SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF ITRACONAZOLE BY SOLID DISPERSION TECHNIQUE

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Similarity factor.

ABSTRACT
Itraconazole, a potent antifungal drug, is a poorly water soluble drug and belongs to BCS class II. The objective of the research work was to formulate and optimize solid dispersions (SDs) of a poorly water soluble drug, itraconazole, with sodium starch glycollate, croscarmellose sodium, eudragit E-100 for the enhancement of the solubility and dissolution rate of the drug. Solid dispersions were prepared by solvent evaporation techniques in different weight ratios of polymers. The physical mixtures and solid dispersions were subjected to drug content and dissolution test. The dissolution was enhanced greatly in the itraconazole with croscarmellose sodium (1:7 ratio). The best formulation, itraconazole with croscarmellose sodium in 1:7 ratio, among all was further adsorbed on neusilin US2 in 1:1 ratio by milling for almost 10min to form ternary mixture. The tablet dosage form prepared from ternary mixture was stable at stressed conditions 40±2°C and 75±5% RH. The release kinetics of drug from formulation and marketed product follows first order release. The similar factor f2 was within limit for the product at stressed conditions with the product at room temperature at the same time. The increased dissolution rate was achieved by more than seven times and ten percent comparatively to the itraconazole API and marketed product respectively.

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INTRODUCTION

The Biopharmaceutics Classification System (BCS) is the scientific framework, given by amidon, classifies drug substances based on their aqueous solubility and intestinal permeability. Dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption\textsuperscript{[1-5]}. The molecules with 10mg/ml or lesser solubility in water over the pH 1 to pH 7 at 37°C exhibit the maximum bioavailability problems. Biopharmaceutical Classification System (BCS) Class II drugs (e.g. glipizide, nifedipine, itraconazole, aceclofenac etc.) are those with solubilities and dissolution rate too low to be consistent with complete absorption, even though they are highly membrane permeable. Maximum molecules developed today are with lesser aqueous solubility and required to improve the solubility and dissolution to get absorb. Various methods e.g., micronization, stabilization of high energy states, inclusion of surfactants, formulation as emulsion or microemulsion systems, salt formation, solvent deposition, ordered mixing, cyclodextrin complexation, solid dispersions etc. are available to increase the solubility and dissolution rate of the Class II drugs so that absorption and thus bioavailability of the formulation can be improved\textsuperscript{[6]}. The solid dispersion (SD) approach, to reduce particle size and therefore increase the dissolution rate and absorption of drugs, was first recognized in 1961. The solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier in a solid state\textsuperscript{[7]}. Itraconazole, (2R,4S)-rel-1-(butan-2-yl)-4-{4-[4-(4-[[2(R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy][phenyl]piperazin-1-yl][phenyl]-4,5-dihydro -1H-1,2,4-triazol-5-one), represented in figure 1, is a antifungals and antiprotozoals drug. Itraconazole is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in tertrahydrofuran and very slightly soluble in alcohol\textsuperscript{[8, 9]}. The aqueous solubility of itraconazole is reported as 1ng/ml at neutral pH, 1.8 µg/ml in pH 1.2 (simulated gastric fluid) and 4 µg/ml at pH 1\textsuperscript{[10]}. It is soluble in 1gm in 10,000ml water or 1000ml of alcohol, more soluble in aciduluted polyethylene glycols\textsuperscript{[11]}. Several approaches has been use to enhance the dissolution of itraconazole. The solid dispersion with poloxomer 188\textsuperscript{[12]}, HPMC\textsuperscript{[13]}, hydrophilic polymers\textsuperscript{[14]}, micronisation of drug by rapidly changing solvent\textsuperscript{[14]} and solid solutions with PEG\textsuperscript{[15]} were prepared for dissolution enhancement of itraconazole.

Figure 1: Chemical Structure of Itraconazole

Neusilin is a fine white powder or granule of magnesium aluminometasilicate manufactured by Fuji Chemical Industry. Compared to other common excipients in the silicate family, Neusilin’s superior physico-chemical properties can resolve formulation problems encountered with oily actives, improve the quality of tablets, powder flow, capsules and many more\textsuperscript{[16]}. The surface adsorption phenomenon of the neusilin to the solid dispersion has been proved\textsuperscript{[17-20]}. Although the solid dispersions has already been formulated to enhance the solubility and dissolution rate of itraconazole, further adsorption of solid dispersion on neusilin us2 may enhance the dissolution rate. Thus the aim of the present study was to improve the solubility and dissolution rate by forming surface solid dispersion or ternary mixture. The solid dispersion formed with excipients further adsorbed on neusilin us2 to form ternary mixture.

MATERIALS AND METHODS

Materials:

Itraconazole E.P. was obtained ex-gratis from Ranbaxy Ltd., Gurgaon, India. Sodium starch glycollate (SSG) and croscarmellose sodium (CCM) was obtained ex-gratis from Maple Biotech Pvt Ltd., Pune., Eudragit E-100, Neusilicne US2 were obtained ex gratis from Evonik Degussa India Pvt. Ltd. Mumbai and Gangwal Chemicals Pvt. Ltd. Mumbai India respectively. All other chemical and reagents were of analytical grade.

Drug Excipient Compatibility Studies:

Itraconazole and excipients (Sodium starch glycollate, Croscarmellose sodium, Eudragit E 100 and Neusilne US2), previously passed through sieve number 60, were taken in 1:1 ratio. Sealed capillary tube was used to mix the components in a glass vial (5 ml). The glass vials were protected from light by covering with aluminum foil. The samples were kept at 50°C for one month. FTIR spectra were taken for entire samples immediately after mixing and after one month storage at 50°C\textsuperscript{[21-23]}.

Standard Calibration Curve:

Accurately weighed (1mg) itraconazole was dissolved in 100ml Hydrochloric Acid Buffer pH 1.2. This stock solution (10µg/ml) was diluted with hydrochloric acid buffer pH 1.2 to prepare solutions of known concentrations, in duplicates, in the range of 2–10µg/ml. One of the prepared solutions was analyzed for maximum (λmax) absorbance in UV spectrophotometer. All the prepared solutions of known concentrations were analyzed for absorbance at λmax 260nm\textsuperscript{[26-28]}.
Preparation of Formulations

Physical mixtures:

Physical mixtures were prepared by blending in a glass mortar of accurately weighed quantities of itraconazole and carrier(s) for about 10 min in different ratio, mentioned in table 1, and stored in desiccators over fused calcium chloride after passing through sieve no.44.

Solid dispersion:

The required amount of drug and the carriers, as shown in table 1, were dissolved in sufficient volume of acetone with continuous stirring. The solvent was then completely evaporated with vacuum oven at 40°C to obtain dry mass. The dried mass was pulverized passed through 44 mesh sieve and stored in desiccators until used for further studies.

Table 1: Formulation batches of itraconazole

<table>
<thead>
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<td>PMT8</td>
<td>PMT12</td>
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<td>SDT10</td>
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<td></td>
<td>1:5</td>
<td>SDT3</td>
<td>SDT7</td>
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<td></td>
</tr>
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<td>8</td>
<td></td>
<td>1:7</td>
<td>SDT4</td>
<td>SDT8</td>
<td>SDT12</td>
<td></td>
</tr>
</tbody>
</table>

Drug content studies:

The drug content was calculated by dissolving itraconazole API, physical mixtures and solid dispersion of itraconazole equivalent to 5mg in a 100ml of methanol. The solution was filtered through 0.45µ filter membrane and assayed further by using UV double beam spectrophotometer at 260nm. Three replicates were prepared, and the average drug contents were estimated.

Determination of in vitro drug release:

The itraconazole API, marketed preparation, physical mixture and solid dispersion equivalent to 5mg of drug added in dissolution media. The dissolution study was carried out using USP apparatus type-II. The dissolution medium was 900ml hydrochloric acid buffer pH 1.2 kept at 37±0.5ºC. The paddle was rotated at 100 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed by spectrophotometer at 260nm. The samples withdrawn were replaced by fresh buffer solutions to maintain sink condition. Each preparation was tested in triplicate and then means values were calculated. The dissolution study was continued for 60min.

Formation of Ternary Mixture

The best preparation among the twenty four formulations was selected and further absorbed on Neusiline US2 in 1:1 ratio by milling for 10min in mortar pestle to prepare ternary mixture. The dried mass was passed through 44 mesh sieve and stored in desiccators until used for further studies.

Evaluation of Ternary Mixture

Percentage practical yield, drug content and in vitro drug release was determination.

Table 2: Composition of tablet of itraconazole from ternary mixture

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<th>Ingredient</th>
<th>Amount (mg)</th>
<th>Amount (%)</th>
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<tr>
<td>Ternary mix (Equivalent to 20mg of</td>
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<td>64</td>
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<td>Itraconazole)</td>
<td></td>
<td></td>
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<tr>
<td>Lactose Monohydrate</td>
<td>80</td>
<td>16</td>
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<tr>
<td>Micro Crystalline Cellulose</td>
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<td>Talc</td>
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<td>5</td>
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<td>Magnesium Stearate</td>
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<td>4</td>
</tr>
<tr>
<td>Total Weight</td>
<td>500</td>
<td>100</td>
</tr>
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</table>
Evaluation of powder blend
The prepared powder blend was evaluated for micromeritic characterizations.

Angle of repose:
Angle of repose determined by following equation: \[ \theta = \tan^{-1}\left(\frac{h}{r}\right) \]
Where, \( h \) = height of pile, \( r \) = radius of the pile base
Approximately 5 gm. of powder blend prepared for tablet is transferred into the funnel and powder emptied from the funnel making a pile whose radius and height is measured using a scale.\[36][44][45]\.

Bulk density:
The bulk density was calculated using equation: \[ \rho_b = \frac{M}{V} \]
Where, \( \rho_b \) = Bulk density, \( M \) = Mass of the powder blend in grams
\( V \) = Final untapped volume of powder blend in ml.

Tapped density:
The tapped density was calculated using equation: \[ \rho_t = \frac{M}{V_p} \]
Where, \( \rho_t \) = tapped density, \( M \) = Mass of powder blend in grams, \( V_p \) = Final tapped volume of powder blend in ml or cm\(^3\).

Hausner Ratio:
It is an indirect index of ease of powder flow. It is calculated from tapped and bulk density by using following formula\[44\].
\[ \text{Hausner Ratio (HR)} = \frac{\text{Tapped density}}{\text{Bulk density}} \]

Compressibility index:
The simplest way for measurement of flow of the powder is its compressibility, an indication of the ease with which a material can be induced to flow. It is expressed as compressibility index (CI). It is calculated from tapped and bulk density by using following formula. It is also known as carr’s compressibility index or carr’s index\[36][44][45]\.
\[ \text{Carr’s index} (\%) = \left(\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}\right) \times 100 \]

Tablet Formulation and Evaluation

Tablet Formulation
The accurately weighed quantity of the ingredients, passed through 44 mesh sieve, mentioned above in table 2 was taken. The ternary mixture for itraconazole was weighed for equivalent quantity of itraconazole to 20mg. All the ingredients were properly mixed. Finally talc and magnesium stearate were then added and again mixed for 5 minutes so that particle surface was coated by lubricant evenly. The resulting blend was compressed to form 500mg tablet by punches using 8mm round shaped dies to form round flat faced tablets\[36][37][43,44]\.

Tablet Evaluation:
The prepared tablets were evaluated for different pharmacopoeial and non pharmacopoeial test.

Evaluation of Release Kinetics of Tablet

Model Independent Parameters:
The dissolution efficiency and mean dissolution time is calculated.

Dissolution Efficiency (DE)
Dissolution efficiency (DE) represents the area under the dissolution curve at time \( t \) (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100 % dissolution in the same time. Dissolution efficiency was calculated at 60 minutes using the following formula.
\[ \text{D.E.}_{60} = \frac{0.5 \times \% \text{ drug release at 60 min}}{\text{Total } \% \text{ drug release}} \times 100 \]

Model Dependent Parameters
Data obtained from \textit{in vitro} release studies was fitted to various kinetics equations to find out the mechanism of release of drug from the formulation compared to the marketed preparation. The kinetics models used were Zero order, First order, Hixon croswell model, Higuchi and Peppas model.
Stability Testing

The stability testing is performed to confirm that whether the drug content or drug product varies with time under the effect of environmental factor such as temperature, humidity and light, and to establish a retest period for the drug substance or a self life for the drug product and recommended storage conditions. Twenty tablets of itraconazole were wrapped individually in aluminum foil and kept in the equipment for three months at 40±2°C and 75±5% Relative Humidity (RH). One set of tablet was kept at room temperature (RT) at the same time. The desired temperature and humidity was set. These tablets were examined for physical appearance and cumulative percent release[37][41][46, 47].

Evaluation after stability study

The product was evaluated after keeping the product at specified temperature and relative humidity. The product kept at accelerated temperature and humidity was compared with the product kept at the room temperature.

Physical Appearance:

The both the tablet products kept at different conditions were observed for the physical appearance.

Dissolution Test:

Three tablets were taken from the humidity cum stability chamber after three months and evaluated in vitro for release profile.

Dissolution profile comparison by determination of similarity factor f2 for product kept at stress condition and normal conditions:

Among several methods investigated for dissolution profile comparison, f2 is the simplest.

$$f_2 = 50 \cdot \log \left[ \frac{1}{1+n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{0.5} \cdot 100$$

where Rt and Tt are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. The factor f2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time-points. The factor f2 measures the closeness between the two profiles. Because of the nature of measurement, f2 was described as similarity factor. In dissolution profile comparisons, especially to assure similarity in product performance, regulatory interest is in knowing how similar the two curves are, and to have a measure which is more sensitive to large differences at any particular time point. For this reason, the f2 comparison has been the focus in FDA guidance document. When the two profiles are identical, f2=100. An average difference of 10% at all measured time points results in a f2 value of 50. FDA has set a public standard of f2 value between 50-100 to indicate similarity between two dissolution profiles.[48-52].

RESULTS AND DISCUSSION

Itraconazole Preformulation Studies

Drug-Excipient Compatibility Studies:

The FTIR spectra of itraconazole and excipients (Sodium starch glycillate, Croscarmellose, Eudragit E 100 and Neusilin US2) mixture at immediate and stress conditions show that there is stability and identity to the reference spectra. Characteristic peaks of itraconazole were not affected and prominently observed in FTIR spectra of itraconazole along with polymers. There was no physical change in drug and mixtures even after 30days, which indicates the absence of physical incompatibility as reported in figure 2 to figure 6.

![Figure 2: Comparative FT-IR of Itraconazole immediate and 30 days storage at 50°C](image-url)
Figure 3: Comparative FT-IR of Itraconazole and Sodium Starch Glycollate immediate and 30 days storage at 50°C.

Figure 4: Comparative FT-IR of Itraconazole and Croscarmellose sodium immediate and 30 days storage at 50°C

Figure 5: Comparative FT-IR of Itraconazole and Eudragit E 100 immediate and 30 days storage at 50°C
Figure 6: Comparative FT-IR of Itraconazole and Neusilin US2 immediate and 30 days storage at 50°C

Standard Calibration Curve:
The standard calibration curve were prepared and represented in figure 7 and figure 8.

Figure 7: Itraconazole UV scan in hydrochloric acid buffer pH 1.2

Figure 8: Itraconazole standard calibration curve in hydrochloric acid buffer pH 1.2 at λ.max 260nm

Preparation and Evaluation of Formulations
Preparation of formulations
Physical Mixtures:
Physical mixtures prepared were white in colour. The formulation were prepared and stored in glass vials.
Solid Dispersion:
Solid dispersions prepared by solvent evaporation method were white cloured and odourless. The formulations were stored in glass vials surrounded by aluminum foil in desiccators.

Evaluation of formulations
Drug Content:
The drug content calculated for all the formulations including itraconazole active pharmaceutical ingredient (API) and marketed preparation was between 98.06 ±0.011 to 100.39±0.010 which is within acceptable limit.

Dissolution study of itraconazole API, marketed product, physical mixtures and solid dispersions of itraconazole:
The comparative cumulative percentage release of pure itraconazole API, marketed product (MP), physical mixtures and solid dispersions is mentioned in table 3. The overall observations from the release data reveals that the croscarmellose sodium in ratio of seven times to the drug improves the release of the drug form the formulation comparatively greater than sodium starch glycocolate and Eudragit E100. The high swelling efficiency improves the release of the itraconazole from the formulation. Thus it was concluded that the SD8 formulation having itraconazole and croscarmellose sodium in 1:7 ratio, have greater percentage practical yield in solid dispersion and highest percentage release of the drug among all the formulations. The SDT8 formulation was selected on these bases for further formation of the ternary mixture with neusilin US2.

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<td>44.47</td>
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Formation of ternary mixture
The best preparation among the twenty four formulations i.e. SDT8 was absorbed on Neusiline US2 in 1:1 ratio by milling for 10min in mortar pestle to prepare ternary mixture.

Evaluation of ternary mixture
Physical Appearance:
The appearance of the ternary mixture was white.
In vitro drug release from the ternary mixture:

In vitro drug release of itraconazole from ternary mixture was further increased from the SDT8 formulation as shown in table 4 and figure 9. The increase in the drug release may be attributed to the characteristics of Neusilin. Neusilin US2 is amorphous, possesses very large specific surface area. This character emphasizes that the solid dispersion may adsorb on the surface of the neusilin US2 and dissolve rapidly. The presence of silanols on its surface makes it a potential proton donor as well as a proton acceptor. The formation of hydrogen bond was previously reported by Gupta et al. on co-grinding carboxylic acid containing drugs such as indomethacin, ketoprofen, nabroxen, and progesterone with Neusilin US2. The itraconazole good proton acceptor property with its amide group, which also make a possibility of formation of H-bonds between Neusilin and solid dispersion of itraconazole formulated with crosscarmellose. These features of Neusilin US2 allow formulators to explore solid dispersion technology to improve bioavailability and overcome problems associated with processing and stability of poorly water soluble drugs. The physical and chemical stability of the amorphous state of drug-neusilin US2 complexes is well documented. Neusilin US2 remains flowable even after absorbing moisture up to 250% of its weight[18][20].

Figure 9: Dissolution profile of formulation Ternary mixture and its comparison to pure itraconazole API, marketed product and SDT8

Table 4: Cumulative % Release of itraconazole from ternary mixture

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time (min)</th>
<th>First Batch</th>
<th>Second Batch</th>
<th>Third Batch</th>
<th>Average</th>
<th>Standard Deviation (SD)</th>
<th>Relative Standard Deviation (%RSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>7.58</td>
<td>7.10</td>
<td>7.26</td>
<td>7.31</td>
<td>±0.25</td>
<td>3.37</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>17.78</td>
<td>16.65</td>
<td>16.49</td>
<td>16.97</td>
<td>±0.70</td>
<td>4.15</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>34.16</td>
<td>33.02</td>
<td>33.18</td>
<td>33.45</td>
<td>±0.62</td>
<td>1.84</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>54.49</td>
<td>52.54</td>
<td>53.99</td>
<td>53.68</td>
<td>±1.01</td>
<td>1.89</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>65.89</td>
<td>65.38</td>
<td>66.04</td>
<td>65.77</td>
<td>±0.34</td>
<td>0.52</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>77.51</td>
<td>77.16</td>
<td>77.33</td>
<td>77.33</td>
<td>±0.18</td>
<td>0.23</td>
</tr>
</tbody>
</table>

DSC thermograph of Itraconazole API and Ternary Mixture

The DSC thermograph of the itraconazole API, shown in figure 10, resulted that there was a single sharp endothermic peak at 168.96°C with an onset from 166.01°C and ending at 171.08°C. The crystalline nature of the drug as reported shows the endothermic peak between 165°C-170°C, as it melts between the said temperatures. The calculated parameters of the melting transition of the itraconazole are also presented in figure 10. The DSC thermogram of the ternary mixture of the itraconazole, represented in figure 11, hardly produces a trend of reduced melting temperature (Tm) of the characteristic endothermic peak of itraconazole. The disappearance of the sharp characteristics peak indicates the transition of the crystalline form of the itraconazole to
the amorphous form. Further appearance of the broader peak at almost 70°C indicates formation of mesophase. This suggests that drug has been molecularly dispersed in the carrier.

**Figure 10: DSC Thermogram of Itraconazole API**

This is further proved fact that the solubility and dissolution rate is greater in the amorphous form of the drug than crystalline. Thus the thermogram of the ternary mixture formed, due to the absence of characteristic peak, reveals the conversion of the itraconazole from crystalline form to the amorphous form.

**Formation of powder blend**

The powder blend was formed for tableting of the ternary mixture in sufficient quantity.

**Evaluation of powder blend prepared**

The overall micromeritic characterization viz. angle of repose, bulk density, tapped density, hausner ration and carr’s index, were obtained in acceptable range and compiled in table 5. The powder blend now may be forward for tableting as the parameters obtained are favourable for flow and compression of the powder blend into tablet.

**Table 5: Compiled micromeritic properties of powder blend**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameter</th>
<th>Average Value</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Angle of Repose</td>
<td>26.66</td>
<td>±1.59</td>
</tr>
<tr>
<td>2</td>
<td>Bulk Density</td>
<td>0.690</td>
<td>±0.025</td>
</tr>
<tr>
<td>3</td>
<td>Tapped Density</td>
<td>0.808</td>
<td>±0.033</td>
</tr>
<tr>
<td>4</td>
<td>Hausner Ratio</td>
<td>1.170</td>
<td>±0.029</td>
</tr>
<tr>
<td>5</td>
<td>Carr’s Index</td>
<td>14.18</td>
<td>±2.00</td>
</tr>
</tbody>
</table>
Tablet Formulation and Evaluation

Tablet Formulation

The ternary mixture for itraconazole was weighed for equivalent quantity of itraconazole to 20mg. Tablet of weight 500mg was compressed. Weight of ingredients equivalent to twenty five tablets were weighed to prepare twenty tablets.

Tablet Evaluation

Following pharmacopoeial and non pharmacopoeial tests were performed for the 500mg tablet of tablet prepared from ternary mixture and shown in table 6.

Table 6: Evaluation of tablet from optimized formulation

<table>
<thead>
<tr>
<th>Weight Variation (mg)</th>
<th>Hardness (Kg.)</th>
<th>Friability (%)</th>
<th>Thickness (mm)</th>
<th>Disintegration Time (min.)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500.06±0.010</td>
<td>4±0.22</td>
<td>0.828%</td>
<td>7.84±0.20</td>
<td>7.02±0.24</td>
<td>98.67±0.27</td>
</tr>
</tbody>
</table>

General Appearance:

The appearance of the tablet, its identity & elegance is essential for consumer acceptance. The appearance of the tablet was round flat faced and white coloured.

Size and Shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled. The diameter was 8mm and round shaped tablet was prepared.

Weight Variation:

Twenty tablets were used for weight variation test as per IP 2007. Each tablet was weighed on the analytical balance and weight was recorded. Percent deviation from the average weight was estimated. All tablet formulations passed the weight variation tests as per Indian Pharmacopoeia (I.P.) 1996.

Tablet Crushing Strength /Hardness Test:

The crushing strength of the tablets was measured with Pfizer Hardness tester which applies compression force diametrically to the tablets. The force required to crush the tablet was recorded as hardness in Kg. Hardness was within the standard limits.

Friability Test:

This test is intended to determine the physical strength of tablets during shipping and packaging stress. Tablets are brushed to remove excess powder prior to their initial weight determination and after 100 revolutions (25 revolutions per minute for four minutes). Ten tablets were used for friability test. The weights of tablets were compared before and after 4 min test (100 rotations). The friability for tablets was less than 1% as required by I.P.

Thickness:

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Digital Vernier Calipers. It was determined by checking twenty tablets from formulation. The average thickness was 7.84mm with standard deviation of ±0.20. The diameter of the tablet was 8mm as the die and punches were of the similar size.

Disintegration Test:

Six tablets were used for the disintegration test. Each tablet was kept in different tube of the disintegration test apparatus and discs were kept inside the tubes. The disintegration medium used was hydrochloric acid buffer pH 1.2. at 37±2°C. All the tablets disintegrated quickly due to presence of large amount of crosscarmellose in the ternary mixture.

Drug Content:

The drug content in the tablet was determined in triplicate.

In Vitro Release Studies:

The drug releases from the tablets were evaluated by carrying out in vitro dissolution studies. The average drug release 76.58percent within 60min as mentioned in table 7 and figure 12.
Table 7: Average cumulative percentage release of itraconazole from the tablet

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time (min)</th>
<th>First Batch</th>
<th>Second Batch</th>
<th>Third Batch</th>
<th>Average</th>
<th>Standard Deviation (SD)</th>
<th>Relative Standard Deviation (%RSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>6.29</td>
<td>6.61</td>
<td>6.94</td>
<td>6.61</td>
<td>±0.323</td>
<td>4.878</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>16.64</td>
<td>16.48</td>
<td>17.62</td>
<td>16.91</td>
<td>±0.612</td>
<td>3.618</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>33.02</td>
<td>33.34</td>
<td>32.70</td>
<td>33.02</td>
<td>±0.319</td>
<td>0.966</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>53.67</td>
<td>54.64</td>
<td>55.77</td>
<td>54.69</td>
<td>±1.053</td>
<td>1.925</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>64.90</td>
<td>65.71</td>
<td>67.01</td>
<td>65.88</td>
<td>±1.066</td>
<td>1.618</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>76.35</td>
<td>77.17</td>
<td>76.22</td>
<td>76.58</td>
<td>±0.515</td>
<td>0.673</td>
</tr>
</tbody>
</table>

Figure 12: Dissolution profile of itraconazole tablet formulated, ternary mixture and its comparison to pure itraconazole API, marketed product and SDT8

Evaluation of Release Kinetics of Tablet

Model independent parameters:

When dissolution data was subjected to model independent parameters, tablet prepared by ternary mixture of SDT8 (optimized formulation) from conventional marketed product showed greater Mean Dissolution Time (MDT) and Percentage Dissolution Efficiency (%DE) within 60min as shown in table 8.

Table 8: Model independent parameters of optimized and marketed product

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulations</th>
<th>%DE (60min)</th>
<th>MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Optimized Tablet formulation</td>
<td>41.14</td>
<td>26.27</td>
</tr>
<tr>
<td>2</td>
<td>Marketed Product</td>
<td>36.58</td>
<td>25.33</td>
</tr>
</tbody>
</table>

Model dependent parameters:

In order to obtained meaningful information for release models, the drug release profiles were fitted to various kinetic models. Table 9 summarized the correlation coefficient for different release kinetic models of itraconazole optimized tablet and marketed formulation. Models with higher correlation coefficient were judged to be more appropriate model for dissolution data.

Model dependent parameters showed that correlation coefficient of optimized formulation was maximum for first order release kinetics compared to marketed formulation.
Table 9: Model dependent parameters of optimized and marketed tablet

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulations</th>
<th>Evaluation parameters</th>
<th>Zero order</th>
<th>First order</th>
<th>Matrix model</th>
<th>Peppas model</th>
<th>Hixon-crowell model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tablet from optimized</td>
<td>R</td>
<td>0.9664</td>
<td>0.9944</td>
<td>0.9607</td>
<td>0.9762</td>
<td>0.9886</td>
</tr>
<tr>
<td></td>
<td>formulation</td>
<td></td>
<td>1.2574</td>
<td>-0.0191</td>
<td>8.0994</td>
<td>1.5298</td>
<td>0.9693</td>
</tr>
<tr>
<td>2</td>
<td>Marketed formulation</td>
<td>R</td>
<td>0.9821</td>
<td>0.9912</td>
<td>0.9568</td>
<td>0.9907</td>
<td>0.9950</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1433</td>
<td>-0.0166</td>
<td>7.3088</td>
<td>1.4961</td>
<td>0.9424</td>
</tr>
</tbody>
</table>

Stability Studies

The tablets were packed in aluminum foil and kept in the equipment for three months at 40±2°C and 75±5% Relative Humidity (RH). One set of tablet was kept at room temperature (RT) at the same time.

Evaluation after stability study

Physical Appearance:

The tablets were examined for physical appearance. The physical appearance of the tablets was not affected during and after the studies.

Dissolution Test:

Three tablets were taken from the humidity cum stability chamber after three months and in vitro release studied. The cumulative % release obtained was 75.05% percent with standard deviation of ±0.48 as reported in Table 10.

Table 10: Average cumulative percentage release of itraconazole from tablets at stresses conditions

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time (min)</th>
<th>Cumulative % Release</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First Tablet</td>
<td>Second Tablet</td>
<td>Third Tablet</td>
<td>Average</td>
<td>Standard Deviation (SD)</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>5.48</td>
<td>5.32</td>
<td>5.81</td>
<td>5.54</td>
<td>±0.25</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>16.48</td>
<td>16.96</td>
<td>17.93</td>
<td>17.12</td>
<td>±0.74</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>32.21</td>
<td>31.24</td>
<td>31.73</td>
<td>31.73</td>
<td>±0.48</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>53.33</td>
<td>53.98</td>
<td>54.63</td>
<td>53.98</td>
<td>±0.65</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>63.92</td>
<td>63.60</td>
<td>64.42</td>
<td>63.98</td>
<td>±0.41</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>75.05</td>
<td>75.53</td>
<td>74.58</td>
<td>75.05</td>
<td>±0.48</td>
</tr>
</tbody>
</table>

Dissolution profile comparison by determination of similarity factor f2 for product kept at stress condition and normal conditions:

There was no significant variation in the in vitro drug release profile over a period of three months. The similarity factor (f2 value) was found 51.83 which is more than 50 indicates similarity between both the dissolution profiles. Thus the results of the stability studies confirmed that the developed formulation is stable.

CONCLUSION

It can be concluded that the physical mixture, solid dispersion of itraconazole can be prepared with sodium starch glycollate, croscarmellose sodium, Eudragit E-100. The solid dispersions prepared can further be converted into ternary mixture and formulated in tablet dosage form. The model drug, itraconazole, with croscarmellose sodium in 1:7 ratio have excellent solubility and dissolution rate from the formulations. The ternary mixture with addition of certain excipients further compressed into tablet dosage form. The ternary mixture containing croscarmellose sodium and neusilin US2 have greater solubility and dissolution rate comparatively to the existing marketed product. Thus this approach of adsorption of solid dispersion on neusiline us2 to enhance the dissolution may be used. Further development in the best formulation and at large scale are to be proven.

ACKNOWLEDGMENT

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