Formulation Development and Characterization of Itraconazole Granules

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ABSTRACT

Itraconazole is practically insoluble in water; large inter-individual and intra-individual variations of its oral bioavailability are reported. The main purpose of this study was to prepare and evaluate itraconazole granules for immediate release as drug delivery formulations. As a part of formulation optimization, different concentrations of hydroxypropyl-methyl cellulose (HPMC) E5 were taken for the preparation of itraconazole granules, and were optimized with different characteristic like size, shape, surface roughness, density, moisture content, assay and dissolution. Formulation optimization includes a detailed study of itraconazole granules with different concentrations of polymer. The results of the study showed that 6% of HPMC E5 is sufficient as a binding agent and gave good shape and surface, low moisture content, 100% assay and 98.24% drug release within one hour. Based on these results, it can be concluded that 6% HPMC E5 is suitable for formulation of itraconazole granules.

KEYWORDS: Granules; HPMC E5; itraconazole.

Introduction

Itraconazole is an oral antifungal agent with a broad-spectrum of activity. Itraconazole is most effective when drug concentration is maintained above the minimum effective concentration. Itraconazole is weakly basic (pKa = 3.7) and highly hydrophobic (octanol/water partition coefficient at pH = 8.1, log P = 5.66) (Grant et al., 1989). It is practically insoluble in water. Itraconazole belongs to the Biopharmaceutical Classification Systems Class II drugs categorized with low water solubility and high permeability (Amidon et al., 1995).

Granules are agglomerates of fine powders or granules of bulk drugs and excipients with sizes ranging from about 0.1-2.0 mm. The term “pelletization” is used synonymously with granulation, but in pharmacy, this term usually refers to the manufacturing of aggregates, preferably spherical, with a narrow size distribution in the range of about 0.5-1.5 mm. They consist of small, free-flowing, spherical or semi-spherical solid units, typically about 0.5-1.5 mm, and are intended usually for oral administration (Swarbrick et al., 1992; Aulton, 2002). Granules can be prepared by many methods. The most common techniques of granulation are dry granulation, which includes roller compaction and slugging, and wet granulation, which includes wet massing, fluid bed granulation, spray drying, pan granulation, extrusion and palletizing, and other granulation processes such as humidification and melt pelletization (Conine et al., 1970; Ghebre et al., 1985; Leon et. al., 1991; Niskanen, 1992; Parikh, 1997a; Parikh, 1997b).

The layering process comprises of the deposition of successive layers of drug entities from solution, suspension or dry powder on the nuclei which may be crystals, granules of the same material or inert starter seeds (Gamlen, 1985; Jackson et al. 1989). Itraconazole is most effective when drug concentration is maintained above the minimum effective concentration. The main purpose of this study is to prepare itraconazole granules that release the maximum possible amount of drug within one hour.

Materials and Methods

Drugs and Chemicals

Itraconazole was procured from Metrochem API Pvt. Ltd (Hyderabad, India). HPMC E5 supplied by Ruitai Pharmaceutical Company, China. Crospovidone, calcium carbonate, sodium lauryl sulphate were supplied by Loba Chemie Pvt Ltd (Mumbai, India). Tween-80, diethyl phthalate, isopropyl alcohol and dichloromethane are procured from S.D. Fine Chemicals Ltd (Mumbai, India). All the reagents used in this study were of analytical grade.
Preparation of Granules

The layering process was comprised of the deposition of successive layers of drug entities from solution, suspension, or dry powder on nuclei which may be crystals, granules of the same material or inert starter seeds. The itraconazole drug solution for layering is prepared by dissolving itraconazole, different concentration of HPMC E5, crospovidone, calcium carbonate, tween-80 and sodium lauryl sulphate in a mixture of the required amount of methylene dichloride and isopropyl alcohol using mechanical stirrer.

The total size 2000 g the batch is adjusted by adding the required quantity of mannitol in the solution. The 700 sugar granules (Size 30 # 40) are loaded into the fluid bed processor having 5 kg capacity. The drug solution is sprayed over the sugar granules using a peristaltic pump and the granules were prepared at previously optimized parameters (i.e. at atomizing air pressure 2 bar, peristaltic pump with 2 rpm, inlet air temperature 45°C). After completion of drug loading, the granules are dried in the fluid bed processor for 10 minute at 45°C (Ghebre, 1989).

Investigation of Physicochemical Compatibility of Drug and Excipients

The physicochemical compatibility between drug and excipients used in the granules was studied by using a Fourier transform infrared spectrophotometer (FTIR-8400S, Shimadzu Corporation, Japan) (Patel et al., 2009). The infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm–1. The spectra were obtained for excipient blend, itraconazole, and granules/pellets and analyzed in a comparative fashion.

Characterizations of Granules

Size: The size of granules is determined by different methods. The most common and widely used method is sieve analysis. The reasons for its extensive use are simplicity, lower costs, low time consumption and low turnover of operators. Hence, here the size distribution was also done by sieve analysis (Kristensen et al., 2000).

Shape and Surface Roughness. One of the important objects of granules/pellet preparation is to produce spherical and smooth particles, suitable for subsequent successful products. Different methods can be used for measuring the shape and surface roughness of the granules/pellets. The commonly used method is the analysis of microscopic or non-microscopic pictures of objects of interest. Here, the shape and surface roughness is measured visually and given a grade from 1 to 10, ten being best (Shah et al., 2009).

Density. The density of granules can be affected by changes in the formulation and/or process, which may affects other process or factors, such as capsule filling, coating, and mixing. Variation of density from batch to batch affect the potency of the finished capsule, causes problems in batch size determination during coating and produces segregation during mixing. Here, density is measured by weighing accurate amounts (g) of granules pouring them into measuring cylinder and measuring the total volume occupied by granules (Leon et al., 1991).

Moisture Content. Moisture content generally affects the stability of the product. Therefore, for most pharmaceutical products, analysis of moisture content is mandatory. Here the moisture content was measure by the Karl-Fischer method of determination of water content.

Assay of Itraconazole. Itraconazole was estimated by the ultraviolet visible (UV/Vis) spectrophotometric method (Shimadzu UV-1800 UV/Vis double beam spectrophotometer, Kyoto, Japan). Solutions of itraconazole were prepared in Methanol:HCl. (99:1) and absorbance was measured on UV-visible spectrophotometer at 258 nm. The method was validated for linearity, accuracy, and precision.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Ingredients</th>
<th>Quantity in gm for 2000 gm of granules</th>
<th>Formulation Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Itraconazole</td>
<td>440.00 440.00 440.00 440.00 440.00 440.00 440.00</td>
<td>SF 1 SF 2 SF 3 SF 4 SF 5 SF 6 SF 7</td>
</tr>
<tr>
<td>2</td>
<td>Sugar Sphere (30#40)</td>
<td>700.00 700.00 700.00 700.00 700.00 700.00 700.00</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Mannitol</td>
<td>730.00 710.00 690.00 670.00 650.00 630.00 610.00</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>HPMC E 5</td>
<td>20.00 20.00 20.00 20.00 20.00 20.00 20.00</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Calcium carbonate</td>
<td>40.00 40.00 40.00 40.00 40.00 40.00 40.00</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Crospovidone</td>
<td>40.00 40.00 40.00 40.00 40.00 40.00 40.00</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Tween – 80</td>
<td>8.00 8.00 8.00 8.00 8.00 8.00 8.00</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Titanium dioxide</td>
<td>8.00 8.00 8.00 8.00 8.00 8.00 8.00</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Sodium lauryl sulphate</td>
<td>14.00 14.00 14.00 14.00 14.00 14.00 14.00</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1
Composition of itraconazole granules.
In Vitro Drug Release Study

The drug release study was performed using the USP XXIII type II apparatus (Electrolab, TDT-06T, Mumbai, India) at 37°C ± 2°C with 100 rpm using 900 ml of 0.1 N HCl (pH 1.2) as a dissolution medium. Itraconazole granules equivalent to 100 mg (454.5 mg of granules) were used for the test. Sample aliquots of 5 ml were withdrawn periodically and the withdrawn samples were estimated for drug content through UV spectroscopy. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer’s equation.

Results and Discussion

Investigation of Physicochemical Compatibility of Drug and Excipients

Drug-excipient interactions play a vital role in respect to the release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between the drug and excipients used. Infrared (IR) spectra of excipient blends of optimized batch SF6, pure drug, and granules/pellet shown in Figure 1, are taken for characterization study. Ash shown in Figure 1, it was observed that there were no changes in these main peaks in IR spectra of drug and excipients blend, which show there were no physical interactions because of some bond formation between drug and excipients.

Characterization of Granules

Size: As per the data shown in the Table 2 when the concentration of HPMC E5 was 20 g/2000 g (1% of the total weight of granules) of granules, the percentage of granules laying in between predetermined size range is 84.2, and for 140 g/2000 g (7% of the total weight of granules), it was 90.3. So, we can conclude that the increase in concentration of HPMC E5 was increased the percentage of granules laying in predetermined size range because of the binding property of HPMC E5.

Shape and Surface Roughness. Table 2 shows that when the concentration of HPMC E5 is 20 g/2000 g of granules, the grade of shape and surface roughness was six, while for 140 g/2000 g it was nine. So, it may conclude that, the increase in concentration of HPMC E5 gave good shape as well surface.

Density. Results shown in Table 2 conclude that the granules having concentrations of HPMC E5 20 g/2000g have a density of 1 g/ml while granules having 140 g/2000 g of HPMC E5 have density of 0.7 g/ml. It says that the increase in concentration of HPMC E5 was decreased the density of the granules, i.e. as the concentration increased the less amount of fines are produced during the preparation.

Moisture Content. As shown in Table 2, there is no major change in the moisture content of the granules while the increasing the concentration of HPMC E5.

TABLE 2

Evaluation of itraconazole granules.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Parameters</th>
<th>SF 1</th>
<th>SF 2</th>
<th>SF 3</th>
<th>SF 4</th>
<th>SF 5</th>
<th>SF 6</th>
<th>SF 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Size Distribution (% of granules between 12#20)</td>
<td>84.2</td>
<td>86.0</td>
<td>86.5</td>
<td>88.0</td>
<td>89.0</td>
<td>90.0</td>
<td>90.3</td>
</tr>
<tr>
<td>2</td>
<td>Shape and Surface Roughness (Grade out of 10)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Bulk Density (gm/ml)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>4</td>
<td>Moisture Content (%)</td>
<td>1.60</td>
<td>1.63</td>
<td>1.63</td>
<td>1.69</td>
<td>1.70</td>
<td>1.72</td>
<td>1.75</td>
</tr>
<tr>
<td>5</td>
<td>Assay (%)</td>
<td>20.45</td>
<td>20.68</td>
<td>21.02</td>
<td>21.69</td>
<td>21.94</td>
<td>22.53</td>
<td>22.10</td>
</tr>
<tr>
<td>6</td>
<td>Drug Release at 1 hr. in 0.1 N HCl (pH 1.2)</td>
<td>98.68</td>
<td>98.89</td>
<td>98.76</td>
<td>98.87</td>
<td>98.53</td>
<td>98.24</td>
<td>87.9</td>
</tr>
</tbody>
</table>
Assay of Itraconazole. As shown in Table 2, we may conclude that granules having concentrations of HPMC E5 20 g/2000 g have assay of 20.45%, while granules having 140 g/2000 g of HPMC E5 have assay of 22.10%. It says that the granules having lower in concentrations of HPMC E5 had lesser assay because of lower amounts of HPMC E5 as a binding agent, and some material separated from the surface of the granules.

In Vitro Drug Release Study

As shown in Figure 2, and Table 2, there is no major change in the data of % drug release in 1 hour, only slightly release is decreased, 98.24% to 87.9 as the concentration of HPMC E5 was increased from 120 g/2000 g to 140 g/2000 g respectively.

![Release Profile of Itraconazole Granules in 0.1 N HCl (pH 1.2)](image)

Based on the above results, we can conclude that 6% of HPMC E5 is sufficient for the preparation of granules. Less amount of HPMC E5 gives lower amount of granules laying in the predetermined size range and higher amounts of HPMC E5 decrease the dissolution velocity of itraconazole. Hence here optimized concentration of 6% of HPMC E5 gives the highest amount of granules in predetermined size range, and 98.24% drug release within one hour with good shape and surface. So, 6% of HPMC E5 can be used in large scale production of itraconazole granules in future.

Conclusion

From these experimental findings, it is concluded that the optimum concentration of HPMC E5 (6%) provides better quality of granules. From this data, it is suggested that the batch SF-6 containing HPMC E5 120 g/2000 g (6% of the total weight of granules) has good quality of granules with acceptable physic-chemical criteria.

References


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