Preparation and Evaluation of Sildenafil Rapidly Disintegrating Tablets

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ABSTRACT

Sildenafil citrate is an oral therapy for erectile dysfunction (ED). Sildenafil, a selective inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase type 5 (PDE5), has been reported to be effective in men with ED associated with diabetes and prostate cancer, and in psychogenic ED. The main objective of this study is to prepare more effective, rapidly disintegrating and rapid onset of action sildenafil oral tablets. Sildenafil tablets were prepared using the newly introduced Pharmaburst® as a direct compression vehicle in comparison with the well-known excipients, namely mannitol, anhydrous lactose and primojel. The formula containing Pharmaburst® showed the most rapidly-disintegrating effect (15 sec) compared to the other formulations. Thus, Pharmaburst® can be utilized as an effective direct compression vehicle as well as a superdisintegrant with very rapid disintegration time in vitro and in the oral cavity. The rapidly-disintegrating sildenafil tablets showed maximum serum concentration within only two minutes (Cmax of 0.76 µg) by applying the tablets to the oral cavity of rabbits, whereas, the conventional sildenafil tablets have a comparatively lower Cmax (0.56µg) through about 45 minutes.

KEYWORDS: Sildenafil; OD tablets; Pharmaburst®; erectile dysfunction; rabbits.

Introduction

With an increase in the average human life, drug administration for elderly patients has become more important. Due to a decline in swallowing ability with age, a great many elderly patients complain that it is difficult to take medication in the form of tablets. Recently, useful dosage forms, such as rapidly disintegrating or dissolving tablets have been developed and applied clinically. This dosage form can be used also for children instead of syrup, as well as for local action within the oral cavity, local anesthetics for toothache, cold sores, or teething products. These tablets can be used also instead of chewable tablets as antacid. An important variable in any tablet system is the rate at which the drug substance dissolves. For many solid dosage forms, disintegration precedes drug dissolution, so superdisintegrants are now frequently used in tablet formulation to improve the rate and extent of tablet disintegration and thereby increase the rate of drug dissolution, which may lead to decreasing in the onset of action, minimizing the effect of the drug on the GIT, as well as avoiding first pass effect (Sugihara 1995; Mallet, 1996; Sallam et al., 1998; Bi et al., 1999; Ishikawa et al., 1999).

Sildenafil citrate is an oral therapy for erectile dysfunction. Sildenafil is a selective inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase type 5 (PDE5). The physiologic mechanism of erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood (Martindale, 2009). The efficacy of sildenafil citrate in men with erectile dysfunction has been studied (Ridwan et al., 2010, Vera et al., 2010, Safarinejad and Stroberg, 2010). Primojel or Explotab, which is low substituted carboxymethyl starch, sodium carboxy methyl cellulose (Ac-Di-Sol) were evaluated as superdisintegrants for producing rapidly disintegrating tablets (Watanabe, 1998; Bi et al., 1999; Bix et al., 2010; Aly et al., 2011). Lyophilization or the freeze-drying method was evaluated also, for this purpose (Jennings, 1995; Clarke, 2001; Aly, 2003). The camphor sublimation method has been evaluated for the production of oral disintegrating tablets (Koizumi et al., 2005; Aly et al., 2008).

In the present study, we prepared sildenafil rapidly-disintegrating tablets with different superdisintegrant materials using direct compression and performed in vivo study of these tablets in comparison with conventional oral tablets.

Materials and Methods

Chemicals

Sildenafil was from Rum Pharmaceutical Manufacturing Co. (Amman, Jordan). Mg- stearate:
Preparation of Sildenafil tablets by Direct Compression

Four sildenafil tablet formulations were prepared by mixing (in a cubic mixer) for 5 minutes, sildenafil (12.5 mg), aspartame (10 mg), magnesium stearate (2 mg), menthol (1 mg), with 75.5 mg of each of the following disintegrants: mannitol (A), primogel (B), anhydrous Lactose (C), and Pharmaburst® (D). The mixture of each formulation was compressed into 100 mg flat tablets (8 mm in diameter) using a Korsch constant rate tablet machine (EK/O, Germany). All tablet formulations were prepared by adjusting the machine to produce tablets of hardness values of 25-27 Newtons.

The disintegration time results of the prepared tablet formulations revealed that the tablet formula containing Pharmaburst® showed a very rapid disintegration time (15 sec) compared to the other tablet formulations. So, another sildenafil tablet formulations were prepared containing Pharmaburst® (49.5 mg) with 15 mg of other disintegrants, namely Primogel (E), AcDiSol (F), or Kollidon CL (G) in order to study the effect of adding these disintegrants to Pharmaburst®-containing tablets on the disintegration time.

On the other hand, conventional sildenafil (100 mg) oral tablets (for in vivo study) were prepared by mixing the ingredients and using direct compression according to the following formula:

- Sildenafil: 12.5 mg
- Avicel: 57.25 mg
- Anhydrous lactose: 28.75 mg
- Talc: 1.5 mg

Evaluation of Sildenafil Tablets

Uniformity of Weight

Twenty tablets taken randomly were weighed individually and tested according to the USP/NF (1995) test. Also, the average weight, the standard deviation, and the coefficient of variation (CV %) were calculated.

Uniformity of Diameter and Thickness

The diameter and thickness of twenty tablets were determined individually using an Erweka Hardness Tester TBH™, Germany. Also, the average and CV % were calculated.

Hardness Test

The crushing strength of ten tablets selected randomly was determined using an Erweka TBH™ Hardness tester.

Friability Test

The percentage weight loss was determined after rotation of two previously weighted tablets for four minutes at 25 rpm using Erweka Friabilitator TAR 20.

Disintegration Time

The average of time required for the disintegration of 6 tablets was also determined using the Pharma Test (Italy) apparatus.

Disintegration Time in the Oral Cavity

The time required for complete disintegration of a tablet in the oral cavity was collected from ten healthy volunteers who were administered each formula at 24 hour intervals as discussed by Bi et al., (12).

Drug Content Test

Drug content for each formula was determined by dissolving 10 tablets from each formula and analyzing using HPLC and determines the mean Sildenafil content in each formula.

In vivo Study in Rabbits

Two groups of rabbits, each containing six, were chosen for in vivo study of the amount of Sildenafil that can be absorbed through the buccal cavity. One group applied the prepared Sildenafil tablets that contain Pharmaburst® over the tongue of each rabbit (after anesthetizing by ether) and closed the mouth then, blood samples from the ear vein were taken according to the following time intervals: 2, 2.5, 5, 12, 15, and 25 min. The other group was orally administered the prepared conventional Sildenafil tablets using an intragastric tube (after anesthetizing by ether), then the blood samples were taken from the ear vein according to the following time intervals: 2, 5, 15, 25, 45, 60, and 90 min.

The collected blood samples were analyzed using the HPLC method for the determination of sildenafil concentration by high-performance liquid chromatography (HPLC). The drug was chromatographed on a reverse-phase C18 column using mixtures of buffer–acetonitrile, and the eluents were monitored at various wavelengths. The method was validated statistically for its linearity, accuracy, robustness, and precision. The mobile phase was a mixture of 0.02 M disodium hydrogen phosphate and acetonitrile (60:40 V/V). The pH was adjusted to 4.0 by adding orthophosphoric acid. 290nm and attenuation of 0.01 absorbance unit per full scale (AUFS) was used (20). The samples were prepared by mixing 0.1 ml of plasma with 0.4 ml of methanol (to precipitate plasma) and filtered by filter paper then injected into HPLC system.

Results and Discussion

More effective, more rapid onset of action, better independency of the gastric content, and rapidly disintegrating sildenafil tablets were prepared using Pharmaburst® as the direct compression vehicle in
comparison with the well-known excipients, namely Mannitol, Primojel and Anhydrous lactose. The typical composition of sildenafil tablets are listed in Tables 1 and 2. All the prepared tablet formulations fulfilled the USP/NF24 requirements for the uniformity of weight and diameter. The friability values were acceptable in all cases except for those of anhydrous lactose (2.4% loss) (Table 3). The formula containing Pharmaburst® showed the most rapid disintegrating (15 sec) compared to the other formulas. Thus, it may be considered as rapidly disintegrating substance in addition to its effectiveness as the direct compression vehicle. For more confirmation of its rapid-disintegration effect, other sildenafil tablet formulations containing Pharmaburst® with other well-known superdisintegrants, Primojel, AcDisol and KollidonCL were prepared. As shown in Table 2, the results obtained revealed that Pharmaburst® alone has very effective rapid disintegration without the need of addition of other disintegrants. The only disintegrant that can improve its effect is KollidonCL (produced 8 sec disintegration time) while the other two disintegrants showed no significant effect on the tablet disintegration.

**TABLE 1**
Composition of sildenafil tablets prepared by direct compression method.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Materials (mg)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Aspartame</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mg. stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Menthol</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>74.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Primojel</td>
<td>-</td>
<td>74.5</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anhydrous Lactose</td>
<td>-</td>
<td>-</td>
<td>74.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pharmaburst®</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>74.5</td>
<td></td>
</tr>
</tbody>
</table>

*Total weight of each formula is 100mg.

**TABLE 2**
Composition of sildenafil tablets prepared by direct compression method.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Materials (mg)</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Aspartame</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mg. stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Menthol</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>59.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pharmaburst®</td>
<td>-</td>
<td>59.5</td>
<td>59.5</td>
<td>59.5</td>
<td></td>
</tr>
<tr>
<td>Primojel</td>
<td>15</td>
<td>15</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>AcDisol</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kollidon</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

*Total weight of each formula is 100mg.

**TABLE 3**
Physical properties of the prepared sildenafil tablets with different excipients.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Mannitol (A)</th>
<th>Primojel (B)</th>
<th>Anhydrous lactose (C)</th>
<th>Pharmaburst® (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>98</td>
<td>99.3</td>
<td>102</td>
<td>100</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>1.83 (0.54)</td>
<td>1.69 (2.79)</td>
<td>1.77 (1.42)</td>
<td>1.85 (1.45)</td>
</tr>
<tr>
<td>Friability Value (%)</td>
<td>0.80</td>
<td>0.75</td>
<td>2.4</td>
<td>0.75</td>
</tr>
<tr>
<td>Disintegration Time (Sec)</td>
<td>50</td>
<td>45</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>Hardness (Newton)</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>

Values between parentheses are the coefficient of variation (C.V) %.

The oral disintegration (disintegration time in the oral cavity) of tablets containing Pharmaburst® showed nearly similar results to those of the in vitro disintegration time values. This may be attributed to the high aqueous solubility of Pharmaburst® because it needed very small amount of water to dissolve in the oral cavity. Previous studies in this aspect revealed that the in vitro disintegration time was faster than the oral disintegration due to the higher volume of water in the former. Figure 1 shows a photographic picture of each formula after one minute when in contact with water, the swilling and destruction of tablets containing Pharmaburst®, and intact swilling of tablets of AcDiSol or Kollidon CL. To study the in vivo drug release of the prepared rapidly-disintegrating sildenafil tablets using Pharmaburst®, in comparison with conventional tablets, two groups of rabbets, each containing six, were orally administered the two types of tablets. As shown in
Figure 2, the results obtained revealed that rapidly disintegrating sildenafil tablets showed maximum serum concentration within only two minutes (C_{max} = 0.76 µg), whereas the conventional sildenafil tablets have a comparatively lower C_{max} (0.56 µg) through about 45 minutes.

**Fig. 1.** Photograph showing the effect of water on sildenafil tablets containing (a) Ac-di-Sol, (b) KollidonCL or (c) Pharmaburst® before hydration (the upper photos) and after hydration (the lower photos).

**Fig. 2.** Pharmacokinetic profile of rapidly disintegrating tablets of sildenafil as compared to conventional tablets in rabbits.

## Conclusions

From the results obtained it could be concluded that Pharmaburst® can be used as a direct compression vehicle for the production of sildenafil rapidly disintegrating tablets without the need of adding any disintegrating agent. The maximum serum sildenafil concentration could be obtained within only two minutes by applying the tablets to the oral cavity of rabbits. In conclusions, these studies suggest that sildenafil rapidly-disintegrating tablets may provide a faster drug release and thereby may provide rapid onset of action.

## References


