Formulation and evaluation of metformin HCl micro beads by ionotropic gelation method

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ABSTRACT

The Metformin HCL Micro Beads is formulated by the Ionotropic Gelation Method. The CMC is a Swellable polymer is responsible for the Sustained release action or activity. A combination of CMC (Carboxy Methyl Cellulose) and Sodium Alginate shows better sustained release activity. The Prepared Sustained released Micro Beads is Evaluated In terms of bulk density, tapped density, angle of repose, Carr’s Index, Swelling Index, Drug Content, % Encapsulation Efficiency and vitro study. The result associated in Optimized batch is good to Satisfactory and having a good free flowing property. The Drug Content and % Encapsulation Efficiency values are within the pharmacopeia limit. The in vitro Dissolution studies shows Maximum percentage of release of drug (71.15) with in end of 4 Hours.

Keywords: Ionotropic Gelation, Micro beads, Sodium Alginate, Sustained released

INTRODUCTION

The Oral Route of administration is one of the specific route of administration having more patient acceptance or convenience. The Metformin HCL Micro Beads is made by Ionotropic Gelation Method. The Metformin HCL Micro beads is important for Maintaining the Stability of Vitamins and it is Important to Improve the Floability of Vitamins. The beads are Encapsulated Material is used to reduce the Hygroscopicity of Nacl Solution. The Beads are formulated with help of Carboxy Methyl Cellulose (CMC). The CMC is important for giving Sustained release action or activity. This are the Beads is release in prolonged action in extended Period of Time. The Metformin HCL Micro Beads is Antihyperglycemic agent to reduce the blood sugar level and it is mainly used for the Type II Diabetes Mellitus. [1-6]

MATERIAL AND METHODS

MATERIAL

Metformin HCL and all Formulation Excipient or Polymer [sodium Alginate, Calcium Chloride (cacl₂), Carboxy Methyl Cellulose (CMC)] was obtained from Pharmaceutics Laboratory of R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur 425405, Maharashtra State, one of the NBA and NAAC accredited and AICTE approved institutes in India.

METHOD

The parameters of Authentication and Preformulation is carried out by pure drug Metformin HCL for Maintaining their Quality, Purity and Standard.
AUTHENTICATION PARAMETERS

Melting Point Method
Melting Point determination is one of the preformulation property in which the temperature at which it changes state from solid to liquid at atmospheric pressure. At the melting process the solid and liquid can exist equilibrium. The Melting point of Metformin HCL pure drug is determine by using two types of method one is Conventional method and another is Digital method.

Log P Value
Log p value is determined by using Partition Coefficient Phenomenon. In which The 1 gm of drug is added in separating funnel containing equal portion of 25 ml of Octanol and 25 ml of Water. The separating funnel is shake 20 – 25 min. and stabilized the mixture. After stabilizing the mixture to remove water phase from separating funnel and filter it. Take Absorbance of Filtrate and calculate the log p value (concentration of drug soluble in water phase divided by concentration of drug soluble in organic phase)

Solubility Studies
The Term Solubility is defined as maximum amount of solute that can be dissolved in a given amount of solvent to form a homogenous system at specified temperature and Specific Pressure to from Saturated Solution.

Procedure
- To Prepare a different solutions Water, PH 1.2 Acidic Buffer, PH 6.8 Phosphate Buffer, PH 7.4 Phosphate Buffer.
- The drug material is added in to above solutions till Supersaturated Solution is from.
- The Mixture can Placed in Orbital Shaker for 24 hrs. After 24 hrs. Filter the mixture Take Filtrate and Give Absorbance.
- To detect the Concentration of Drug is Soluble in Different Solutions.

Calibration Curve of Metformin HCL
Calibration Curve is determined by using UV Spectrophotometric methods. In which 10 mg drug is added in 100 ml of water (100 µg/ml Solution). To Prepared different Dilutions (0, 2, 4, 6, 8, 10, 12) of above solution (100 µg/ml Solution). Take Absorbance in respective λmax 240 nm.

PREFORMULATION STUDIES

Drug-Excipient Compatibility Studies
Drug is an active part of dosages form and it is mainly responsible for therapeutic value and Excipient substances which are included along with drugs being formulated in a dosage form so as to impart specific qualities to them. It is important for determination of Stability of the dosage forms. It’s also used for development of new drug delivery system as well as investigation of new drug Product.

Procedure
The Equal portion of Drug and Excipient (1:1 ratio) is added in Ampules and the Ampules are placed in Stability Chamber for one Weak, After One Weak the Drug Excipient Compatibility Study is Determine by using TLC (Thin Layer Chromatography) (In TLC mobile phase is methanol: water: glacial acetic acid) , IR (Infrared Spectroscopy) (In IR 1:9 ratio (drug : KBR))

METHOD OF FORMULATION
The Mucoadhesive Micro beads is Prepared by Ionotropic Gelation Method. The 1 gm of Carboxy Methyl Cellulose (CMC) and 1 gm of sodium Alginate is added in 100 ml Water Containing Beaker. (Continuous Stirring is required for addition of CMC and Sodium Alginate) The solution was put in Mechanical Stirrer for 30 min till formation of clear solution and 200 mg Drug was added in this solution, the drug containing Solution Mix. Was under High Pressure Homogenizer (HPH) for 20 min. till Homogeneous Solution is formed. In Another Beaker add 10 gm of Calcium Chloride (cacl\textsubscript{2}) in 100 ml of Iso Propyl Alcohol (I.P.A.) (10 % Solution). By using Syringe with 24 needle size, Take Solution of (Drug and CMC, Sodium Alginate) by using Needle 24 size and add drop to drop in Calcium Chloride 10% Solution to from Spherical Micro beads. This Micro beads is Dried over Night in room Temperature. After Drying Micro beads is formed and evaluated. All Formulation Ingredient is Reported in Table No. 1

EVALUATION PARAMETER [7-18]

Bulk density
It is a ratio of weight mass and Bulk Volume is known as Bulk Density. Amount of Powder is Weighed Separately and transferred into 100 ml of measuring cylinder, initial volume of Powder Material is measured and calculated bulk density according to following formula.
Bulk density = Mass / Volume

**Tapped Density**
It is a Ratio of weight Mass and Tapped Volume is known as Tapped Density. Tapped density is Important Evaluation Parameter is determined by placing a graduated cylinder containing a known mass of powder Undergoes Tapping in Manually (100 Tapes) as well As Using a Mechanical apparatus under powder bed volume has reached a minimum volume. The Tapped Density is calculated by following Formula.

\[
\text{Tapped density} = \frac{\text{Weight of Powder}}{\text{tapped volume of Powder}}
\]

**Compressibility Index or Carr’s Index**
The Calculation of Compressibility index is based on the Tapped density and Bulk density. It is a ratio of Tapped density and Bulk Density i.e. Compressibility Index.

**Angle of Repose**
It defines as the Pile surface of Powder is known as Angle of Repose. In this method of determination of angle of repose in which the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle. The Following Formula for determination of angle of repose:

\[
\theta = \tan^{-1}\left(\frac{h}{r}\right)
\]

Where,
\[
\theta - \text{Angle of repose},
\]
\[
h - \text{Height of the powder cone},
\]
\[
r - \text{Radius of the powder cone}.
\]

**Swelling Index**
The Equal weight of 100 mg Metformin HCL is Placed in Two Different Petri dish (one Petri dish contain Water and another contain PH 1.2 Acidic Buffer) Kept aside for 1 hr. After one Hour take weight of Swelled Beads and Calculate the Swelling Index of Metformin HCL Beads.

Swelling index was calculated using Following Formula:

\[
\text{Swelling index} = \frac{\text{Weight of wet beads} - \text{weight of dry beads}}{\text{100}} \times \frac{100}{\text{Weight of dry beads}}
\]

**Encapsulation Efficiency**
The 100 mg of Metformin Micro Beads are added in 100 ml of water, the mixture was placed in orbital shaker for 24 hrs. After 24 hrs. Filter the solution and Take Filtrate of Solution and give Absorbance. Calculate the % Encapsulation efficiency.

The following Formula for Determination of % Encapsulation efficiency:

\[
\text{Actual content of Drug / Theoretical Content of drug} \times 100
\]

**Drug Content**
The 100 mg of Beads was crushed and add 100 ml of PH 1.2 Acidic Buffer to prepared 100 ppm Solution and Take Absorbance by using UV Spectroscopy Technique at 240 nm.

The Drug Content is calculated by Following Formula:

\[
\text{Drug content : Actual drug content/Theoretical drug content} \times 100
\]

**Particle Size Distribution**
The Particle size distribution is calculated in Motic Microscopy Method In which 100 mg of Beads was put in to glass slide and add Menthe oil to formed Suspension. It is conducted in Motic Microscopy to conduct the Imaging of Beads and Size Distribution was calculated.

**In vitro drug release studies**
Dissolution of Micro Beads is determined by Basket Type (USP I) of Dissolution Apparatus. The Beads was added into cylindrical vessel containing 900 ml PH 1.2 Acidic media having 75 rpm for 4 hours and tem. 37±0.5°C having 30, 60, 90, 120, 150, 180, 210, 240 Min. of interval. After every 30Min. 5 ml sample was Withdrawn and
appropriate quantity of sample take absorbance by using U.V. spectroscopy technique and determine rate of dissolution of Micro Beads.

RESULTS AND DISSCUSION

AUTHENTICATION PARAMETERS

Melting Point Method
The Melting Point of Metformin HCL is determined by Conventional and Digital Method and Melting Point of Metformin HCL is Reported in Table No.2.

Log P Value
Log P Value is determined by Partition Coefficient Phenomenon and Log P Value of Metformin HCL is reported in Table No.2.

Solubility Studies
The Solubility of Metformin HCL in Given Solution. (Water, PH 1.2 Acidity Buffer, PH 6.8 Phosphate Buffer, PH 7.4 Phosphate Buffer) is Reported in Table No.3.

Calibration Curve of Metformin HCL in water
The Calibration Curve of Metformin HCL is determined by using U.V. Spectroscopic Method. In which the Absorbance of Metformin HCL in Different Concentration (0, 2, 4, 6, 8, 10, and 12) is reported in Table No.4. And The Calibration Curve is shown in Figure No.1.

PREFORMULATION STUDIES

The Drug and Excipient Compatibility studies determined by TLC (Thin Layer Chromatography) and IR (Infrared Spectroscopy) Method In which The TLC of Drug, Drug and Excipient before Stability Chamber and After Stability Chamber is reported in Table No.5. And the IR of Pure drug Metformin HCL is shown in Figure No.2.

EVALUATION PARAMETERS

Bulk density
It is important parameter for determination of Flow characteristic in which the Bulk Density of Metformin HCL Beads is reported in Table No.6.

Tapped Density
It is important parameter for determination of Flow characteristic in which the Tapped Density of Metformin HCL Beads is reported in Table No.6.

Compressibility Index or Carr’s Index
The compressibility index is determined on the basis of Tapped density and bulk density and it is important for determination of flow characteristic in which the Compressibility Index or Carr’s Index of Metformin HCL Beads is reported in Table No.6.

Angle of Repose
It is important flow property for determination of flow of material and the value associated in angle of repose is less than 40° is indicate good flow property in which angle of repose of Metformin HCL Beads tablet is reported in Table No.6.

Swelling Index
The swelling Index of Metformin HCL Beads is reported in Table No.6.

Drug Content
The % Drug Content of Metformin HCL Beads Reported in Table No.6.

Particle Size Distribution
The Particle Size Distribution of Metformin HCL Beads by using Motic Microscopy and Particle Size Distribution is reported in Table No.6.

In vitro drug release studies
The In vitro drug release studies of mucoadhesive Beads is determined in PH 1.2 Acidic Buffer, the absorbance of Metformin HCL in PH 1.2 Acidic Buffer is reported in Table No.7. Calibration curve of Metformin HCL in PH 1.2
Acidic Buffer shown in Figure No.3. The absorbance of concentration of Metformin HCL soluble in dissolution medium in different time of interval and % CDR of Metformin HCL is reported in Table No.8. And the in vitro drug released of Metformin HCL Beads is shown in Figure No.4.

Table No.1: Formulation Ingredients of Metformin HCL Beads

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredient F</th>
<th>F1</th>
<th>F2</th>
<th>F OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Metformin HCL (Mg)</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>2</td>
<td>Sodium Alginate (gm)</td>
<td>0.85</td>
<td>0.95</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Calcium Chloride (gm)</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Carboxy Methyl Cellulose (CMC) (gm)</td>
<td>0.59</td>
<td>0.86</td>
<td>1</td>
</tr>
</tbody>
</table>

Table No.2: Melting Point and Log P Value of Metformin HCL

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Parameters</th>
<th>Result</th>
<th>Std.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Melting Point (˚c)</td>
<td>223 - 227˚c</td>
<td>223 - 226˚c</td>
</tr>
<tr>
<td>2</td>
<td>Log p Value</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table No.3: Solubility of Metformin HCL in different solvents

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Medium</th>
<th>Concentration of drug Soluble (mg /ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>18.98</td>
</tr>
<tr>
<td>2</td>
<td>PH 1.2 Acidic Buffer</td>
<td>9.22</td>
</tr>
<tr>
<td>3</td>
<td>PH 6.8 Phosphate Buffer</td>
<td>5.27</td>
</tr>
<tr>
<td>4</td>
<td>PH 7.4 Phosphate Buffer</td>
<td>4.79</td>
</tr>
</tbody>
</table>

Result: Class of drug BCS Class III

Table No.4: Calibration of Metformin HCL in Water

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.228</td>
</tr>
<tr>
<td>4</td>
<td>0.439</td>
</tr>
<tr>
<td>6</td>
<td>0.651</td>
</tr>
<tr>
<td>8</td>
<td>0.85</td>
</tr>
<tr>
<td>10</td>
<td>1.061</td>
</tr>
<tr>
<td>12</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Table No.5: TLC of Drug and Drug: Excipient Before and after stability Chamber

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Samples (Pure From of Drug material) (Drug + Excipient Mixture)</th>
<th>Retention factor of drug Before the Stability Chamber</th>
<th>Retention factor of drug After the Stability Chamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pure Drug Metformin HCL</td>
<td>0.76</td>
<td>0.78</td>
</tr>
<tr>
<td>2</td>
<td>Metformin HCL + Sodium Alginate</td>
<td>0.79</td>
<td>0.77</td>
</tr>
<tr>
<td>3</td>
<td>Metformin HCL + Calcium Chloride</td>
<td>0.80</td>
<td>0.84</td>
</tr>
<tr>
<td>4</td>
<td>Metformin HCL + Carboxy Methyl Cellulose (CMC)</td>
<td>0.78</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Table No.6: Evaluation of Metformin HCL Beads

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Parameters (gm/cm³)</th>
<th>F OP</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bulk Density</td>
<td>0.62</td>
<td>Pass</td>
</tr>
<tr>
<td>2</td>
<td>Tapped Density</td>
<td>0.74</td>
<td>Pass</td>
</tr>
<tr>
<td>3</td>
<td>Angle of Repose</td>
<td>20.12</td>
<td>Pass</td>
</tr>
<tr>
<td>4</td>
<td>Carr’s Index (%)</td>
<td>19.35</td>
<td>Pass</td>
</tr>
<tr>
<td>5</td>
<td>Swelling Index (hrs.)</td>
<td>78</td>
<td>Pass</td>
</tr>
<tr>
<td>6</td>
<td>Particle Size Distribution (μm)</td>
<td>1162.18 ± 0.38</td>
<td>Pass</td>
</tr>
<tr>
<td>7</td>
<td>Encapsulation Efficiency (%)</td>
<td>79.69</td>
<td>Pass</td>
</tr>
<tr>
<td>8</td>
<td>Drug Content (%)</td>
<td>1.58</td>
<td>Pass</td>
</tr>
<tr>
<td>9</td>
<td>In Vitro Drug release (%)</td>
<td>71.15</td>
<td>Pass</td>
</tr>
</tbody>
</table>

Table No.7: The absorbance of Metformin HCL in PH 1.2 Acidic Buffer (In vitro drug release studies)

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.223</td>
</tr>
<tr>
<td>4</td>
<td>0.375</td>
</tr>
<tr>
<td>6</td>
<td>0.579</td>
</tr>
<tr>
<td>8</td>
<td>0.763</td>
</tr>
<tr>
<td>10</td>
<td>0.935</td>
</tr>
</tbody>
</table>
### Table No.8: % CDR of Metformin HCL Beds (In vitro drug release studies)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Abs</th>
<th>Conc µg/ml</th>
<th>DF</th>
<th>Conc µg/ml</th>
<th>Conc mg/ml</th>
<th>Conc mg/900ml</th>
<th>CDR</th>
<th>% CDR</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>
</tr>
<tr>
<td>30</td>
<td>0.086</td>
<td>0.765</td>
<td>10</td>
<td>7.650</td>
<td>0.0076</td>
<td>0.038</td>
<td>6.88</td>
<td>6.88</td>
</tr>
<tr>
<td>60</td>
<td>0.088</td>
<td>0.786</td>
<td>10</td>
<td>7.866</td>
<td>0.0078</td>
<td>0.0393</td>
<td>7.079</td>
<td>7.11</td>
</tr>
<tr>
<td>90</td>
<td>0.121</td>
<td>1.142</td>
<td>10</td>
<td>11.422</td>
<td>0.0114</td>
<td>0.0571</td>
<td>10.28</td>
<td>10.31</td>
</tr>
<tr>
<td>120</td>
<td>0.145</td>
<td>1.40</td>
<td>10</td>
<td>14.008</td>
<td>0.0140</td>
<td>0.070</td>
<td>12.607</td>
<td>12.66</td>
</tr>
<tr>
<td>150</td>
<td>0.161</td>
<td>1.57</td>
<td>10</td>
<td>15.732</td>
<td>0.015</td>
<td>0.078</td>
<td>14.15</td>
<td>14.22</td>
</tr>
<tr>
<td>180</td>
<td>0.189</td>
<td>1.87</td>
<td>10</td>
<td>18.75</td>
<td>0.0187</td>
<td>0.093</td>
<td>16.875</td>
<td>16.95</td>
</tr>
<tr>
<td>210</td>
<td>0.212</td>
<td>2.12</td>
<td>10</td>
<td>21.228</td>
<td>0.0212</td>
<td>0.1061</td>
<td>19.105</td>
<td>19.19</td>
</tr>
<tr>
<td>240</td>
<td>0.234</td>
<td>2.35</td>
<td>10</td>
<td>23.599</td>
<td>0.0235</td>
<td>0.1179</td>
<td>21.23</td>
<td>21.34</td>
</tr>
</tbody>
</table>

### Figure No.1: Calibration curve of Metformin HCL in Water

- \( y = 0.0416x + 0.0155 \)
- \( R^2 = 0.9995 \)

### Figure No.2: IR of Pure drug Metformin HCL
CONCLUSION

The Metformin HCL Micro Beads is formulated by the Ionotropic Gelation Method. The Beads are Stable in GI tract (stomk and Intestine). The CMC is a Swellable polymer is responsible for the Sustained Release action or activity. The Combination of Sodium alginate and CMC is responsible for prolonged released and sustained released activity. The result associated in Optimized batch is good to Satisfactory and having a good free flowing property. The Drug Content, % Encapsulation Efficiency and Swelling Index in these values are within the pharmacopoeia limit. The in vitro Dissolution studies shows Maximum percentage of release of drug.

Acknowledgement

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