DESIGN, DEVELOPMENT AND EVALUATION OF RAPIDLY DISSOLVING ORAL STRIPS OF HALOPERIDOL

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ABSTRACT

An attempt was made to design and evaluate Rapidly dissolving oral strips of Haloperidol which is an Anti-psychotic agent. Fast dissolving drug delivery system offers a solution for those patients facing problem in swallowing of solid dosage forms such as Pills, Tablets & Capsules etc. Pure Haloperidol Drug has less water solubility which is improved by using Beta-cyclodextrin complexation which was proved by phase solubility study. The Rapidly dissolving strips were prepared by solvent casting technique by using HPMC 5cps, Sodium CMC and PVA as the film forming polymers. The prepared strips were evaluated for the thickness, folding endurance study, surface pH, drug content and in-vitro disintegration and in-vitro dissolution studies. All the formulations fulfilled criteria for evaluating parameters. Drug content of formulations was found to be 89% to 98 %, disintegration time in the range of 17-29s, in vitro dissolution studies showed 76.86% to 98.53%. Hence it was concluded from the results obtained that, the Rapidly dissolving oral strips of Haloperidol can be successfully developed in order to enhance the dissolution rate, thereby better patient compliance and effective therapy.

Keywords: Fast dissolving oral strips; Rapidly dissolving oral strips; Haloperidol
Introduction:

Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. Many pharmaceutical firms have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of the lamina propria and submucosa by an undulating basement membrane. It is interesting to note that the permeability of the buccal mucosa is greater than that of the skin, but less than that of the intestine. Hence the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration. However, the primary barrier to permeability in the oral mucosa is the result of intercellular material derived from the so-called ‘membrane coating granules’ present at the uppermost 200 micron layer.

To make the ease of administration and swallowing, pharmaceutical research has led to the develop the Oral Disintegrating Tablets (ODTs). ODTs have been defined as “A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”. United States Food and Drug Administration further defines ODTs as solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30s or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative. Also, Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/capsules/Pills to modified release tablets/capsules/Pills to oral disintegrating tablet (ODT) to wafer to the recent development of oral strip (OS). Basically the OS can be considered as an ultra-thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other excipient. The advantages of convenience of dosing and portability of OS have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

Materials and Method :-

1) Material :-
Haloperidol obtained from Life sciences Ltd. Mumbai. Beta-cyclodextrin obtained from Yarrow Chem Products, Mumbai, India.
Hydroxy Propyl Methyl Cellulose (HPMC), Poly vinyl Alcohol (PVA) & Sodium CMC Were obtained from Loba chemicals Ltd.

Preparation of Phosphate buffer pH 6.8 :
It was prepared by placing 250 ml of potassium di-hydrogen orthophosphate solution and 112 ml of 0.2 M NaOH solution and volume was make up to 1000 ml with distilled water. the pH of buffer solution was found to be 6.8
Method Of Preparation Of Rapidly Dissolving Strips :-

One or more of the following process can be used combinely to manufacture the mouth dissolving films.

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

Solvent casting method

In solvent casting method excipient are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried.

Formulation of rapidly dissolving strips of Haloperidol :

1) Solvent casting technique:

The strips were prepared by using polymers HPMC 5cps, Sodium CMC, PVA and Glycerine was used as a plasticizer. The calculated amount of polymer was dispersed in three forth volume of Haloperidol with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. Calculated amount of Haloperidol was incorporated in the polymeric solution after levigation with the required volume of Glycerine. The solution was casted and kept in hot air oven at 37°C strips of various formulations are mentioned in table. By carrying out the trial and error method different concentrations of strips forming polymers were used like HPMC, Sodium CMC & PVA. Concentrations of strips were prepared by dissolving different quantities of film forming polymers in 10 ml of water.

Analytical Methods :-

1) Identification of Drug :

- Description:
  The sample of Haloperidol was analysed for physical appearance, powder nature and from COA (Certificate of analysis) of the drug.

  Melting point
  Melting point of the pure drug was determined by using melting point apparatus. The thermometer used was previously calibrated. The method consists of placing the powdered compound in a calibrated tube
and heated in Thiele apparatus. The temperature at which sample start melting is considered as lower limit and at which completely melt is considered as upper limit of melting range. The obtained result compared with the values in literatures.

2) Calibration curve for the estimation of Haloperidol\textsuperscript{59} :-

50 mg of Haloperidol was weighed and dissolved in 50 ml of phosphate buffer (pH 6.8) in a volumetric flask (stock solution I), 2 ml was taken and the made up to 100 ml with phosphate buffer (pH 6.8) (stock solution II). From Stock solution II, serial dilutions were made to make series of 2, 4, 6, 8, 10, µg/ml solution and UV Absorbance was noted at 242.2 nm, using phosphate buffer (pH 6.8) as blank.

- Compatibility of drug with excipients\textsuperscript{60,61} -

1) FTIR Spectroscopy:
IR spectra of pure drug and mixture of drug and excipients were taken to check the compatibility of drug with excipients. IR Spectra were taken from 600-4000 cm\textsuperscript{-1}.

2) Differential Scanning Calorimetry:
From thermal analysis techniques, particularly Differential Scanning Calorimetry (DSC), when critically examined has been found useful in rapid screening for possible drug-additive and drug-drug interactions. Thermal analysis can be used to investigate and predict any physico-chemical interactions between components in a formulation and can therefore be applied to the selection of suitable chemically compatible excipients. An interaction on DSC will show as changes in melting point, peak shape and area and/or the appearance of a transition.

3) Phase Solubility Studies\textsuperscript{62}

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Haloperidol was added to 15 ml portions of 6.8 pH buffer medium each containing variable amount of β-CD in 0, 2, 4, 6, 8,10 x 10\textsuperscript{-3} moles/liter. All the above solutions with variable amount of β -CD were shaken for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 242.2 nm. The solubility of the Haloperidol in every β –CD solution was calculated and phase solubility diagram was drawn between the solubility of Haloperidol and different concentrations of β –CD as shown in fig.7

- Formulation of rapidly dissolving strips of Haloperidol:

Solvent casting technique:

The strips were prepared by using polymers HPMC 5cps,Sodium CMC,PVA and Glycerine was used as a plasticizer (in table no 4). The calculated amount of polymer was dispersed in three forth volume of Haloperidol
with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. Calculated amount of Haloperidol was incorporated in the polymeric solution after levigation with the required volume of Glycerine. The solution was casted and kept in hot air oven at 37˚c strips of various formulations are mentioned in table. By carrying out the trial and error method different concentrations of strips forming polymers were used like HPMC, Sodium CMC & PVA. Concentrations of strips were prepared by dissolving different quantities of film forming polymers in 10 ml of water.

**Evaluation Of Strips**

Prepared fast dissolving strips were evaluated for the following parameters.

a) Physical appearance and surface texture

b) Weight uniformity of strips

c) Thickness of strips

d) Folding endurance of strips

e) Surface pH

f) *In vitro* disintegration time

g) Drug content uniformity

h) *In vitro* drug release

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**a) Physical appearance and surface texture**

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

**b) Weight uniformity of strips**

Three strips in a formulation batch were weighed individually using digital balance and average weights were calculated.

**c) Thickness of strips**

Thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the strips and average was taken.

**d) Folding endurance of strips**

The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking was considered as folding endurance value.
e) **Surface pH**

The film to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 1 hr. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition.

f) **In-vitro disintegration time**

Disintegration test was performed by placing the strip in the glass petri dish containing 20 ml of water. It was stirred at every 10 second time interval. The time required for the strip to disintegrate was recorded.

g) **Drug content uniformity**

Weight equivalent to 5 mg was taken and transferred to 100 ml of 6.8 pH phosphate buffer in volumetric flask. The volume was made with 100ml pH phosphate buffer, the solution was filtered through Whatman filter paper and absorbance was measured at 242.2 nm by using UV Spectrophotometer.

h) **In-vitro drug release study**

*In-vitro* dissolution was performed by using the following conditions:

- USP-II apparatus
- Rotation speed- 50 rpm
- Temperature- 37 ± 0.5°C
- Media – pH 6.8 phosphate buffer
- Media volume- 900 ml
- Sample withdrawal- 5ml
- The sample was filtered and absorbance was measured at 242.2 nm.
- An equivalent volume of phosphate buffer was replaced with fresh buffer into the dissolution bath, to maintain the constant dissolution medium.

4.6.1 Stability studies:

**Introduction:**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-life.

Stability studies were carried out at 40°C/75% RH for the selected formulation for the period of 30 days. Samples were taken after 30 days & strips were evaluated for surface PH, drug content study, *In-vitro* disintegration time, *In-vitro* drug release study.
Results and Discussion :

1) Calibration Curve of Haloperidol :

The UV Spectrum of drug in the range of 200-400 nm on UV Spectrophotometer revealed that $\lambda_{\text{max}}$ of Haloperidol was at 245 nm. From the plot of absorbance vs Concentration of pure Haloperidol, it was observed that the drug obeys beer’s-lambert’s law in the concentration

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Vol. Made up to (ml)</th>
<th>Conc. (μg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>2</td>
<td>0.097</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>4</td>
<td>0.168</td>
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<td>4</td>
<td>10</td>
<td>6</td>
<td>0.250</td>
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<td>5</td>
<td>10</td>
<td>8</td>
<td>0.360</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>10</td>
<td>0.434</td>
</tr>
</tbody>
</table>

Table No. 1 : Calibration Curve of Haloperidol
2) **Differential Scanning Calorimeter Study** :-

![DSC Curves](image.png)

**Figure No. 2 - Differential Scanning Calorimetry Curves**

3) **Phase Solubility Study of Haloperidol** :-

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Haloperidol (200 mg) was added in 15 ml of portions of distilled water, each containing variable amount of β-CD in 0, 2, 4, 6, 8, 10 X 10^{-3} moles/litre. All the above solutions with variable amount of β-CD were shaken for 72 hr. After shaking, the solutions were filtered and their absorbance were noted at 245 nm. The solubility of the Haloperidol in every β-CD solution was calculated and phase solubility diagram was drawn between the solubility of Haloperidol and different concentrations of β-CD.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Concentration of Beta-cyclodextrin (mM)</th>
<th>Concentration of Haloperidol (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.56</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1.00</td>
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<tr>
<td>3</td>
<td>4</td>
<td>1.50</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>1.97</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>2.45</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>2.95</td>
</tr>
</tbody>
</table>

**Table No. 2 - Phase Solubility Study**
Figure No. 3 - Phase Solubility Study Curve

4) Folding Endurance Test :-

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Folding Endurance (times to break)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>200.66±30.53</td>
</tr>
<tr>
<td>F2</td>
<td>241.33±09.01</td>
</tr>
<tr>
<td>F3</td>
<td>233.66±27.53</td>
</tr>
<tr>
<td>F4</td>
<td>247.00±17.77</td>
</tr>
<tr>
<td>F5</td>
<td>282.33±09.45</td>
</tr>
<tr>
<td>F6</td>
<td>227.66±12.50</td>
</tr>
<tr>
<td>F7</td>
<td>255.00±12.30</td>
</tr>
<tr>
<td>F8</td>
<td>234.00±12.50</td>
</tr>
<tr>
<td>F9</td>
<td>250.34±10.25</td>
</tr>
<tr>
<td>F10</td>
<td>270.50±11.45</td>
</tr>
<tr>
<td>F11</td>
<td>246.24±10.32</td>
</tr>
</tbody>
</table>

Table No. 3 . Folding endurance of fast dissolving Oral Strips of Haloperidol
5) Surface pH, Disintegration Time & Percent Drug Content :-

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Surface pH</th>
<th>Disintegration time (sec)</th>
<th>Drug Content %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.03</td>
<td>28.64</td>
<td>95.73±0.745</td>
</tr>
<tr>
<td>F2</td>
<td>7.10</td>
<td>25.33</td>
<td>89.12±0.432</td>
</tr>
<tr>
<td>F3</td>
<td>7.06</td>
<td>19.66</td>
<td>98.45±0.206</td>
</tr>
<tr>
<td>F4</td>
<td>7.01</td>
<td>22.64</td>
<td>96.83±0.257</td>
</tr>
<tr>
<td>F5</td>
<td>6.87</td>
<td>19.00</td>
<td>96.00±0.296</td>
</tr>
<tr>
<td>F6</td>
<td>6.92</td>
<td>17.66</td>
<td>98.30±0.605</td>
</tr>
<tr>
<td>F7</td>
<td>7.04</td>
<td>18.27</td>
<td>94.56±0.297</td>
</tr>
<tr>
<td>F8</td>
<td>6.60</td>
<td>20.22</td>
<td>97.63±0.745</td>
</tr>
<tr>
<td>F9</td>
<td>7.00</td>
<td>24.23</td>
<td>92.32±0.296</td>
</tr>
<tr>
<td>F10</td>
<td>6.90</td>
<td>21.21</td>
<td>95.21±0.432</td>
</tr>
<tr>
<td>F11</td>
<td>6.80</td>
<td>19.90</td>
<td>94.24±0.257</td>
</tr>
</tbody>
</table>

Table No. 4 - Surface pH, Disintegration time and Drug Content of Rapidly dissolving Oral Strips of Haloperidol.
6) Dissolution study :-

![Dissolution Profile Of Formulation F1-F11](image)

Figure No. 5 - Dissolution profile of Rapidly Dissolving oral strips of Haloperidol

7) Percent Drug Release :-

<table>
<thead>
<tr>
<th>Time</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>
<th>F10</th>
<th>F11</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>18.00</td>
<td>18.00</td>
<td>19.00</td>
<td>15.00</td>
<td>18.00</td>
<td>23.00</td>
<td>15.00</td>
<td>23.00</td>
<td>24.00</td>
<td>21.00</td>
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<tr>
<td>100</td>
<td>27.01</td>
<td>38.1</td>
<td>30.01</td>
<td>32.08</td>
<td>29.01</td>
<td>28.12</td>
<td>18.08</td>
<td>28.12</td>
<td>28.13</td>
<td>37.11</td>
<td>29.11</td>
</tr>
<tr>
<td>150</td>
<td>42.15</td>
<td>42.31</td>
<td>46.17</td>
<td>42.25</td>
<td>35.26</td>
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<tr>
<td>200</td>
<td>60.38</td>
<td>61.54</td>
<td>71.32</td>
<td>63.48</td>
<td>42.45</td>
<td>43.45</td>
<td>43.34</td>
<td>42.45</td>
<td>42.36</td>
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<td>250</td>
<td>79.71</td>
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<td>64.68</td>
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<td>75.70</td>
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<tr>
<td>300</td>
<td>82.14</td>
<td>79.28</td>
<td>82.15</td>
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<td>71.03</td>
<td>74.04</td>
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<td>72.95</td>
<td>83.35</td>
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<tr>
<td>350</td>
<td>81.59</td>
<td>82.71</td>
<td>85.6</td>
<td>85.72</td>
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<td>76.44</td>
<td>83.33</td>
<td>74.43</td>
<td>74.34</td>
<td>86.80</td>
<td>74.4</td>
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<td>400</td>
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<td>86.16</td>
<td>87.06</td>
<td>87.18</td>
<td>76.45</td>
<td>80.85</td>
<td>85.78</td>
<td>75.80</td>
<td>76.83</td>
<td>91.26</td>
<td>79.87</td>
</tr>
<tr>
<td>450</td>
<td>91.50</td>
<td>88.69</td>
<td>97.52</td>
<td>88.64</td>
<td>76.86</td>
<td>84.28</td>
<td>86.24</td>
<td>77.21</td>
<td>80.24</td>
<td>98.27</td>
<td>84.03</td>
</tr>
</tbody>
</table>

Table No. 5 - Drug Release Percentage Values

8) Scanning Electron Microscope (SEM) Photograph :-

![ SEM Photograph ](image)
9) Stability Test of F4 & F10 formulation :-

The selected formulations were based on disintegration time & % drug release evaluated for stability studies which were stored at 40°C at 75% RH tested for 30 days and were analysed for their physical parameters, disintegration time, % drug content & % drug release at the end and the results were shown in Table. No. 6
Among the oral drug delivery systems, The oral strip formulations gives a solution to the patients who facing swallowing difficulties for administration of pills, tablets & such type of formulations. Hence, On the basis of study carried out & their results obtained it can be concluded that, The fast dissolving strips of haloperidol with swellable polymer like HPMC, Sod. CMC & PVA could developed successfully by solvent casting technique with respect to enhance the dissolution rate. There by a better patient compliance can be achieved for better hypertension therapy.

**Table No. 6 - Stability data of F4 & F10 formulation**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Physical appearance</th>
<th>Disintegration time (Sec)</th>
<th>% drug content</th>
<th>% drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F4</td>
<td>F10</td>
<td>F4</td>
<td>F10</td>
</tr>
<tr>
<td>1st Day</td>
<td>++</td>
<td>+++</td>
<td>21.21</td>
<td>21.21</td>
</tr>
<tr>
<td>30th Day</td>
<td>++</td>
<td>+++</td>
<td>21.16</td>
<td>21.18</td>
</tr>
</tbody>
</table>

++ indicates good, +++ indicates excellent

## Conclusion

Among the oral drug delivery systems, The oral strip formulations gives a solution to the patients who facing swallowing difficulties for administration of pills, tablets & such type of formulations.

References -

8. Mucoadhesive drug delivery systems; A Review.


34. Londhe VY, Umalikar KB. Formulation development and Eval fast dissol film of Telmisartan Indian J Pharm Sci 2012.


47. Swamy NG, Shiv kumar S; Formulation and Evaluation of fast dissolving oral films Palonosetron hydrochloride; Int J Pharm Chem Res; Res Article 2014, 3 (1).
60. Indian pharmacopoeia, Govt. of India, Ministry of health and family welfare, Delhi: controller of India: New Delhi, India, 2007:1; appendix 4.4, 550, 135-7, 179-83.


