TO ENHANCE THE SOLUBILITY OF IVERMECTIN WITH PHYSICAL MIXING METHOD FOR THE PREPARATION OF ORODISPERSE TABLETS

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Abstract

This study was aimed to enhance solubility of ivermectin and developed the orodispersible tablet (ODT) in solid unit dosage forms which administer orally it is dissolve and disintegrate instantly within few seconds. Fast disintegrating tablet is useful for paediatric, geriatric, it improve the patient compliance. In this article the ivermectin fast disintegrating tablet were prepared by using superdisintegrant ingredient like cross carmellose sodium. The solubility of ivermectin was enhanced by using solid dispersion techniques in these technique PEG 600 are used it increased the solubility of FDT. Total 06 formulation prepared and evaluated. And the formulation F2 was shown best result as per ICH guideline. Optimized formulation F2 contained cross carmallose sodium and show better result in disintegration time 16 sec and maximum in vitro drug release of FDT is 98 %.

Keywords: Ivermectin, Crosscarmellose sodium, Sodium starch glycolate. ODT.

INTRODUCTION

Drug delivery system is tool for in market external product life. The oral route is mostly preferred route of administration of therapeutic drug because it has low cost have accurate dosing self-medication and easy to administer and high patient compliance. The most popular dose is conventional tablet.

The oral route of administration is used for mostly conventional drugs like tablets, capsules & solution. Most of the things of oral route of administration consist of the desire characteristics like easy to administration flexibility of dosage form, fast disintegration and also convenience. FDT have most advantages like easy manufacturing, accurate dosing, good stability, and also ideal alternative for both geriatric and paediatric patients. Fast disintegrating tablet absorbed fastly orally disintegrating tablet is developed by combined hardness, dosage uniformity, stability, and other parameters.

Ivermectin (IVM) is new wide spectrum, efficient, less toxic antibiotics antiparasitic agent, to internal ectoparasite Be respectively provided with it is good kill effect, it is preferable especially for the repelling and killing efficacy of nematode and arthropod.

The mostly found drawback of these dosage form is difficulty in swelling for many patient above 50% peoples are affect by this difficulty but in recent trademark the fast disintegration drug delivery started to gain popularity and it is also acceptable a new drug delivery system because of easy administration and it is also show better patient compliance according to the centre of drug evaluation and research USFDA define FDT it is a solid dosage form which contains medicinal substance which
disintegrated rapidly with in few second when place upon the tongue. The fast disintegrating tablet are formulating by using super disintegrates like crosscarmellose sodium crosspovidone and sodium starch glycolate.

The varies technology use for the manufacturing FDT and these are prepared by direct compression method. Ivermectin is oral anthelmintic agent use for to treat strongyloidosis. [1]

MATERIALS AND METHOD

Materials

The drug Ivermectin was purchased as a gift sample from tosc International Pvt. Ltd. New Delhi. The solvent polyethylene glycol (PEG) was purchased from Research lab fine chem. Crosscarmellose sodium was purchased from Vishal chem. Magnesium stearate, cross povidone, fructose, was purchased from Pallav chemicals & solvents Pvt. Ltd. sodium, starch, glycolate was purchased from Yarrow chem products. MCC (microcrystalline cellulose) was purchased from Loba chemie Pvt. Ltd. Talc was purchased from Chemdyes corporation, mannitol was purchased from Merck Specialities Pvt. Ltd. fructose.

Method:

For preparation of solid dispersion the physical mixing method are used.

Physical Mixing:

In the physical mixing method of drug is prepared by geometric mixing of drug and carrier respectively without allying pressure. An excess quantity of drug and carrier is taken in a glass mortar and mix for 20 minutes. [2]

Formulation of Tablet:

Tablets were formulated using solid dispersion containing equivalent quantity of 12mg of ivermectin by the physical mixing techniques. In the formulation were prepared using direct compression technique and different concentration of superdisintegrants as shown in Table 1.

Powder mixture was compressed into tablets by using 6mm diameter punch in rotary tablet machine. Ivermectin, super disintegrating, microcrystalline cellulose, mannitol, magnesium stearate and talc, fructose were accurately weighed. All the materials were passed through 60#screen prior to mixed uniformly. The mixture evaluated for pre-compression parameters. After the powder mixing compress the tablet by using 6mm diameter punch in a rotary tablet machine. [3]

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Cross carmellose Na</td>
<td>6</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cross povidone</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sodium starch glycoate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Mannitol</td>
<td>58</td>
<td>55.5</td>
<td>58</td>
<td>55.5</td>
<td>55</td>
<td>52</td>
</tr>
<tr>
<td>MCC</td>
<td>63</td>
<td>64</td>
<td>63</td>
<td>64</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1: Formulation of Ivermectin Orodisperible Tablet
RESULTS

Preformulation Studies

UV Spectroscopy of Drug:

Absorption maxima($\lambda_{max}$):

100mg drug dissolved in HCL (0.1 N) solution and dilute to 100ml with same solvent Solution. Then dilute 1 ml of solution to 100ml with HCL (0.1 N). This test solution take in cubets and spectra was run from 200- 400 nm and absorption maxima peak were discovered and result shown in Table number 2.

Fourier-transform infrared spectroscopy:

The FT-IR spectrum was recorded for pure drug Ivermectin and Orodispersible tablet of ivermectin. The FT-IR spectrum was recorded in the region of 4000-600cm-1.

Bulk Density:

Apparent bulk density was determined by pouring a weigh quantity of tablet blend into graduated cylinder and measuring the height. Bulk density is the ratio of mass of tablet blend to bulk volume. Result shown in Table number 3.

Tapped Density:

Tapped density is the ratio of mass of tablet blend to tapped volume of tablet blend. Accurately to weighed amount of tablet blend poured in graduate cylinder and height is measured. Cylinder was allowed to 100 tapped under its own weight on to hard surface. The tapping was continue until no further changes in height was noted. Result shown in Table number 3.

Angle of Repose:

Angle of repose was determined using fixed funnel method. Result shown in Table number 3. The blend was poured thought a funnel that can be raised vertically until maximum cone height was obtained. Radius of the heap was measured and angle of repose was calculated by using following formula:

$$\Theta = \tan^{-1} \left( \frac{h}{r} \right)$$

Where, $\Theta$ is angle of repose, h is height of pile, r is the radius of base piles

Hausner Ratio:

Hausner ratio is an indirect index of ease of powder flow. Result shown in Table number 3. It is calculated by using this formula.

$$\text{Hausner ratio} = \frac{p_t}{p_b}$$

Where, $p_t$ is tapped density and $p_b$ is bulk density.

Carr's Compressibility Index:

<table>
<thead>
<tr>
<th>Talc</th>
<th>3</th>
<th>3</th>
<th>3</th>
<th>3</th>
<th>3</th>
<th>3</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructose</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><strong>Total (mg)</strong></td>
<td><strong>150</strong></td>
<td><strong>150</strong></td>
<td><strong>150</strong></td>
<td><strong>150</strong></td>
<td><strong>150</strong></td>
<td><strong>150</strong></td>
<td><strong>150</strong></td>
</tr>
</tbody>
</table>
Compressibility is the ability of powder to decrease in a volume under pressure using bulk density and tapped density. Result shown in Table number 3. The percentage compressibility of powder were determined which is given as a carr’s compressibility index which is calculated by using following formula. \[ I = \{( pb - pt)/ pt \} \times 100, \]

\[ \text{Table 2: Calibration curve of Ivermectin in 0.1 N HCL} \]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameters</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \lambda ) max</td>
<td>248 nm</td>
</tr>
<tr>
<td></td>
<td>Regression equation</td>
<td>( y = 0.0002x + 0.0359 )</td>
</tr>
<tr>
<td></td>
<td>Correlation Coefficient (r2)</td>
<td>0.9993</td>
</tr>
</tbody>
</table>

\[ \text{Table 3: Evaluation of mixed blend of drug and excipients} \]

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (( \Theta ))</th>
<th>Bulk density (g/cm(^3))</th>
<th>Tapped density (g/cm(^3))</th>
<th>Hausner’s ratio</th>
<th>Carr’s compressibility index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>30.11</td>
<td>0.38</td>
<td>0.5</td>
<td>1.66</td>
<td>24%</td>
</tr>
<tr>
<td>F2</td>
<td>22.02</td>
<td>0.37</td>
<td>0.47</td>
<td>1.27</td>
<td>21%</td>
</tr>
<tr>
<td>F3</td>
<td>25.61</td>
<td>0.40</td>
<td>0.55</td>
<td>1.37</td>
<td>27%</td>
</tr>
<tr>
<td>F4</td>
<td>29.37</td>
<td>0.4</td>
<td>0.52</td>
<td>1.32</td>
<td>23%</td>
</tr>
<tr>
<td>F5</td>
<td>35.37</td>
<td>0.39</td>
<td>0.51</td>
<td>1.30</td>
<td>23%</td>
</tr>
<tr>
<td>F6</td>
<td>35.23</td>
<td>0.38</td>
<td>0.51</td>
<td>1.30</td>
<td>25%</td>
</tr>
</tbody>
</table>
Figure 2: FTIR of Pure drug Ivermectin Drug

Figure 3: FTIR of Ivermectin Orodispersible Tablet

Post – Compression Tablet

Tablet Hardness:

The hardness of tablet is the force applied across the diameter of the tablet in the in order to break the tablet. A hardness of tablet of each formulation was determined by using Monsanto hardness tester. Result shown in Table number 4.

Tablet Thickness:

The thickness of tablet can be determined by using simple procedure. A thickness was measured by using tablet between two arms of the vernier calipers. Result shown in Table number 4.

Friability:
The measured of a mechanical strength of tablet. Roche friabilitor was used to measure the tablet. As per the weight of tablet was placed in friabilator. Result shown in Table number 4. It consists of a plastic chamber that revolves at 25 rpm dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilitor for at least 4 minutes. At the end of tablet were dusted and reweighted. The loss in the weight is measured of friability and is expressed in a percentage as:

\[
\% \text{ friability} = \frac{\text{loss in weight}}{\text{initial weight}} \times 100.
\]

**Table 4: Evaluation of Fast Disintegrating Tablet of Ivermectin**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Disintegration time (sec)</th>
<th>Friability (%)</th>
<th>Average weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3±0.098</td>
<td>3±0.577</td>
<td>18±0.577</td>
<td>0.60±0.0057</td>
<td>149±1.00</td>
</tr>
<tr>
<td>F2</td>
<td>2.8±0.251</td>
<td>2.93±0.598</td>
<td>16±1.00</td>
<td>0.32±0.01</td>
<td>150±1.154</td>
</tr>
<tr>
<td>F3</td>
<td>2.8±0.098</td>
<td>3.3±0.173</td>
<td>25±0.577</td>
<td>0.31±0.015</td>
<td>149±1.00</td>
</tr>
<tr>
<td>F4</td>
<td>3±0.144</td>
<td>3±0.577</td>
<td>20±1.527</td>
<td>0.35±0.025</td>
<td>151±1.154</td>
</tr>
<tr>
<td>F5</td>
<td>2.7±0.15</td>
<td>3.3±0.173</td>
<td>26±1.00</td>
<td>0.30±0.026</td>
<td>149±1.00</td>
</tr>
<tr>
<td>F6</td>
<td>3±0.188</td>
<td>3±0.173</td>
<td>23±0.577</td>
<td>0.31±0.015</td>
<td>150±1.153</td>
</tr>
</tbody>
</table>

**Disintegration Time:**

In the test was carried out with 6 tablet using distilled water at 37°C±2 °C was used as a disintegration media and the time in a second taken for a complete disintegration of the tablet with no palatable mass remaining in the apparatus measuring in the seconds. Result shown in Table number 4 and figure number 4.[7-9]

**Figure 4: Disintegration Time**

![Disintegration Time](image)

**Uniformity of Weight:**

As per IP procedure for uniformity of weight was followed by using 20 tablets and there weight was determined individually and correctly on a digital weighing balance the average weight was the tablet was determined from the collective weight.
In Vitro Drug Released Studies:

The immediate released tablets are subjected to in vitro drug release studies in pH 0.1 N HCL for 25 minutes to access the ability of the formulation for providing immediate drug delivery.

Drug release studies were carried out in dissolution test apparatus using specified volume 900ml of dissolution media maintained 37±2 °C. the tablet are kept in a cylindrical basket or directly placed in a medium with paddle then rotate at a 100 rpm . .5 ml of the sample for the dissolution medium are withdrawn at each time interval (1, 5, 10, 15, 20, 25, 30, minutes) and 5ml fresh medium was replaced each time . the sample are filtered 1ml was taken in diluted in 10ml. This sample where analysed spectrophotometrically and the further calculation are carried out of drug release. The in vitro dissolution kinetics parameter, dissolution rate constant, co relation co-efficient and dissolution efficiency were calculated.[10-11]

**DISCUSSION**

The fast disintegrating tablet of Ivermectin were prepared by using super disintegrating agents are croscarmellose sodium, cross povidone, sodium starch glycolate at different concentration by direct compression methods. The powder blends are evaluated by using different Preformulation parameters and results in table no.2. The angle of repose was in the range of 22.02°–35.37° indicates the good and passable flow properties. Then bulk density found in the range of 0.4-0.40 g/cm³. Hausner’s ratio was in the range of 1.27-1.66 it’s indicate good flow ability. The Carr’s compressibility index was found to between 21–27%. The powder blend containing drug was compressed by using direct compression methods and Ivermectin fast disintegrating tablet were prepared. The compressed tablets were evaluated for physical properties and the results arrange in table no 3. The hardness was in the range of 2.8±0.251–3±0.188 kg/cm². The thickness varies between 2.93±0.598–3.3±0.173 mm. The uniformity of average weight was found to be in the range of 149±1.00-151±1.154mg. The friability of all formulation was found to be less than 1.0% & was in the range of 0.30±0.026–0.60±0.0057% indicates good mechanical resistance of tablet. The disintegration time of all the formulated tablets was found to be in the range of 16±1.00-26±1.00 sec. The formulation F2 show slowest disintegration time i.e. 16 sec. The result of in vitro drug released was 98 %.

**Figure 5: In vitro Drug released of all formulations**

![Graph showing drug release over time for different formulations](image-url)
CONCLUSION:

The fast disintegrating tablet of Ivermectin can be successfully prepared by direct compression techniques used in different concentration of super disintegrant crosscarmellose sodium, cross povidone, sodium starch glycolate, alone and its combination. The prepared FDT were evaluated for varies parameters like disintegration time, wetting time, drug content, in vitro drug released study etc. and shows, the satisfactory results. Among two super disintegrants used, cross carmellose sodium showed better results in disintegration time and in vitro drug released when compared to sodium starch glycolate. The formulation of F2 containing cross carmellose sodium (5%) showed better results in disintegration time 16 sec. and maximum in vitro drug released.

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