Formulation and evaluation of orodispersible tablet of Risperidone

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ABSTRACT

The present study was aimed towards the formulation and in vitro evaluation of orodispersible tablets by direct compression method using Risperidone as a model drug to enhance patient compliance. Orodispersible tablet of Risperidone was prepared by masking the bitter taste by cetyl alcohol using different ratios of drug with cetyl alcohol (2:1). Here crosspovidone and sodium starch glycolate in different concentrations (2%, 4%, 6% and 8%) are used as superdisintegrant. All the batches were prepared by direct compression method. Prepared tablets were evaluated for weight variation, hardness, friability, in vitro disintegration time, in vivo disintegration time, dispersion time, thickness, drug content and dissolution study. By considering disintegration time and concentration of superdisintegrant, formulation with drug to cetyl alcohol concentration (2:1) and crosspovidone 4% was optimised. Optimised tablet formulation was subjected to stability studies for three months at room temperature and 40°C/75% RH.

Key words: Orodispersible tablet; crosspovidone; sodium starch glycolate; cetyl alcohol, Risperidone.

INTRODUCTION

The concept of orodispersible tablet emerged from the desire to provide the patient with more conventional means of taking their medication. The most important dosage form for oral delivery are tablets and capsules, however, one important drawback of these dosage form is difficult to swallow. Moreover, swallowing problem problem is associated with young individuals because of their under developed muscular and nervous systems. Further, mentally ill, developmental disability and uncooprative patients and patients with reduced liquid intake plans or nausea may experience problem in swallowing. In some cases such as motion sickness, sudden episode of allergic attack or coughing and non availability of water, swallowing tablet may become difficult. To fulfil all these needs, the concept of melt in mouth or orodispersible tablet has been
developed, a tablet that disintegrates in saliva, without need of drinking water within 15 to 60 seconds and which offers fast absorption and onset of action.  

The present investigation deals with ‘Risperidone’ a benzisoxazole derivative psychotropic agent which is lipophilic in nature, practically insoluble in water and exhibits a pH dependent solubility. It is soluble in 0.1 N HCl, slightly soluble at pH 4.0 and sparingly soluble at pH 7.0-10.0. It is a potent drug used frequently in the treatment of schizophrenia and bipolar mania.  

On the basis of these considerations, in the present study it was proposed to formulate an oral delivery device, in the form of orodispersible tablet, using direct compression technology. In this study efforts has been made to formulate ODT by masking the bitter taste of Risperidone by cetyl alcohol and using crosspovidone and ssg as superdisintegrant. Then all parameters are evaluated.

MATERIALS AND METHODS

Risperidone was gift sample from Alkame Laboratories, Mumbai. Crospovidone, sodium starch glycolate, mannitol, cetyl alcohol and aspartame were obtained as a gift sample from Themis Laboratories, Mumbai. All the other chemicals used were of analytical reagent grade.

i) Preparation of complex of Risperidone with cetyl alcohol
Risperidone was granulated with cetyl alcohol by melting it in drug to wax ratio 3:1 and 2:1. The congealed mass was sieved through 40 mesh.

(ii) Preparation of tablets containing a complex of Risperidone and cetyl alcohol
Tablet containing 1 mg of risperidone was prepared by direct compression method. Drug – cetyl alcohol complex equivalent to 1 mg was taken and pass through the # 40. Diluents, superdisintegrants, sweetener and flavor were passed through # 40. All above ingredients were mixed and blended properly. Magnesium stearate was passed through # 40 and mixed properly with above blend. Powdered lubricated blend was compressed into tablet by 10 station tablet compression machine using 6 mm flat punches.

Table 1 Formulation of Respiridone Tablets

<table>
<thead>
<tr>
<th>Sr.no.</th>
<th>Ingradients</th>
<th>1a</th>
<th>2a</th>
<th>3a</th>
<th>4a</th>
<th>1b</th>
<th>2b</th>
<th>3b</th>
<th>4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Risperidone</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Cetyl alcohol</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>Crosspovidone</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Sodium starch glycolate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Aspartame</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Menthol</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Aerosil</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Magnesium stearate</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Mannitol</td>
<td>91.5</td>
<td>89.5</td>
<td>87.5</td>
<td>85.5</td>
<td>91.5</td>
<td>89.5</td>
<td>87.5</td>
<td>85.5</td>
</tr>
<tr>
<td>10</td>
<td>Total weight</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Evaluation parameters of risperidone orodispersible tablets

(i) Weight Variation
Twenty tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet was determined from the collective weight.

(ii) Hardness and Friability
Hardness is the tensile strength of tablets expressed in kg/cm², which was determined using Monsanto Hardness Tester. Preweighed sample of tablets was placed in the friabilator (Roche friabilator), and operated for 100 revolutions. Tablets were dusted and reweighed. The test complies if tablets not loose more than 1% of their weight.

(iii) Dispersion time
In vitro dispersion time was measured by dropping tablets in a measuring cylinder containing 0.1N HCl. Three tablets from each formulation were randomly selected and invtro dispersion time was performed.

(iv) Disintegration Time
Disintegration time for ODT was determined using USP disintegration apparatus using 0.1N HCl, 900 ml at 37°C) as the disintegrating medium. To comply the test all tablets should disintegrate within 60 sec as per new USFDA guidelines.

(v) Content Uniformity
Ten tablets were weighed and powdered, 1 mg equivalent of risperidone weighed and dissolved in suitable quantity of 0.1N HCl. Solution was filtered, diluted and analyzed for drug content.

(vi) In vitro Drug Release
In vitro dissolution study was performed in 500 ml 0.1N HCl using USP type II (paddle) apparatus at 75 rpm for 25 minutes (37 ± 0.5°C). Aliquots of the dissolution medium (10 ml) were withdrawn at specific time interval (5, 10, 15, 20, and 25 min) and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 mm membrane filter disc and analyzed for drug content by measuring the absorbance at 238 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved.

(vii) Stability study
Optimized ODT Batch was packed in 30 cc HDPE bottles, sealed and kept at 40 °C and 75% relative humidity in stablity chamber for a period of 3 months as per ICH guidelines. Samples withdrawn at 1, 2 and 3 months were analysed for drug content, hardness, disintegration time and dissolution test.

RESULTS AND DISCUSSION
Cetyl alcohol was chosen for the taste masking of the risperidone. Drug cetyl alcohol complex (Taste masked complex) were prepared in the ratio of 3:1 and 2:1. DCC in the ratio of 2:1 gave

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the best result. Eight formulations RCcp1 to RCssg4 were prepared using various excipients and crosspovidone and sodium starch glycolate as a superdisintegrant in different concentrations. ODT were prepared by direct compression and evaluated for hardness, weight variation, friability, content uniformity, dispersion time and disintegration time. The % drug content was found in the range of 98.6% to 101.4% which shows good content uniformity. Dispersion time was found in the range of 16.33 to 30.33 s. Hardness was found between 2.9 to 3.8 kg/cm2 which indicate good mechanical strength. Friability was found below 1% indicating good resistance against mechanical shear. (Table 2)

Table 2 Post-compression parameters

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness</th>
<th>Friability</th>
<th>Drug content</th>
<th>Dispersion time</th>
<th>Disintegration time</th>
<th>Weight variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCcp1</td>
<td>3.6 ± 0.28</td>
<td>0.57</td>
<td>98.8</td>
<td>24.66</td>
<td>30</td>
<td>99.33</td>
</tr>
<tr>
<td>RCcp2</td>
<td>3.3 ± 0.57</td>
<td>0.58</td>
<td>100.3</td>
<td>16.66</td>
<td>14</td>
<td>101.33</td>
</tr>
<tr>
<td>RCcp3</td>
<td>3.3 ± 0.57</td>
<td>0.63</td>
<td>100.1</td>
<td>18.33</td>
<td>14.33</td>
<td>100.66</td>
</tr>
<tr>
<td>RCcp4</td>
<td>3.8 ± 0.28</td>
<td>0.59</td>
<td>100.7</td>
<td>16.66</td>
<td>14.66</td>
<td>99.33</td>
</tr>
<tr>
<td>RCssg1</td>
<td>2.9 ± 0.28</td>
<td>0.54</td>
<td>98.6</td>
<td>30.33</td>
<td>22.66</td>
<td>99.66</td>
</tr>
<tr>
<td>RCssg2</td>
<td>3.3 ± 0.28</td>
<td>0.65</td>
<td>99.9</td>
<td>20.33</td>
<td>16</td>
<td>102</td>
</tr>
<tr>
<td>RCssg3</td>
<td>3.8 ± 0.28</td>
<td>0.62</td>
<td>101.2</td>
<td>18.66</td>
<td>15.66</td>
<td>100.33</td>
</tr>
<tr>
<td>RCssg4</td>
<td>3.3 ± 0.57</td>
<td>0.58</td>
<td>101.4</td>
<td>16.33</td>
<td>15.33</td>
<td>101.66</td>
</tr>
</tbody>
</table>

Dissolution profile of Risperidone (RCcp1 to RCcp4)

Optimization of Formula
From the above tables and graphs of all formulations it was found that the Formulations RCcp2 containing Risperidone : cetyl alcohol (2:1) and crosspovidone 4% shows the fast disintegration & more drug release, also contains less concentration of crosspovidone. So as compared to other formulations this formulation is optimized for further studies.

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The Stability study for all formulation according to ICH guidelines at 40°C/75%RH showed that formulations are stable after 3 months as there is no significant change in the hardness, disintegration time and drug content (Table 3).

### Table 3 Stability data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ROOM TEMP</th>
<th></th>
<th></th>
<th>40°C/75%RH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1M</td>
<td>2M</td>
<td>3M</td>
<td>1M</td>
<td>2M</td>
</tr>
<tr>
<td>Hardness</td>
<td>3.2</td>
<td>3.1</td>
<td>3.0</td>
<td>3.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Friability</td>
<td>0.59</td>
<td>0.62</td>
<td>0.64</td>
<td>0.65</td>
<td>0.67</td>
</tr>
<tr>
<td>D.T. (sec)</td>
<td>16.6</td>
<td>18.6</td>
<td>19.3</td>
<td>15.6</td>
<td>14.3</td>
</tr>
<tr>
<td>Drug Content (%)</td>
<td>100.1</td>
<td>99.8</td>
<td>99.2</td>
<td>100</td>
<td>99.3</td>
</tr>
</tbody>
</table>

### CONCLUSION

One of the problems encountered in the preparation of ODTs of Risperidone was the bitter taste of the drug. Results suggested that by complexing drug with Cetyl alcohol in 2 : 1 ratios masked the bitter taste of drug. Overall results suggested that RCcp2 formulation containing crosspovidone in 4% concentration was better and satisfy all the criteria of ODTs.

### REFERENCES