Research Article

Development and Characterization of Sildenafil Citrate Oral Thin Films

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A B S T R A C T

The current work aimed to develop sildenafil citrate (SC) oral thin films. SC oral thin films (OTF) were prepared by solvent casting method. The ingredients include hydroxypropyl methylcellulose (HPMC), E4 (as film former), glycerol (as lubricating agent), polyethylene glycol 600 (as plasticizer), rose oil (as flavoring agent), and de-ionized water (as solvent). The SC-OTFs were successfully prepared by the solvent casting method. The drug excipient compatibility studies showed the absence of drug excipient interactions in fourier transform infrared spectroscopy (FTIR) spectra. All the prepared formulations (F1 to F6) were evaluated for several physicochemical parameters like morphology (i.e., size, shape, color), thickness, uniformity (i.e., content and weight), surface pH measurement, in vitro disintegration time, in vivo studies (i.e., taste), tensile strength, folding endurance and in vitro drug release and all were found within pharmacopoeial limits. In vitro, drug release studies (F1 to F6) in simulated salivary fluid (6.8 pH phosphate buffer) showed that 98 ± 1.26% drug was released from F4 in 60 sec. The OTF is a promising formulation for SC that results in high solubility, rapid onset of action, and enhanced systemic bioavailability (BA).

I N T R O D U C T I O N

To discover or develop a new chemical entity or a molecule or a drug is a time being and expensive also. Hence the industries, particularly in the pharmaceutical field, are just beginning innovative concepts for existing drugs.14 One of the advanced drug delivery systems is oral thin films. As per the United States of Pharmacopeia (USP), “Films” or “Oral films” are defined as single or multi-layer thin sheets with or without drug substance to be placed in the oral cavity.2-4 The fast disintegrating tablet, which is devoid of friability and choking risk, is more acceptable to pediatric, bedridden, and geriatric patients.5-7 The oral films are generally prepared by ‘solvent casting or ‘extrusion’, which is intended for fast disintegration and may allow more rapid mucosal absorption of the loaded drugs.8-10 A comprehensive spread review of the literature was initially performed to collect up to date and allowed for new oral film technology supplementary progress. Marketed oral films were analyzed to develop experimental knowledge and suitable quality and process parameters.11 The mainstream of the fast disintegrating oral films was designated by oro-dispersible films (ODFs) based on hydrophilic polymers. The characteristics of ODF’s are usually associated with undesirable texture, lower stability, and appearance, especially when exposed to ordinary environmental conditions.12-13 Oral films are complex polymeric matrices, usually in a postal stamp shape, which may be used efficiently as a drug release platform. Oral films are relatively recent dosage forms, especially in the pharmaceutical market, in which the first prescription product was introduced in 2010.14-15 The recent inclusion of this dosage form in the...
European Pharmacopeia (EP) accelerated research in the field during the last years. OTF’s are relatively new, thin polymeric films formulated to disintegrate or dissolve almost instantaneously when placed on the tongue without water. A drug in an OTF is absorbed through the oral mucosa and enters the systemic circulation without undergoing the first-pass metabolism. This formulation is administered easily and provides fast pharmacological action, improving patient compliance and convenience.

Sildenafil citrate (SC), a biopharmaceutical classification system (BCS) class I drug which is bitter and thus masking is a critical factor for patient acceptance. SC is one of the most successful agents for the treatment of erectile dysfunction. SC has been successfully proved effective in curing erectile dysfunction. Patients may take from 0.5 to 4 h. before starting sexual activity. It is in existing tablet form (i.e., Viagra) in the market. Still, it has some significant problems such as extensive first-pass metabolism, dyspepsia, and burning sensation in the gastrointestinal tract (GIT).

Extensive research work pays attention to flash release dosage forms, and films are widely acceptable in patients, too, because of the quick onset of action and user-friendliness. The present work emphasizes potential benefits, design, and development of robust, stable, innovative orally fast disintegrating thin films.

**Materials and Methods**

**Materials**

Sildenafil citrate was received as a gift sample from Shilpa Health care, Hyderabad, Telangana, India), hydroxypropyl methylcellulose (HPMC) E4 was received from DOW chemical company, USA. Polyethylene glycol (PEG) 600 and glycerine were procured from Finar Chemicals Ltd, Ahmedabad, India. Sucralose was purchased from JK sucralose Inc., India. Rose oil and other excipients were either pharmaceutical or analytical grade.

**Methods**

**Drug Excipient Compatibility Study**

Fourier transforms infrared spectroscopy (FTIR) studies were carried out to find the interaction between the pure drug (SC) and other excipients such as polymer and plasticizer. An FTIR (Bruker) was used for the analysis in the frequency range between 4000–400 cm⁻¹ and with 4 cm⁻¹ resolution.

**Construction of Sildenafil Citrate Calibration Curve**

Accurately weighed, 100 mg of SC was transferred to a 100 mL volumetric flask and dissolved in de-ionized water. The medium was adjusted up to the mark (i.e., 100 mL) with de-ionized water to get 1000 µg/mL (i.e., stock solution) of the drug. The 1000 µg/mL was further diluted to get the SC concentrations in the range of 5 to 25 µg/mL in the buffer. These solutions scanned for the maximum absorbance using a UV-visible spectrophotometer (Shimadzu, Kyoto, Japan). The absorbance of all drug solutions estimated at a maximum wavelength (λ_max) 226 nm.

**Preparation of Sildenafil Citrate Oral Thin Films**

In the formulation study, particular preference was given to selecting a suitable plasticizer and disintegration time to prepare the blank film, which could disintegrate fast and had a suitable elasticity and flexibility. The formulation with HPMC E4 was developed using 5, 10, 15, 20, 25, and 30% polymer in formulations. The drug and polymer mixed uniformly formulated as a film. Different concentrations of HPMC E4 were transferred into a 50 mL beaker and dissolved in de-ionized water and other excipients according to quantities (i.e., F1 to F6) shown in Table 1. By using a magnetic stirrer, mixed the formulations until they cloudy appearance. Keep the solution on an ice bath until the clear solution is received, then add SC to the above solution under continuous stirring. Initially, the cloudy nature is obtained and continues the mixing until getting a transparent and thick viscous solution. Add glycerine (1 mL), rose oil (1 mL), sucralose (2 mL) to the resultant mixture, and continue stirring until you get a clear solution. After that, the solution was placed on the ultrasonicator for 30 minutes to remove the air bubble from the formulation, then poured into molds with equal distribution, then dried by using a hot air oven at 40°C for about 24 h. and cut to pieces of 2×2 cm (i.e., 4 cm²).

**Characterization of Prepared Sildenafil Oral Films**

The disintegration and mechanical properties of films are the essential qualities attributed to evaluating the OTF. Thickness was measured by micrometer at various random locations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
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<tbody>
<tr>
<td>Drug</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>HPMC E4</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>PEG 600</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Glycerine</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Sucralose</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Rose oil</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
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<tr>
<td>De-Ionized water</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 1: Formulation of SC-OTF
locations. Drug content was measured for uniformity using the developed calibration curve. The drug content was determined by UV visible spectrophotometric method. For this, 4 cm² strips from each batch were cut and dissolved in 50 mL of 6.8 pH phosphate buffer; then, the solution was filtered through Whatman filter paper and diluted if necessary. The resulting solution was to measure spectrophotometrically at 226 nm.\(^{30}\)

As the thickness of the film is directly related to the tensile strength, it is necessary to ascertain uniformity in the film's width. It can be measured by micrometer or screw gauge at different strategic locations.

For determining the consistency of drug content in the film, ten films were taken and assayed; the same procedure was repeated for the batches as above.

Three films were randomly selected and weighed individually, and then the mean weight and standard deviation of films were calculated for uniformity of weight. It is a desire that films should have nearly constant weight. It is helpful to ensure that a film contains the proper amount of excipients and drugs.

The surface pH was determined by a digital pH meter to investigate the possibility of any side effects in vivo and keep the surface pH as close to neutral as possible. As an acidic, an alkaline pH may irritate the oral mucosa. The film is slightly wet with the help of water. The procedures repeat in triplicate and calculate the average with standard deviation.

The percent moisture loss study was carried out to check the physical stability and integrity of the films. Place the known weight and pre-determined size of the film in desiccators containing anhydrous calcium chloride (CaCl\(_2\)) for three days. The films were removed and reweighed, and the percent moisture loss of the films was measured using the following formula:

\[
\text{Percent moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100
\]

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. The film should be free of physical imperfections was placed between two clamps. The applied load calculates it at rupture divided by the cross-sectional area of the strip as given in the equation below:

\[
\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness} \times \text{Strip width}}
\]

The folding endurance was repeatedly determined by wrapping a small strip of the film simultaneously until the number of times the film could be folded at the same place without cracking until it broke or folded up to 300 times was considered satisfactory to reveal excellent film properties.

\textit{In vitro} disintegration time is the time when the film starts to break and is determined visually in a Petri dish containing 20 mL of 6.8 pH phosphate buffer with swirling every 10 seconds. All the results were shown in Table 2.

These studies were performed on all the film formulations (F1 to F6). Using an apparatus called Franz diffusion cell apparatus maintained a volume capacity of 15 mL used for the study. The film equivalent to 50 mg of SC placed in between the two compartments of an apparatus, and pipette 15 mL of 6.8 pH buffer (i.e., pH of saliva) added to the receptor compartment. The cell kept on a magnetic stirrer, and bead in the cell maintained at a specified speed RPM (i.e., revolution per minute), and medium maintained at a temperature of nearly 37°C ± 0.5°C. It withdrew 1 mL of sample each time at specified time intervals. Dilute with 6.8 pH phosphate buffer and measure the absorbance at 226 nm against the same medium.

**RESULTS AND DISCUSSION**

\textbf{Fourier Transformed Infrared Spectroscopy (FTIR)}

FTIR spectra of pure SC shows significant peaks at 3327.94 cm\(^{-1}\) (N-H stretch-secondary amine), a peak at 1718.79 cm\(^{-1}\) (C=O stretch of amide), a peak at 1437.72 cm\(^{-1}\) (CH\(_3\) group terminal), a peak at 1248.31 cm\(^{-1}\) (SO\(_2\) stretching) and some of the minor peaks also observed. FTIR spectra of F4 formulation shows significant peaks at 3282.47 cm\(^{-1}\) (N-H stretch-secondary amine), a peak at 1678.96 cm\(^{-1}\) (C=O stretch of amide), a peak at 1441.83 cm\(^{-1}\) (CH\(_3\) group terminal), a peak at 1343.46 cm\(^{-1}\) (SO\(_2\) stretching), some of the additional minor peaks also observed. It was confirmed with the literature studies as well (ref) and shown in Fig. 1 and 2.

\textbf{Construction of Sildenafil Citrate Calibration Curve}

A standard concentration of SC prepared in 6.8 pH phosphate buffer, and the absorbance's measured at 226 nm. Sildenafil was showed excellent linearity between 5 to 25 µg/ml with a correlation coefficient (R\(^2\)) = 0.998 and shown in Fig. 3.

Three film strips of 4 cm\(^2\) were cut from each film, estimated for uniformity of drug content using a UV visible

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**Fig. 1:** FTIR spectra of a pure drug (i.e., Sildenafil)

**Fig. 2:** FTIR spectra of optimized formulation (F4)
spectrophotometric method. They observed that all the formulations were found within limits (46.98 ± 0.15 (F6) to 49.82 ± 0.03 (F4)).

A screw gauge measured each sample’s thickness at five locations, and the mean widths were calculated. As the formulations contain different polymers concentrations, the films’ thickness was found in the range of 0.45 ± 0.002 mm (F1) to 0.52 ± 0.003 mm (F6).

The drug content was found to be low for F2 formulation and more for F4 formulation and found to be in the range of 98 ± 2.1 % to 102 ± 1.5 %, respectively.

The surface pH of all the selected formulations ranged from 6.65 ± 0.005 (F5) to 6.78 ± 0.049 (F6); since the film’s surface pH around neutral pH, there will not be any irritation to the oral mucosal cavity.

The moisture loss of all the formulations was measured, ranging from 1.6 ± 0.001 (F6) to 2.1 ± 0.046 (F2), and the F6 formulation showed the lowest moisture loss than other formulations; hence, it is more stable.

The results revealed that all the films showed moderate to high tensile strength values ranged from 5.37 ± 0.24 (F2) to 13.06 ± 0.90 (F3). The results were given in Table 2.

The film was folded at the same place around 180° angles, till it broke and found between 98 ± 3.5 (F2) to 102 ± 1.5 (F4). The values indicate that the films have excellent flexibility. The formulation with a high concentration of polymers has a low amount of folding endurance because it offers a specific increase in the concentration of polymers decreases in folding endurance due to film thickness. More thickness lower will be folding endurance. The studies performed in a trice and calculated the average mean.

In-vitro disintegration time was found between 25 ± 1.3 sec. (F4) to 32 ± 1.7 sec. (F6) seconds. The formulation F4 had shown fast disintegration as compared to other formulations.

In vitro drug release studies were carried out using 6.8 pH phosphate buffer. The cumulative drug release of all the formulations (F1-F6) showed rapid solubility and quick release. The study was carried out for 60 seconds. And release rates of all prepared formulations were compared. The release profiles of all formulations were shown in Fig. 4.

The maximum release rate was observed in F4 formulation, with 98.68 ± 1.6% within the specified time. The formulation (F5) exhibited a slow drug release rate with 81 ± 0.3%, and the F3 formulation released 99.4 ± 0.8%. Based on various factors that play a vital role in regulating the release rates, including particle size, shape, drug wettability, and the particle’s nature, i.e., amorphous or crystalline, a ratio of drug and polymer and solubilization of drug and polymer formulation F4 was optimized.

**Conclusion**

All the formulations show excellent physicochemical properties. It was observed that the polymer concentration
has a more significant impact on the property and release rate. The physicochemical properties of all the formulations were established to be within the prescribed official limits. This drug delivery platform is being under surveillance from both start-up and established pharmaceutical companies. The companies strive to design a wide range of thin films for oral, buccal, sublingual, ocular, and transdermal routes. Therefore, as an alternative to conventional dosage forms, polymeric thin films are expected to stand out as a dosage form to overcome the limitations of existing dosage forms. The film dosage form encounters several challenges during the phases of formulation development and manufacture. Such issues should be addressed to optimize the overall formulation even after transferring to large-scale manufacturing.

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All authors have contributed equally.

**REFERENCES**


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