipients. Physicochemical and solid-state 
properties, as well as the dissolution behavior of the tablets were evaluated. Moreover, 
SILD bioavailability in human volunteers from the prepared ODSTs was compared to 
that of the conventional tablet available in the market.

EXPERIMENTAL

Materials

Sildenafil citrate was kindly supplied by Eva Pharm, Egypt. Polyethylene glycol 
(PEG4000, PEG6000, PEG8000), Poloxamer188, Xanthum gum, xylitol and mannitol were 
purchased from Sigma Aldrich. PVPK30 was purchased from HIMEDIALaboratories Pvt.
Ltd. Maltodextrin DE 29 was purchased from RoquettePharma. Spray dried mannitol and Avicel PH 101 were kindly supplied by EPICO, Egypt. AC-Di-SOL, magnesium stearate, sodium starch glycolate, glycine and gelatin were purchased from EL NASR Pharmaceutical Chemicals, Egypt. Pharmaburst®500 was kindly supplied by SPIPharma.

Preparation of sildenafil-polyethylene glycol and sildenafil-poloxamer188 solid dispersion (SD) sublingual tablets

Preparation of physical mixtures

Physical mixtures of SILD and PEG 4000, PEG 6000, PEG 8000 and Poloxamer 188 were prepared in ratios of 1:1, 1:2 and 1:3 by mixing calculated amounts of the drug and polymers in a mortar. The resulting mixtures were sieved using sieves of mesh size 0.2–0.25 mm. The physical mixtures were stored in a desiccator at room temperature until evaluation.

Preparation of SD

PEG 4000, PEG 6000, PEG 8000 and Poloxamer 188 were mixed with SILD in ratios of 1:1, 1:2 and 1:3. The mixtures were fused under constant stirring on a thermostatically controlled hot plate (Hot Plate & Stirrer, The Netherlands). After melting, the mixtures were allowed to cool and were then stored in tightly closed containers in desiccators over calcium chloride (0 % relative humidity) at room temperature until dryness. SDs were then ground using a mortar and pestle and the particle size was controlled by sieving through sieves of mesh size 0.2–0.25 mm.

Solubility studies

Excess amounts of SILD, SILD-PEG and SILD-Poloxamer 188 physical mixtures as well as SDs were suspended in distilled water in tightly closed screw-cap vials, equilibrated in a shaking water bath at room temperature for 48 hours, then filtered using a 0.45-μm Millipore filter and assayed spectrophotometrically (Shimadzu 2450, Japan) at predetermined λmax. Three determinations were carried out to calculate the saturated solubility of SILD.

Dissolution studies

In vitro dissolution studies were carried out in 500 mL of distilled water in order to maintain sink conditions (10). Briefly, an amount of 20 mg of SILD free drug and an equivalent amount of drug loaded SDs were transferred to a USP Dissolution Tester, Apparatus II (Hanson SR8 dissolution test station, USA) rotating at 100 rpm and maintained at 37 ± 0.5 °C. At predetermined time intervals (5, 10, 15, 30, 45 and 60 min), an aliquot of dissolution medium was withdrawn and analyzed spectrophotometrically for drug content. Withdrawn samples were replaced by freshly distilled water. All the determinations were carried out in triplicate.

Bitterness evaluation by a taste panel

This test was done to evaluate the effectiveness of SDs in masking the bitter taste of SILD. The test was carried out on six healthy human volunteers. The protocol of the
study was reviewed and approved by the institutional review board of the Genuine Research Center, Cairo, Egypt. Before the test, all volunteers received a detailed explanation of the purpose of the study and gave their written consent. The volunteers were informed about numerical scale grading the bitterness before the test. Pure SILD and SDs of an amount equivalent to 20 mg SILD were held in the volunteers’ mouth for 10 s, and then they were asked to report their results after 10 s (11).

Differential Scanning Calorimetry (DSC)

Thermal studies were performed to examine the effect of the polymers used as dispersing carriers on SILD using differential scanning calorimetry (DSC 60 Shimadzu, Japan). Pure SILD, polymer, and SDs were sealed in aluminum pans and heated over a temperature range of 20–300 °C at a linear heating rate of 10 °C min–1 in a nitrogen atmosphere.

X-ray powder diffraction analysis (XRPD)

X-ray powder diffraction (XRPD) patterns of the SILD, polymer and the selected SD were recorded on an X-ray diffractometer (X-Pert Graphics &Idenify, Philips Analytical, The Netherlands) with an area detector operating at a voltage of 40 kV and a current of 30 mA using CuKa radiation. The scanning rate was 1.2 degree min–1 and the scanning scope of 2θ was from 5 to 40° at room temperature.

Fourier transform infrared spectroscopy (FTIR)

SILD, polymer and the selected SD were examined by FTIR (ThermoScientificNicolet 6700, USA). Samples of 2–3 mg were ground with 100 mg of dry potassium bromide powder and compressed into a disc with a hydrostatic press. The scanning range was 400–4000 cm–1.

Preparation of tablets by direct compression

SILD SD tablets were prepared by the direct compression technique. Each tablet was composed of SD containing an amount equivalent to 20 mg of SILD, magnesium stearate as lubricant, xylitol and peppermint as sweetening and flavoring agents, respectively. Two types of superdisintegrants were used, either sodium starch glycolate (SSG) together with PVP K30, Avicel PH 101 as binder and spray dried mannitol as diluent (S1-S4) or Pharmaburst®500 (S5-S8). All ingredients were used at different concentrations, as shown in Table I. Before compression, the previously sieved SDs and excipients were mixed in a glass mortar, followed by tumbling for 15 min in a Turbulamixer, then the lubricant was added and mixing was continued for further 5 min. The powder mix was compressed using a single tablet machine with a flat-faced punch of 7-mm diameter (MiniPress II, Karnavaty, India).

Preparation of SILD lyophilized sublingual tablets

Two groups of lyophilized tablets were prepared using two different matrix formers; the first was maltodextrin which also acts as diluent and collapse protectant, together with Xantham gum (X.gum) as binder and viscosity enhancer, xylitol as sweetener and PEG 8000; these formulae were coded as F1-F3. The second matrix former was gelatin formulated together with mannitol as diluent, glycine as collapse protectant and PEG
8000; these formulae were coded as F4-F9. All ingredients were used at different concentrations, as shown in Table II. Briefly, an accurately weighed amount of SILD powder was dispersed in an aqueous solution of the matrix former and other excipients under stirring with a magnetic stirrer to result in a dose of 20 mg of SILD per 0.4 milliliter. An amount of 0.4 milliliter of each prepared suspension was then poured into the pockets of a PVC blister pack, resulting in tablets of 20 mg each. Tablet blister packs were then kept in a freezer at –28 °C for 24 hours. Frozen tablets were placed in a lyophilizer for 24 hours using a Novalyphene-NL 500 Freeze Dryer. The condenser temperature was –45 °C and the pressure was $7 \times 10^{-2}$ mbar. Lyophilized tablets were then kept in tightly closed containers in desiccators at room temperature.

**Evaluation of prepared tablets**

Prepared SILD tablets were subjected to the quality control tests, namely, mass uniformity, drug content, hardness, friability, and *in vitro* disintegration tests.

**Table I. Composition of SILD SD sublingual tablets**

<table>
<thead>
<tr>
<th>Ingredient (mg)</th>
<th>S8</th>
<th>S7</th>
<th>S6</th>
<th>S5</th>
<th>S4</th>
<th>S3</th>
<th>S2</th>
<th>S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD1</td>
<td>–</td>
<td>40</td>
<td>–</td>
<td>40</td>
<td>–</td>
<td>40</td>
<td>–</td>
<td>40</td>
</tr>
<tr>
<td>LparSD10</td>
<td>40</td>
<td>–</td>
<td>40</td>
<td>–</td>
<td>40</td>
<td>–</td>
<td>40</td>
<td>–</td>
</tr>
<tr>
<td>Pharmaburst</td>
<td>78</td>
<td>78</td>
<td>58</td>
<td>58</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SSG</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>25</td>
<td>25</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Alocel PH 101</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>PVP K30</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Peppermint</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Xylitol</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Spray dried Mannitol</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>20</td>
<td>20</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Mg-stearate</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Total tablet mass</td>
<td>120</td>
<td>120</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table II. Composition of SILD lyophilized sublingual tablets**

<table>
<thead>
<tr>
<th>Ingredient (g/40 mL)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>SILD</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>3</td>
<td>4</td>
<td>4.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>X-gum</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gelatin</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PEG8000</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Mannitol</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Xylitol</td>
<td>2</td>
<td>1</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Glycine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Moisture content

A Karl Fischer titrator was used for assessment of residual moisture in the tablets processed by lyophilization. Each tablet was crushed, placed in the titration vessel containing dried methanol (Karl Fischer grade) and titrated with Hydranal Composite 5 reagent (Riedel-de-Haen, Seelze, Germany) after stirring for 3 minutes. The test results presented are the mean ± SD.

Wetting time and water absorption ratio

Ten milliliters of distilled water containing the water-soluble dye eosin were added into a Petri dish of 10 cm diameter. The tablets were placed in the center of the Petri dish and the time required for water to reach the upper surface of the tablets was recorded as the wetting time. The results are the mean value ± SD.

For the water absorption ratio (R), tablets were weighed before wetting ($W_b$) and after wetting ($W_a$) and the ratio was calculated according to the following equation (12):

$$R = 100 \frac{(W_a - W_b)}{W_b}$$

In vivo oral disintegration time

Oral disintegration time was tested on six healthy volunteers. The protocol of the study was reviewed and approved by the institutional review board of the Genuine Research Center, Cairo, Egypt. Before the test, all volunteers received a detailed explanation of the purpose of the study and gave their written consent. Each of the six volunteers was asked to rinse his mouth with distilled water and was then given a coded tablet and instructed to place the tablet under the tongue. The time required for complete disintegration of the tablet was recorded. The volunteers were allowed to spit out the content of the oral cavity after tablet disintegration and rinse their mouth with distilled water (13). The test results are presented as the mean value ± S.D.

In vitro dissolution studies

In vitro dissolution studies of sublingual and lyophilized tablets containing 20 mg of SILD together with the conventional market product Revatio® 20 mg oral tablets (Pfizer, USA) were carried out as previously done for the dissolution of SDs. At predetermined time intervals (1, 2, 3, 5, 7, 10, 15, 20, and 30 min), an aliquot of the dissolution medium was withdrawn and analyzed spectrophotometrically for drug content. Withdrawn samples were replaced by freshly distilled water. All determinations were carried out in triplicate.

Dissolution profiles of the prepared tablets were compared with the commercial product using the similarity factor ($f_2$) defined by the following equation (14):

$$f_2 = 50\log \left[ 1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i) \right]^{0.5} \times 100$$

where $n$ is the number of sampling time points, $R_i$ and $T_i$ are the mean percent dissolved of the reference (commercial product) and the test (prepared sublingual tablets), respec-
tively, up to each time point $t$. $f^2$ represents a logarithmic transformation of the sum-squared error of differences between the reference and the test products over all time points. In order to consider similar dissolution profiles, $f^2$ values should be higher than 50 (50–100).

**Statistical analysis**

All statistical analyses were made using ANOVA, followed by Fisher’s PLSD (pair-wise least significant difference) for multiple comparisons at $p < 0.05$ using the StatView statistical software program.

**Pharmacokinetic study on healthy volunteers**

**Subject selection**

Six healthy volunteers aged between 20 and 40 years were chosen. None of the volunteers had any history of drug or alcohol abuse, nor did they have any acute or chronic gastrointestinal, cardiac, vascular, hepatic or renal diseases. The protocol of the study was reviewed and approved by the institutional review board of the Genuine Research Center, Cairo, Egypt. The research was carried out in accordance with the international clinical research guidelines, enunciated in the Declaration of Helsinki, adopted in Helsinki in 1964 and amended in Seoul, South Korea, October 2008 (15). The purpose of the study was fully explained and the volunteers gave their written consent. The informed consent forms were carefully read before signing. All questions were discussed in detail with the clinical staff. Special emphasis was placed on the adherence of subjects to the study protocol and on the possible adverse events. The subjects were instructed to take no drugs for one week prior to and during the course of the study.

**Study design**

Randomized, single dose, three-way crossover open-label study was performed using three SILD formulations, viz., the prepared F4 and S7 sublingual tablets and the conventional market product Revatio® 20 mg oral tablets (Pfizer, USA). Following an overnight fast of at least 10 hours in all phases, subjects swallowed the conventional oral tablet (Revatio® 20 mg tablets) with a cup of water, and the sublingual formulations were properly put under the tongue and were not swallowed. No additional water or fluids were allowed until 2 hours after the dose. A standard meal was provided at approximately 4 hours after drug administration. Meal plans were identical in the three periods and were served approximately at the same time. Subjects were housed after dosing until the 12-hour blood draw. Seven days were allowed between the three doses, as washout periods.

**Sample collection**

Venous blood samples were collected in glass tubes before administration of the dosage form, and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, and 12.00 hours after drug administration. All samples were collected and plasma was immediately separated from blood cells by centrifugation at 3000 rpm for 10 min and stored frozen at −20 °C until analysis.
Determination of SILD in human plasma

A sensitive, selective and accurate LC-MS/MS method was developed and validated before the study for determination of SILD in human plasma. The method was validated following international guidelines (16). Torsemide internal standard (IS) stock solution was prepared by dissolving 10 mg in methanol and was serially diluted with the mobile phase to give a final working concentration of 50 ng mL\(^{-1}\). A Shimadzu Prominence (Shimadzu, Japan) series LC system equipped with a degasser (DGU-20A3), solvent delivery unit (LC-20AB) and an auto-sampler (SIL-20 AC) was used to inject 20 \(\mu\)L aliquots of processed samples on a Luna C (Phenomenex, USA) \((50 \times 4.6)\) mm, having a 5-\(\mu\)m particle size. All analyses were carried out at room temperature. The isocratic mobile phase (pH 4.5) consisted of acetonitrile and \((0.02 \text{ M})\) ammonium acetate buffer (70 \%, 30 \%, \(V/V\)) and 0.1 \% formic acid delivered at a flow rate of 1.0 mL min\(^{-1}\) into the mass spectrometer’s electrospray ionization chamber. Quantitation was achieved by MS/MS detection in the positive ion mode for both SILD and IS, using a MDS Sciex (Foster City, CA, USA) API-3200 mass spectrometer, equipped with a turbo ionspray interface at 300 °C. The ion spray voltage was set at 5500 V. Common parameters, \(viz.,\) nebulizer gas, curtain gas, auxiliary gas and collision gas were set at 30, 22, 20 and 5 psi, respectively. Compound parameters, \(viz.,\) declustering potential (DP), collision energy (CE), entrance potential (EP) and collision exit potential (CXP) were 76 V, 63 V, 10 V, 4 V for SILD and 31 V, 23 V, 6 V, 4 V for Torsemide (IS), respectively. Ion detection was performed in the multiple reaction monitoring (MRM) mode, monitoring the transition of the \(m/z\) 475.2 precursor ion to the \(m/z\) 58.2 for SILD and \(m/z\) 348.9 precursor ion to the \(m/z\) 263.9 for IS. Quadrupoles Q1 and Q3 were set at unit resolution. Analytical data were processed using Analyst Software (Version 1.4.2).

Sample preparation

Frozen human plasma samples were thawed at ambient temperature. Human plasma samples (1.0 mL) were placed in 5-mL glass tubes, and 1 mL acetonitrile containing IS was added to each and vortexed for 1 min. The upper layer was then transferred to the autosampler vial and 20 \(\mu\)L was injected into the system.

Pharmacokinetic and statistical analyses

Plasma concentration-time data of SILD was analyzed for each subject by non-compartmental pharmacokinetic models using Kinetica\(^{\text{®}}\)Software (version 4.4.1). Peak plasma concentrations \((C_{\text{max}})\) and the time of their occurrence \((T_{\text{max}})\) were directly obtained from the concentration-time data. The area under the plasma concentration-time curve \((AUC_{0-12})\) from time zero to the last measured concentration was calculated according to the linear trapezoidal rule. The terminal elimination rate constant \((\lambda z)\) was estimated by linear regression of the terminal portion of the ln (concentration)-time curve, and the elimination half-life was calculated. Relative bioavailability of SILD sublingual tablets compared to the commercial product was calculated according to the following equation:
Relative bioavailability (\%) = \frac{AUC_{Sublingual\ tablets}}{AUC_{Commercial\ oral\ tablets}}

Analysis of variance was used to assess the effect of the formulation on pharmacokinetic parameters. Differences between two related parameters were considered statistically significant for \(p\)-value equal to or less than 0.05.

RESULTS AND DISCUSSION

Characterization of SDs

Solubility and dissolution

There was a significant increase in the solubility of prepared physical mixtures compared to the plain drug (results not shown). Moreover, Table III shows that SDs significantly increased the solubility of SILD up to 1.65 fold, except for PEG 6000 which showed a non-significant increase in solubility (\(p<0.05\)). It is worthy to note that the solubility of SILD from SDs was significantly higher than from their physical mixture counterparts, so physical mixtures were excluded from further testing.

SDs prepared using poloxamer 188, PEG 4000 and PEG 8000 enhanced SILD dissolution compared to the plain drug and physical mixtures; the percentage of SILD dis-
solved after 5 min. was more than 93, 88 and 87 % from SDs prepared using poloxamer, PEG 4000 and PEG 8000, respectively. However, the percentage of SILD dissolved after 5 min. from SDs prepared using PEG 6000 was in the range of 65 to 83.5 %.

The efficiency of SDs in enhancing the solubility and dissolution of SILD could be due to the formation of a high energy metastable state of SDs (17) and a reduction in particle size in addition to the presence of carrier, which prevented aggregation of fine drug particles, thus providing a larger surface area for dissolution (18).

The superiority of poloxamer in enhancing the solubility and dissolution of SILD is due to its wetting property and surface activity, which resulted in a decrease in the interfacial tension between the medium and the drug and, hence, higher SD dissolution. Moreover, the presence of a larger number of H-bond forming groups resulted in the development of a strong force that inhibited agglomeration and recrystallization of the drug, leading to optimal dispersion of the system (19–20).

**Bitterness evaluation**

Bitterness evaluation revealed reduction in the bitterness score of the plain drug from very strong to moderate, slight and very slight when incorporated in SDs (Table III). This is due to the efficiency of SDs in masking the bitter taste (21).

The above results indicate that SD1 and SD10 prepared using a small polymer amount (drug to polymer ratio 1:1) showed high solubility (with no significant difference from other SDs of high solubility) and high dissolution rate and extent along with good masking of bitterness and were hence chosen for further studies.

**Differential scanning calorimetry (DSC)**

The DSC thermograms (Fig. 1) of SILD, poloxamer and PEG8000 gave sharp endothermic peaks at 198, 52 and 63 °C, respectively. SD1 thermogram showed two endothermic peaks at 198 and 63 °C, respectively. SD10 thermogram showed two endothermic peaks at 198 and 63 °C, respectively. SD1 thermogram showed two endothermic peaks at 198 and 63 °C, respectively.

Fig. 1. DSC thermograms of A) SILD, B) SD1, C) poloxamer 188, D) SD10, E) PEG8000.
mic transitions. One was very close to poloxamer melting temperature at 55 °C, and the other corresponded to the drug at 200 °C. SD10 thermogram showed two endothermic transitions. One was very close to PEG8000 melting temperature at 65 °C, and the other corresponded to the drug at 204 °C. The peaks corresponding to the drug in SDs were shortened and broadened, indicating an interaction that may suggest formation of a hydrogen bond between the lone pair of electrons of the drug nitrogen atom and the OH group of the polymer.

**X-ray powder diffraction analysis (XRPD)**

The XRPD pattern (Fig. 2) shows sharp peaks for SILD at 2° theta 4.3°, 7.3°, 8.07°, 10.27°, 14.4° and 19.8° indicating crystallinity of the drug. PEG8000 shows sharp peaks at 19.1°, 22.97°, 23.22° and 23.5° whereas those for poloxamer are shown at 19.2°, 23.35° and 23.48°. SD1 and SD10 show a decrease in peak number and intensity in comparison with pure SILD, where in case of SD10 peak intensity at 8.08° decreased from 4840 to 1124, at 10.2° from 1467 to 680, at 14.3° from 3385 to 557 and at 19.8° from 865 to 496, while small peaks at 4.3°, 14.67° and 15.08° had disappeared. Peaks of PEG 8000 at 19.1 decreased from 1391 to 1056, at 22.9 from 1377 to 953 and at 23.5 from 1237 to 734. SD1 also showed a decrease in major peak intensity and number, at 8.08 from 4840 to 1024, at 14.3 from 3386 to 482 and at 19.8 from 865 to 482, peaks at 4.3 and at 15.08 had disappeared. The decrease in peak number and the decrease in peak intensity of SILD indicate a reduction in its crystallinity in the formulated solid dispersions. Moreover, it might have dispersed as a microcrystalline form that enhances its solubility and dissolution.

**Fourier transform infrared spectroscopy (FTIR)**

FTIR study (Fig. 3) shows peaks for PEG8000 at 3481, 2887 and 1105 cm⁻¹ and at 3437, 2887 and 1147 cm⁻¹ for poloxamer 188, corresponding to the stretching associated
with O-H, C-H and C-O bonds, respectively. The drug shows peaks at 1170 and 1359 cm\(^{-1}\) for symmetric and asymmetric SO\(_2\), respectively, at 1582 and 1702 cm\(^{-1}\) for symmetric and asymmetric COOH, respectively, at 3301 cm\(^{-1}\) for the N-H group, and peaks from 3030 to 2733 cm\(^{-1}\) corresponding to aliphatic C-H. Analysis of the spectra of SDs shows broadening of peaks at 3430 cm\(^{-1}\), suggesting the formation of a hydrogen bond between the lone pair of electrons of the drug nitrogen atom and the OH group of the polymer (22), which explains the enhanced solubility of SD together with the decrease in drug crystallinity.

**Evaluation of the prepared tablets**

**SILD SD sublingual tablets**

As shown in Table IV, SILD SD sublingual tablets showed uniformity in thickness and diameter with average diameter ranging from 6.86 ± 0.05 to 6.94 ± 0.07 mm and average thickness ranging from 2.04 ± 0.03 to 2.35 ± 0.09 mm, indicating uniform die fill. None of the prepared tablets deviated from the stated limit (±5 %) of mass variation, indicating proper mixing of excipients with SD. All the assayed tablets are within the pharmacopoeial limit (±15 %) for drug content. Friability of the tested tablets ranged from zero to 0.13 % and their hardness ranged from 35 to 57 N with an average of 44.7 N, indicating good mechanical strength that can withstand mechanical and physical stress during handling. However, S3 was sticking to the punch and was excluded from the study.
Wetting time and water absorption ratio

Table IV shows that the formulations containing Pharmaburst (S5, S6, S7, S8) gave a shorter wetting time, ranging from 3.8 to 5.7 s, and higher water absorption ratio, ranging from 32 to 37%. On the other hand, those containing SSG (S1, S2, S4) gave a significantly higher wetting time, ranging from 35 to 87 s, and lower water absorption ratio, ranging from 9 to 18%. It is worthy to note that increasing the SSG concentration from 10 to 25% shortened the wetting time from 87 to 35 s and increased the water absorption ratio.

In vitro disintegration time (DT)

In vitro disintegration time (DT) of formulations prepared using Pharmaburst was significantly lower than that of those prepared using SSG, with values ranging from 88 to 180 s and from 250 to 300 s, respectively (Table IV).

In vivo oral DT

In vivo oral DT (Table IV) ranged from 75 to 180 s for Pharmaburst formulations while those of SSG ranged from 180 to 300 s. These results indicate a good correlation between in vitro and in vivo studies and again show that Pharmaburst significantly shortened DT in comparison with SSG.

The short wetting time, increase in absorption ratio together with shorter DT of Pharmaburst formulations may be explained by the fact that Pharmaburst is a coprocessed excipient composed of crospovidone, mannitol, sorbitol and precipitated silicon dioxide. It dissolves quickly with a good mouthfeel. It was developed to provide optimum compaction, friability, rapid disintegration and creamy mouthfeel. Moreover, crospovidone as a superdisintegrant possesses porous particle morphology that enables rapid absorption of liquids, up to 50%, into the tablet by capillary action and generates rapid volume expansion and hydrostatic pressure that result in tablet disintegration and increased absorption ratio and consequently short wetting time (23).

Table VI. Evaluation of SILD SD sublingual tablets

<table>
<thead>
<tr>
<th>Code</th>
<th>Diameter (mm)</th>
<th>Thickness (mm)</th>
<th>Drug content (%)</th>
<th>Hardness (N)</th>
<th>Friability (%)</th>
<th>Wetting time (s)</th>
<th>Water absorption (%)</th>
<th>In vitro DT (s)</th>
<th>In vivo oral DT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>6.92 ± 0.06</td>
<td>2.29 ± 0.07</td>
<td>98.5 ± 0.2</td>
<td>35 ± 0.7</td>
<td>zero</td>
<td>40 ± 0.15</td>
<td>300 ± 0.11</td>
<td>240 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>6.94 ± 0.07</td>
<td>2.04 ± 0.03</td>
<td>100 ± 0.41</td>
<td>36 ± 0.8</td>
<td>zero</td>
<td>87 ± 0.3</td>
<td>250 ± 0.1</td>
<td>180 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>S4</td>
<td>6.86 ± 0.05</td>
<td>2.3 ± 0.10</td>
<td>104 ± 0.2</td>
<td>44 ± 0.2</td>
<td>0.7</td>
<td>35 ± 0.21</td>
<td>180 ± 0.3</td>
<td>300 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>S5</td>
<td>6.93 ± 0.03</td>
<td>2.27 ± 0.03</td>
<td>102 ± 0.2</td>
<td>45 ± 0.7</td>
<td>zero</td>
<td>48 ± 0.2</td>
<td>88 ± 0.4</td>
<td>75 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>S6</td>
<td>6.92 ± 0.05</td>
<td>2.20 ± 0.05</td>
<td>110 ± 0.1</td>
<td>57 ± 0.1</td>
<td>zero</td>
<td>4.5 ± 0.1</td>
<td>90 ± 0.17</td>
<td>85 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>S7</td>
<td>6.9 ± 0.01</td>
<td>2.3 ± 0.01</td>
<td>105 ± 0.3</td>
<td>50 ± 0.5</td>
<td>0.13</td>
<td>5.7 ± 0.1</td>
<td>90 ± 0.6</td>
<td>80 ± 0.33</td>
<td></td>
</tr>
<tr>
<td>S8</td>
<td>6.93 ± 0.02</td>
<td>2.33 ± 0.09</td>
<td>112 ± 0.5</td>
<td>46 ± 0.1</td>
<td>0.08</td>
<td>3.8 ± 0.3</td>
<td>180 ± 0.12</td>
<td>180 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>
In vitro dissolution

Results of the in vitro dissolution study illustrated in Fig. 4 show that not all the prepared SD sublingual tablets prepared by direct compression were superior to the conventional market product. The dissolution profile of S1 and S4 was similar to the commercial product, with $f_2$ values of 51.26 and 52.44, respectively, while the dissolution profile of S2 was significantly lower than the market product with the $f_2$ value of 43.25. However, only S5, S6, S7 and S8 showed significantly higher dissolution profiles compared to the commercial product, with the $f_2$ values of 33.83, 37.89, 27.92 and 33.72, respectively.

Comparing the profiles of the sublingual tablets prepared using direct compression, it was observed that formulations prepared using Pharmaburst (S5, S6, S7 and S8) gave a higher release rate and extent of SILD compared to those prepared using SSG where 100% of SILD was released from Pharmaburst formulations after 7 min; however, S1, S2 and S4 prepared using SSG released 100% of the drug after 15, 20 and 15 min., respectively. These findings come in agreement with the results of the wetting time, water absorption ratio and DT.

By further inspection of Fig. 4, it was observed that formulations prepared using poloxamer as a solid carrier (SD1) were superior to those prepared using PEG8000 (SD10), as manifested by higher dissolution of S5 compared to S6, S7 compared to S8, and S1 compared to S2. As previously mentioned, this might be due to the presence of a larger number of H-bond forming groups, which resulted in the development of a strong force that inhibited agglomeration and recrystallization of the drug, leading to optimal dispersion of the system.

Fig. 4. Dissolution profiles of SILD SD sublingual tablets in 500 mL distilled water.
It is worthy to note that incorporation of SD of poloxamer188 in sublingual tablets together with Pharmaburst gave a better extent and release rate than SD of PEG8000, as evidenced by the higher dissolution of S5 and S7 compared to S1, and S6 and S8 compared to S2.

It was also observed that increasing the concentration of Pharmaburst from 58 to 78 mg and SSG from 10 to 25 mg enhanced dissolution (S5 vs. S7, S6 vs. S8 and S2 vs. S4).

According to the above results, S7 was proven to be superior compared to other formulations and was hence subjected to further in vivo studies.

**Lyophilized sublingual tablets**

Formulations prepared using maltodextrin as a matrix former (F1, F2, and F3) showed low mechanical strength and inelegant appearance and could not withstand manual handling, so these formulations were excluded from further testing. All other formulations were within acceptable pharmacopoeial requirements for both mass variation and drug content uniformity (Table V). Friability of tested tablet formulations was zero %, except for F5 which was 2.2 % that deviated from the acceptable limit and was excluded from further testing. This might be due to the low concentration of gelatin, which decreases mechanical strength (24), along with the effect of PEG8000, a low melting point glycol, that caused a decrease of tablet hardness and accordingly an increase in tablet friability (25). The residual moisture content in lyophilized tablets was very small, not exceeding 5 %, indicating that lyophilization was efficient in removing water from the tablets. The remaining moisture is required to maintain the integrity of tablets and prevent them from cracking (Table V).

**Wetting time and in vitro disintegration time (DT)**

Wetting time increased with increasing gelatin concentration, where F4, F6 and F8 gave wetting times of 9, 10, and 20 s, respectively. Moreover, increasing the gelatin concentration caused an increase in the in vitro disintegration time, with F4 having the shortest disintegration time (Table V). This is due to a decrease in the binding properties of gelatin by decreasing its concentration (26).

**Table V. Evaluation of SILD lyophilized sublingual tablets**

<table>
<thead>
<tr>
<th>Code</th>
<th>Theoretical mass</th>
<th>Mass after lyophilization</th>
<th>Drug content (%)</th>
<th>Friability (%)</th>
<th>Residual moisture (%)</th>
<th>Wetting time (s)</th>
<th>In vitro DT (s)</th>
<th>In vivo DT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4</td>
<td>80</td>
<td>76.5 ± 1.87</td>
<td>100 ± 0.7</td>
<td>zero</td>
<td>4.46 ± 0.11</td>
<td>9 ± 0.4</td>
<td>3 ± 0.2</td>
<td>10 ± 0.3</td>
</tr>
<tr>
<td>F6</td>
<td>90</td>
<td>86 ± 1.69</td>
<td>96.3 ± 1.7</td>
<td>zero</td>
<td>4.38 ± 0.87</td>
<td>10 ± 0.6</td>
<td>22 ± 0.35</td>
<td>15 ± 0.4</td>
</tr>
<tr>
<td>F7</td>
<td>110</td>
<td>109.4 ± 1.7</td>
<td>96.8 ± 3</td>
<td>zero</td>
<td>4.23 ± 0.5</td>
<td>12 ± 0.2</td>
<td>26 ± 0.55</td>
<td>20 ± 0.7</td>
</tr>
<tr>
<td>F8</td>
<td>100</td>
<td>95 ± 3</td>
<td>99.2 ± 3</td>
<td>zero</td>
<td>2.53 ± 0.6</td>
<td>20 ± 0.1</td>
<td>25 ± 0.9</td>
<td>23 ± 0.4</td>
</tr>
<tr>
<td>F9</td>
<td>120</td>
<td>115 ± 3</td>
<td>103.5 ± 0.7</td>
<td>zero</td>
<td>3.4 ± 0.7</td>
<td>Long time</td>
<td>120 ± 0.3</td>
<td>115 ± 0.9</td>
</tr>
</tbody>
</table>
In vivo oral DT

Table V shows that the in vivo oral DT could be arranged in the following ascending order, F4 < F6 < F7 < F8 < F9 where F4 prepared using 1 % gelatin showed the shortest DT of 10 s, while F9 prepared using 3 % gelatin showed the longest DT of 115 s. The increase in DT with an increase in gelatin concentration might be explained by the fact that during the freeze-drying process the aqueous solutions of gelatin are rapidly cooled, leading to the formation of a 3D gel network with water trapped inside, and then the trapped frozen water sublimates, leaving behind only the 3D network. By increasing gelatin concentration, a larger number of crosslinks and inter-chain H-bonds are formed between the gelatin strands (27) and since the mechanism of disintegration is due to the weakening of intermolecular bonds upon penetration of the disintegration medium between the tablet’s excipients, increasing gelatin concentration delays DT.

Studying the effect of PEG 8000 as disintegrant on the in vivo disintegration time, it was found that PEG 8000 did not decrease DT – the in vivo DT was 20 s for F7 vs. 15 s for F6 and 115 s for F9 vs. 23 s for F8. This was due to the increase in the solid concentration of the prepared formulae on adding PEG, which decreased the ability of ice to grow during the freezing step and hence decreased the number of pores left after the sublimation stage, resulting in longer DT (28).

Comparing the in vivo DT of lyophilized tablets with that of SD tablets prepared by direct compression, it was observed that the DT of lyophilized tablets ranged from 10 to 115 s and that of SD prepared by direct compression ranged from 75 to 240 s, indicating that the lyophilization process is more efficient in formulation of sublingual tablets.

In vitro dissolution study

The cumulative percent of drug dissolved as a function of time from lyophilized tablets is illustrated in Fig. 5. All the prepared lyophilized sublingual tablets gave significantly higher dissolution than the market product in the first 5 minutes, with the f2 values of 15.2, 16.8, 20.86, 33.65 and 46.2 for F4, F6, F7, F8 and F9, respectively.

The percentage of drug dissolved from lyophilized tablets in 1 min can be arranged in the descending order as follows F4 > F6 > F7 > F8 > F9 with values of 100, 89, 51, 38 and 24 %, respectively. These results indicate that lyophilization enhanced the dissolution of SILD; complete dissolution was achieved from F4 in 1 min and from F6 and F7 within 5 min and was retarded by 20 min in cases of F8 and F9. Decrease in the dissolution rate in case of F8 and F9 was due to the high content of gelatin compared to other formulations, which was correlated with both disintegration time and wetting time that were increased by the increase in gelatin concentration.

By inspection of Fig. 5, it was observed that the percentage of SILD dissolved from formulations containing PEG was lower than from their counterparts with no PEG. This might be due to the decrease in PEG solubility due to its high molecular mass.

It is worthy to note that the lyophilization process was superior in enhancing dissolution compared to direct compression; 100 % of SILD was dissolved after only one minute (F4) compared to 7 min (S7) in direct compression.

Lyophilization is a robust process; it imparts a glassy amorphous porous structure to the bulking agent, thereby enhancing the dissolution characteristics of the formula-
Tablets prepared by this technique have usually a light mass, with a very high specific surface area and a very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in the mouth (29–30).

Overall results showed that F4 was the best formula; hence it was subjected to further *in vivo* studies to be compared with the S7 compressed tablet.

**PHARMACOKINETIC STUDY IN HEALTHY VOLUNTEERS**

Revatio® is absorbed after oral administration, with a mean absolute bioavailability of 41%. The $T_{\text{max}}$ ranges from 30 to 120 minutes (median 60 min) from oral dosing in the fasted state. A high-fat meal delays the absorption of sildenafil citrate (7–8), with a mean delay in $T_{\text{max}}$ of 60 min and a mean reduction in $C_{\text{max}}$ of 29%. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations (31).

The mean plasma concentration *versus* time curves of SILD following administration of SD sublingual tablets (S7), lyophylized sublingual tablets (F4) and the commercial oral tablets (Revatio®) to human volunteers are shown in Fig. 6. The corresponding mean pharmacokinetic parameters calculated from the individual curves are collectively summarized in Table VI.

The plasma concentration-time profiles as well as the calculated pharmacokinetic parameters showed that the prepared sublingual tablets improved the oral absorption of SILD, expressed by the significantly higher $C_{\text{max}}$(1.5–2 fold), significantly shorter $T_{\text{max}}$
and the significantly higher AUC_{0-12} (nearly 1.5 fold) (p< 0.05) compared to the conventional oral tablet. The improved rate and extent of absorption and hence bioavailability of SILD might be due to the rapid disintegration and fast dissolution of sublingual tab-

**Table VI. Pharmacokinetic parameters of SILD after administration of SD sublingual tablets, lyophilized sublingual tablets and commercial oral tablets (Revatio\textsuperscript{\textregistered}) to human volunteers**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>F4</th>
<th>S7</th>
<th>Revatio\textsuperscript{\textregistered}</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng mL\textsuperscript{-1})</td>
<td>220.6 ± 44.7</td>
<td>187.2 ± 63.5</td>
<td>123.8 ± 39.9</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>0.5 ± 0.0</td>
<td>0.75 ± 0.0</td>
<td>0.91 ± 0.12</td>
</tr>
<tr>
<td>AUC_{0-12} (ng mL\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>603.3 ± 93.0</td>
<td>531.7 ± 144.6</td>
<td>377.5 ± 132.6</td>
</tr>
<tr>
<td>Lz (h\textsuperscript{-1})</td>
<td>0.11 ± 0.03</td>
<td>0.20 ± 0.04</td>
<td>0.17 ± 0.08</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>6.96 ± 2.94</td>
<td>3.58 ± 0.75</td>
<td>4.99 ± 2.84</td>
</tr>
<tr>
<td>Relative bioavailability (%)</td>
<td>159.81</td>
<td>140.85</td>
<td>–</td>
</tr>
</tbody>
</table>

C_{max} (ng mL\textsuperscript{-1}): (Commercial), (F4, S7).
T_{max} (h): (Commercial), (F4, S7).
AUC_{0-12} (ng mL\textsuperscript{-1} h\textsuperscript{-1}): (Commercial), (F4), (S7).
t_{1/2} (h): (Commercial, F4, S7).
* All formulae within the same brackets are not significantly different from each other but differ significantly from those in other brackets (p < 0.05).

Fig. 6. Mean plasma concentration-time profiles of SILD after sublingual administration of F4, S7 and oral administration of the commercial product to human volunteers.
lets with no variation in $T_{\text{max}}$(32). Moreover, the rapid transport of SILD across a single epithelial layer of the sublingual mucosa into the interstitial fluid on the basolateral side of the epithelial cells and then into the venous circulation might be the reason for the observed shorter $T_{\text{max}}$ (30, 33).

It is worthy to note that the method of sublingual tablet preparation had a significant effect on the bioavailability of SILD, as evidenced by the significantly shorter $T_{\text{max}}$ of lyophilized tablets (F4) compared to directly compressed tablets (S7), with values of 0.5 and 0.75 h, respectively. Moreover, the $\text{AUC}_{0-12}$ of lyophilized tablets (F4) was significantly higher than that of the directly compressed tablets, with relative bioavailability values of 159.81 and 140.85 %, respectively. This may be attributed to the fact that the freeze-drying process imparts a glossy amorphous structure to the bulking agent and sometimes to the drug, with an increase in the surface area and hence the surface free energy, resulting in an increase in the dissolution rate and thereby bioavailability (34).

CONCLUSIONS

This comparative study reveals that both direct compression of SD and freeze-drying were successful techniques in preparing SILDODSTs with significantly higher $T_{\text{max}}$, significantly higher $\text{AUC}_{0-12}$, enhanced bioavailability and a rapid onset of action for treatment of acute attacks of PAH compared to the conventional oral product. Although freeze-dried sublingual tablets showed enhanced dissolution and bioavailability compared to directly compressed SD tablets, the SD technique by the fusion method is advantageous because it is less time consuming and economically less expensive in both processing and equipment.

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SAŽETAK

komparativna in vitro i in vivo studija sublingvalnih tableta dobivenih izravnom kompresijom čvrstih disperzija i liofiliziranog citrata za terapiju plućne arterijske hipertenzije

REHAM ZAYED, AMANY O. KAMEL, MARWA SHUKR I ABD EL-HAMID EL-SHAMY

U radu je opisan razvoj sublingvalnih tableta citrata (SILD) raspršivih u ustima (ODST) za terapiju plućne arterijske hipertenzije (PAH), sa svrhom povećanja raspada nakon peroralne primjene, povećanja oslobađanja i bioraspoloživosti. Primijenjena je metoda izravne kompresije čvrstih disperzija (SD) sildenafila i poloksamera 188 i liofilizacija, a u izradi su upotrijebljena različita pomoćna sredstva. Evaluirana su fizikokemijska svojstva te oslobađanje ljekovite tvari iz tableta. Osim toga, na dobrovoljcima je uspore-
divana bioraspoloživost sildenafila iz ODST-a i standardnih tableta za peroralnu primjenu. Uklapanje SD poloksamera 188 u sublingvalne tablete uz Pharmaburst i korištenje izravne kompresije povećalo je oslobađanje SILD-a tako da je nakon 7 minuta 100 % lijeeka bilo otopljeno. Međutim, liofilizacija se pokazala superiornom za povećanje oslobađanja jer se 100 % SILD-a oslobodilo nakon samo jedne minute. Stoviše, in vitro studije su pokazale da je AUC od liofiliziranih tableta bila značajno veća nego iz tableta dobivenih izravnim komprimiranjem, uz vrijednosti za bioraspoloživost od 159,81, odnosno 140,85 % u odnosu na komercijalno dostupne proizvode.

Ključne riječi: sildenafil, raspršive sublingvalne tablete, plućna arterijska hipertenzija, poloksamer 188, čvrste disperzije, izravna kompresija, liofilizacija

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