Formulation and Evaluation of Controlled Release Drug Delivery System

Pawan Kumar Battu, Amit Kumar Tiwari, Tribhuvan Singh and Naga Lasxmi*

Gurunanak Institutions Technical Campus, School of Pharmacy, Ibrahimpatnam, Telangana, India.

A B S T R A C T
In the present work, an attempt has been made to develop sustained release tablets of Itraconazole. Different gradess of Carbopol polymers used. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations, F4 formulation showed maximum % drug release i.e., 97.55 % in 8 hrs hence it is considered as optimized formulation. The F4 formulation contains Carbopol 934 in the concentration of 50 mg.

Keywords: Itraconazole, carbopol, controlled release.

A R T I C L E  I N F O

REFERENCES

1. Introduction
Itraconazole is a triazole antifungal agent prescribed to patients with fungal infections. The drug may be given orally or intravenously Itraconazole has a broader spectrum of activity than fluconazole (but not as broad as voriconazole or posaconazole). In particular, it is active against Aspergillus, which fluconazole is not. It is also licensed for use in blastomycosis, sporotrichosis, histoplasmosis, and onychomycosis. Itraconazole is over 99%
protein-bound and has virtually no penetration into cerebrospinal fluid. Therefore, it should never be used to treat meningitis or other central nervous system infections. According to the Johns Hopkins Abx Guide, it has "negligible CSF penetration, however treatment has been successful for cryptococcal and coccidioidal meningitis". It is also prescribed for systemic infections, such as aspergillosis, candidiasis, and cryptococcosis, where other antifungal drugs are inappropriate or ineffective. Itraconazole has also recently been explored as an anticancer agent for patients with basal cell carcinoma, non-small cell lung cancer, and prostate cancer. For example, in a phase II study involving men with advanced prostate cancer, high-dose itraconazole (600 mg/day) was associated with significant PSA responses and a delay in tumor progression. Itraconazole also showed activity in a phase II trial in men with non-small cell lung cancer when it was combined with the chemotherapy agent, pemetrexed.

**Oral Controlled Release Drug Delivery Systems**
A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release system
- Diffusion controlled release system
- Diffusion and dissolution systems
- Osmotically controlled release systems
- Gastroretentive drug delivery systems
- Electrically stimulated release devices
- Ion-exchange resins

**Dissolution Controlled Release Systems**
A drug with a slow dissolution rate will sustain release rate of the drug from the dosage form. Here the rate-limiting step is dissolution. This being true, sustained release preparation of drugs could be made by decreasing their rate of dissolution.

**Diffusion Controlled Release Systems**
In these systems, the release rate of drug is determined by its diffusion through a water insoluble polymer. There are basically two types of diffusion devices:

- **Reservoir devices:**
  Reservoir devices are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug. The methods used to develop reservoir type devices include micro-encapsulation of drug particles and coating of tablets containing drug cores.

- **Matrix Devices:**
  The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. The most common method of preparation is to mix the drug with the matrix material and then compress the mixture. The drug release from a porous or granular matrix can be described by

**Diffusion and Dissolution Controlled Systems**
In these systems the release rate of drug is determined by both the diffusion and dissolution mechanisms.

**Osmotically Controlled Release Systems**
The osmotic pump represents a newer concept in extended-release preparations. Drug delivery is controlled by the use of an osmotically controlled device that promotes a constant amount of water into the system, either by dissolving and releasing a constant amount of drug per unit time or by the use of a "push–pull" system that pushes the drug out at a constant rate as water flows into an expandable osmotic compartment. Drug is released via a single laser-drilled hole in the tablet.

**Gastro retentive Drug Delivery Systems**
Dosage forms that can be retained in stomach are called Gastro retentive Drug Delivery Systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.

**Bio-adhesive Systems**
Bio-adhesion is the process whereby synthetic and natural macromolecules adhere to the biological membranes in the body and remain there for an extended period of time. If the membrane substrate is mucosal layer then the process is referred to as muco-adhesion. The bio-adhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane.

**Swelling and Expanding Systems**
These systems increase the residence time of the dosage form in the stomach. Particles greater than 10 mm are unable to enter the duodenum and are retained in the stomach. The swelling systems incorporate hydrogels, which are polymers that can swell up to 100 times their dry weight. The hydrogels used must be biodegradable.

**High-density systems**
In High-density systems the bulk density of the dosage form must exceed that of normal stomach and should be at least 1.40. In preparing such formulations, drug can be coated on a core with heavy, inert materials such as barium sulfate and titanium dioxide. The weighed pellet can then be covered with a diffusion-controlled membrane.

**Low-density (Floating) systems**
Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. These systems are suitable for drugs that are poorly soluble or unstable in the intestinal medium.

**Electrically Stimulated Release Devices**
These are monolithic devices prepared by using polyelectrolyte gels which swell when an external electrical stimulus is applied, causing a change in pH. The release could be modulated, by the current, giving a pulsatile release profile. Precise control over the release of drug from devices implanted in the body, such as quantity, timing, is highly desirable in order to optimize drug therapy.
Electrically-controllable drug release from polyelectrolyte hydrogels is helpful in achieving these goals.

**Ion-Exchange Resins**

Ion exchange systems use resins composed of water insoluble cross linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

**2. Material and methods**

Itraconazole is a gift sample from Natco Pharma Ltd, carbopol 931(Merck Specialities Pvt Ltd, Mumbai, India), carbopol 934(Merck Specialities Pvt Ltd, Mumbai, India), carbopol 971(Merck Specialities Pvt Ltd, Mumbai, India), isopropyl alcohol(Universal Chemicals, Hyderabad, India).

**Experimental Procedure**

**Standard calibration curve for Itraconazole:**

**a) Determination of absorption maxima:**

A solution of Itraconazole containing the concentration 10 µg/ml was prepared in 0.1N HCl, 7.4 PH & phosphate buffer 6.8 PH respectively, UV spectrum was taken using Double beam UV-VIS spectrophotometer. The solution was scanned in the range of 200–400.

**b) Preparation calibration curve:**

**For Itraconazole:**

10 mg of Itraconazole drug was accurately weighed and dissolved in 10 ml of 0.1N HCl, 7.4 PH, and 6.8 PH in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution(2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4, 6, 8, 10, 12, 14, 16, 18 ,and 20 µg/ml with 0.1N HCl, 7.4 PH, and 6.8 PH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 270 nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

**Drug–excipient compatibility studies:**

**Fourier Transform Infra Red (FTIR) spectroscopy:**

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

**Preparation of blend for Itraconazole:**

The composition of the blend includes Itraconazole, Carbopol which were passed through sieve 80 individually and were mixed with already sieved Talc, Magnesium stearate, mcc in mortar and pestle and were subjected to different pre formulation parameters.

**Pre-formulation parameters:**

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

**Preparation of Itraconazole tablets:**

Each tablet (average weight 100 mg) for in vitro drug release studies consisted of Itraconazole, carbopol, Talc, Lactose and Magnesium stearate, Dicalcium phosphate. The materials were weighed, mixed and passed through a mesh no 60 to ensure complete mixing. The thoroughly mixed materials were then directly compressed into tablets using 12 mm round, flat punches on a tablet punching machine. Tablet quality control tests such as weight variation, hardness, friability, thickness, and dissolution in different media were performed on the tablets.

**Evaluation of Tablets**

The designed formulations of Itraconazole tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

**In-vitro drug release studies**

**Drug release studies of Itraconazole tablets:**

The tablets containing 100 mg Itraconazole of were tested in (pH 6.8), for their dissolution rates. Dissolution studies were performed using USP paddle type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 270 nm.

**Evaluation of Release Rate Kinetics**

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

**3. Results and Discussion**

**Analytical Method:** Graphs of Itraconazole was taken in Simulated Gastric fluid (pH 1.2) and Simulated Intestinal Fluid (pH 6.8 and 7.4)

**Graph of Itraconazole in 0.1N HCl (270nm)**

<table>
<thead>
<tr>
<th>Conc [mg/l]</th>
<th>Abs</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<td>8</td>
<td>0.681</td>
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<td>10</td>
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**Table 1: Observations for graph of Itraconazole in 0.1N HCl.**

<table>
<thead>
<tr>
<th>Conc [mg/l]</th>
<th>Abs</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>0.204</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>0.472</td>
</tr>
<tr>
<td>6</td>
<td>0.566</td>
</tr>
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</table>

**Table 2: Observations for graph of Itraconazole in 7.4 pH**
Itraconazole blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.52 to 0.581 and 0.606 to 0.671 respectively. According to Tables 3 and 4, the results of angle of repose and compressibility index (%) ranged from 32.74±0.12 to 37.08±0.96 and 13.37±0.38 to 14.72±0.62 respectively. The results of angle of repose and compressibility index indicates fair to passable flow properties of the powder mixture. These results show that the core powder mixture has good flow properties. The formulation blend was directly compressed to tablets and in-vitro drug release studies were performed.

**In-Vitro Drug Release Studies**

**Drug release studies of Itraconazole tablets**

The tablets containing 100 mg of Itraconazole were tested in 6.8 pH phosphate buffer solution for their dissolution rates. Dissolution studies were performed using USP dissolution apparatus 2, with 50rpm, at 37±0.5°C. At various time intervals, a sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at 255 nm.

**Figure 1:** Standard graph of Itraconazole in 0.1N HCl

**Figure 2:** Standard graph of Itraconazole in 7.4 pH

From the dissolution data it was evident that the formulations prepared with carbopol 971 as polymer were unable to retard the drug release up to desired time period i.e., 10 hours. Whereas the formulations prepared with Carbopol 931 retarded the drug release in the concentration of 10 mg showed required release pattern i.e., retarded the drug release up to 10 hours and showed maximum of 97.55% in 10 hours with good retardation. The formulations prepared with eudragitrspo showed more retardation even after 10 hours they were not shown total drug release. Hence, they were not considered.

**Figure 3:** Dissolution profile of Itraconazole (F1, F2, F3 formulations).

**Figure 4:** Dissolution profile of Itraconazole (F4, F5, F6 formulations).

**Figure 5:** Dissolution profile of Itraconazole (F7, F8, F9 formulations).

**Figure 6:** Zero order release kinetics graph
Application of Release Rate Kinetics to Dissolution Data:
Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

From the above graphs, it was evident that the formulation F4 was followed Zero order release kinetics.

In-vitro quality control parameters for tablets all the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 3: Composition of Itraconazole tablets

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Ingredients</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>
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<td>Drug</td>
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<td>100</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>2</td>
<td>Carbopol 931</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>3</td>
<td>Carbopol 934</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Carbopol 971</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>100</td>
<td>150</td>
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<td>5</td>
<td>MCC</td>
<td>QS</td>
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<td>QS</td>
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<td>QS</td>
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<td>QS</td>
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<tr>
<td>6</td>
<td>Magnesium stearate</td>
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<td>5</td>
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<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Talc</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Total Weight of tablet (mg)</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
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</table>

Table 4: Pre-compression parameters of itraconazole tablets

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<tr>
<th>Formulation Code</th>
<th>Angle of Repose (°)</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s Ratio</th>
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<tbody>
<tr>
<td>F1</td>
<td>36.01±0.62</td>
<td>0.55±0.27</td>
<td>0.645±0.13</td>
<td>14.72±0.62</td>
<td>0.85</td>
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<tr>
<td>F2</td>
<td>34.87±0.06</td>
<td>0.57±0.18</td>
<td>0.66±0.09</td>
<td>13.63±0.12</td>
<td>0.86</td>
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<tr>
<td>F3</td>
<td>32.74±0.12</td>
<td>0.53±0.22</td>
<td>0.606±0.04</td>
<td>14.19±0.26</td>
<td>0.858</td>
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<tr>
<td>F4</td>
<td>35.33±0.62</td>
<td>0.53±0.31</td>
<td>0.613±0.03</td>
<td>13.37±0.38</td>
<td>0.866</td>
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<tr>
<td>F5</td>
<td>36.24±0.05</td>
<td>0.549±0.14</td>
<td>0.641±0.17</td>
<td>14.35±0.54</td>
<td>0.856</td>
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<tr>
<td>F6</td>
<td>36.12±0.45</td>
<td>0.564±0.32</td>
<td>0.662±0.11</td>
<td>15.31±0.22</td>
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<tr>
<td>F7</td>
<td>35.01±0.64</td>
<td>0.57±0.22</td>
<td>0.65±0.12</td>
<td>14.71±0.67</td>
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<tr>
<td>F8</td>
<td>34.82±0.05</td>
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<td>0.61±0.06</td>
<td>13.66±0.17</td>
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<tr>
<td>F9</td>
<td>32.65±0.72</td>
<td>0.52±0.21</td>
<td>0.60±0.01</td>
<td>14.17±0.21</td>
<td>0.85</td>
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Table 5: Post compression parameters

<table>
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<tr>
<th>Formulation codes</th>
<th>Weight variation (mg)</th>
<th>Hardness (kg/cm2)</th>
<th>Friability (% loss)</th>
<th>Thickness (mm)</th>
<th>Drug content (%)</th>
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<tbody>
<tr>
<td>F1</td>
<td>291.5</td>
<td>4.5</td>
<td>0.50</td>
<td>3.8</td>
<td>99.76</td>
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<tr>
<td>F2</td>
<td>295.4</td>
<td>4.5</td>
<td>0.51</td>
<td>3.9</td>
<td>99.45</td>
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<tr>
<td>F3</td>
<td>298.6</td>
<td>4.4</td>
<td>0.51</td>
<td>3.9</td>
<td>99.34</td>
</tr>
</tbody>
</table>
4. Conclusion
In the present work, an attempt has been made to develop sustained release tablets of Itraconazole. Different grades of Carbopol polymers used. All the formulations were prepared by direct compression method using 6 mm punch on 8-station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations, F4 formulation showed maximum % drug release i.e., 97.55 % in 8 hrs hence it is considered as optimized formulation. The f4 formulation contains Carbopol 934 in the concentration of 50 mg.

5. Acknowledgement
We sincerely thank K.P labs (A DIVISION OF KDPL) for their cooperation and support throughout the project.

6. References