Formulation of Metoprolol Tartarate Containing Lyophilized Oral Disintegrating Tablet

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Abstract
Orally Disintegration Tablet (ODTs) are solid dosage forms containing active pharmaceutical ingredient (API) which disintegrate rapidly, usually less than 60 seconds without the need of water when placed on the tongue. Metoprolol, which is practically water insoluble, shows low bioavailability. Weighed 100mg metoprolol was dissolved in 100ml of methanol solution to get a solution containing 100mcg/ml.

Dilution: Aliquots of (0.1–1.0ml) standard solution were pipetted out into 10ml volumetric flasks. The volume was made up to the mark with methanol solution to produce the concentration ranging from 1–10 mg/ml. The absorbance of each prepared solution was measured at 222nm in Shimadzu UV-1800 spectrophotometer against an appropriate blank (methanol solution).

Lyophilization is one of the techniques that can solve this problem in ODTs formulation. The resulting tablets were evaluated using parameters such as: hardness, friability, disintegration time in vitro, modified disintegration time, disintegration time in the oral cavity, wetting time, water absorption ratio, drug content determination, weight uniformity, and dissolution.

Keyword: ODTs (Oral disintegrating tablet), Lyophilized, Formulation, Metoprolol Tartarate, Disintegration, Gelatin

Introduction
Oral administration of drugs is preferred due to its ease of swallowing, distress avoidance, versatility and most significantly, patient compliance. The large number of patients find it difficult to swallow tablets and capsules, and do not take their medicines as prescribed. It is estimated that 50% of the population affected by this problem, which finally results in a higher chance of noncompliance and ineffective therapy. For these reasons, tablets that can disintegrate in the oral cavity, have attracted enormous attention [1]. ODTs technology, which makes tablets dissolve or disintegrate in the oral cavity without any additional water intake, has drawn a great deal of attention. ODTs are a solid dosage form that provides the rapid disintegration or dissolution of solid to present as suspension or solution form even when placed in the mouth under limited bio-fluid.[2,3] The excipients used in ODT technology are usually hydrophilic in nature and can be selected on the basis of drug’s physicochemical properties like hydrophilicity or hydrophobicity [18,19].

The ODT formulation defined by the Food and Drug Administration (FDA) as “a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of
seconds when placed upon the tongue”. U.S. Food and Drug Administration approved Zydis, ODT formulation of Claritin (loratadine) in December 1996. It was followed by a Zydis ODT formulation of Klonopin (clonazepam) in December 1997, and a Zydis ODT formulation of Maxalt (rizatriptan) in June 1998. Further a number of drugs have been approved by regulatory authorities for ODT formulations [4].

Advantages of ODTs
The advantages of ODTs include [12-17]:

- No need of water to swallow the tablet.
- Compatible with taste masking and have a pleasing mouth feel.
- Can be easily administered to paediatric, elderly and mentally disabled patients.
- No residue in the oral cavity after administration.
- Manufacturing of the tablets can be done using conventional processing and packaging equipments at minimum cost.
- Allow high drug loading.
- Accurate dose can be given as compared to liquids.
- Dissolution and absorption of the drug is fast, offering a rapid onset of action.
- Advantageous over liquid medication in terms of administration as well as transportation.
- Some amount of drugs is absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, thus reducing first pass metabolism, which offers improved bioavailability and thus reduced dose and side effects.

- No risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
- ODTs are suitable for sustained and controlled release actives.
- Unit packaging.

Drug Class: β1 receptor blocker
IUPAC name: (RS)-1-(Isopropyl amino)-3-[4-(2-methoxyethyl) phenoxy]propan-2-ol
Molecular formula: C_{15}H_{25}NO_{3}

Material & Methods :

4.4.1.1 Characterization of drug. Metaprolol Hydrochloride
The drug sample obtained was identified by various analytical techniques such as IR Spectroscopocy, UV spectroscopy, melting point, partition coefficient and solubility etc.[21,23].

### Organoleptic Property

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Properties</th>
<th>Inferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Colour</td>
<td>white or almost white powder</td>
</tr>
<tr>
<td>2</td>
<td>Odour</td>
<td>Odourless</td>
</tr>
<tr>
<td>3</td>
<td>Taste</td>
<td>Bitter</td>
</tr>
</tbody>
</table>
Melting point
Melting point of metaprolol was determined by taking small amount of metaprolol separately in a capillary tube closed one end and placed in a Thief’s apparatus and the temperature at which metaprolol melt was recorded. This was performed in triplicate and average value was recorded.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Specification</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol tartrate</td>
<td>110-115°C</td>
<td>109-112°C</td>
</tr>
</tbody>
</table>

Partition coefficient (P<sub>app</sub>)
Partition coefficient is a measurement of drug’s lipophilicity and its ability to cross cell membrane. Partition coefficient of metaprolol was determined at 37 ± 0.5 °C by taking 5 ml of octanol which was saturated with 5 ml of water by shaking with externally driven magnetic stirrer. After shaking the system remained undisturbed for half an hour. About 100 mg of drug was added to this solution and was shaken on wrist action mechanical stirrer. Two layers were separate through separating funnel and filterer through Whatman grade filter, and the amount of metaprolol solubilized, was determined by measuring the absorbance at 239 nm against reagent blank through double beam UV/Vis spectrophotometer (Shimadzu) in both the solution. Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in water and the value were reported as log P.

\[
(P_{app})_{K_{o/w}} = \frac{\text{Concentration of drug in non-aqueous phase}}{\text{Concentration of drug in aqueous phase}}
\]

Solubility Studies
Solubility studies was carried out with different solvents such as, 0.1 N HCl, phosphate buffer 6.8pH, water, ethanol, methanol in water bath shaker at 25°C and kept it for 24 hours.

FT-IR spectrum: Fourier transform infrared spectroscopy of different compounds was performed for identification of that particular compound. FT-IR Spectroscopy of pure drug, final optimized formulation was done using KBr pellets. Various peaks in FT-IR Spectrum were interpreted for identification of different group in the structure of pure drug and optimized formulation. FT-IR Spectroscopy can also be used to investigate and predict any physicochemical interactions between different components.

Drug Excipient Compatibility Study
Successful formulation of a stable and effective solid dosage form depends on the useful selection of excipients which are added to facilitate administration, promote the consistent release and bioavailability of drug and protect it from degradation. FT-IR analysis of polymers and drug-polymer mixture were carried out in order to access drug-polymer interaction. For this, the FT-IR of drug and polymers were carried out separately as well as in mixture of drug-polymer in the ratio 1:1.

Establishment of calibration plot

Procedure for Standard Curve in methanol solution

Standard Solution: Accurately weighed 100mg metaprolol was dissolved in 100ml of methanol solution to get a solution containing 100mcg/ml.

Dilutions: Aliquots of (0.1-1.0ml) standard solution were pipette out into 10ml volumetric flasks. The volume was made up the mark with methanol solution to produce the concentration ranging from 1-10 mg/ml. The absorbance of each prepared solution was measured at 222nm in Shimadzu UV-1800 spectrophotometer against an appropriate blank (Methanol solution). All the absorbance were conducted in triplicate (n=3).
<table>
<thead>
<tr>
<th>S.No:</th>
<th>Concentration (μg/ml)</th>
<th>Absorbance (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.000±0.00</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.065±0.020</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.148±0.031</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0.229±0.017</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>0.307±0.054</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>0.375±0.002</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>0.458±0.061</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>0.560±0.037</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>0.629±0.053</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>0.719±0.016</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>0.800±0.010</td>
</tr>
</tbody>
</table>

Result & Discussion:-
Preparation of Metaprolol tartarate containing lyophilized oral disintegrating tablet [11-16]

The polymer at different concentrations were weighed and dissolved in 60 g of distilled water with gentle heat to aid faster dissolution at 60–65°C. A viscous polymeric solution was formed. Wheat starch and mannitol were added and dispersed in the polymeric solution. The final weight of the solution was adjusted to 100 g using distilled water. The stirring was continued for 30 min. Each of 1 g of the base was casted into a tablet shaped plastic mould individually. The mould was stored in a freezer at -20°C for 4 h for the base to solidify. The mould was then transferred to a freeze dryer at -40°C for 12 h. The dried FDT was removed from the mould and stored in a desiccator.
Composition of different drug loaded lyophilized oral disintegrating tablet -

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Metaprolol tartarate (mg)</th>
<th>Gelatin (%w/w)</th>
<th>HPMC E 15(%w/w)</th>
<th>Corn starch (%w/w)</th>
<th>Sucrose (%w/w)</th>
<th>Average weight of tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>30</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>20</td>
<td>250.65±0.55</td>
</tr>
<tr>
<td>F2</td>
<td>30</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>20</td>
<td>251.01±0.65</td>
</tr>
<tr>
<td>F3</td>
<td>30</td>
<td>3</td>
<td>-</td>
<td>2</td>
<td>20</td>
<td>250.44±0.38</td>
</tr>
<tr>
<td>F4</td>
<td>30</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>20</td>
<td>250.14±0.61</td>
</tr>
<tr>
<td>F5</td>
<td>30</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>20</td>
<td>251.69±0.41</td>
</tr>
<tr>
<td>F6</td>
<td>30</td>
<td>-</td>
<td>3</td>
<td>2</td>
<td>20</td>
<td>250.55±0.11</td>
</tr>
<tr>
<td>F7</td>
<td>30</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>20</td>
<td>251.01±0.28</td>
</tr>
<tr>
<td>F8</td>
<td>30</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>20</td>
<td>250.19±0.34</td>
</tr>
<tr>
<td>F9</td>
<td>30</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>250.97±0.17</td>
</tr>
<tr>
<td>F10</td>
<td>30</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>30</td>
<td>250.64±0.15</td>
</tr>
</tbody>
</table>

3 In vitro characterization of lyophilized oral disintegrating tablet

1- Weight variation of tablet

Twenty tablets were randomly taken from each batch and the weight of their average weight was determined. Then individual tablet was taken and its weight was calculated. That individual weight was compared with average weight. The weights were measured using weighing balance.

2- Hardness

The tablet hardness was evaluated using a TA. XT plus texture analyser (UK) equipped with a computer software Exponent Stable Micro Systems (Ver 5.1.1.0). A 2-mm flat surface probe was equipped on the texture analyser with a load of 100 g. The penetration force applied on the sample which penetrated a 2-mm depth into the sample was defined as the hardness of the tablet.

3- Thickness

The thickness of each FDT formulation was measured using a micrometre at the centre. Ten samples of each FDT formulation were measured.[15]

4- Friability test

Ten FDTs were used for the friability test using a friabilator. The FDTs were weighed and the initial total weight of ten tablets was determined by Analytical balance. After 100 rotations at 25 rpm, the FDTs were removed from the friability tester and again weighed. [14].

5- In-vitro disintegration time test

The disintegration time test determines whether tablets disintegrate within a prescribed time when placed in a liquid medium under experimental conditions. The in vitro disintegration time of the FDTs formulations was determined using a disintegration tester with 0.1N HcL at 37.0 ± 0.5°C. The disintegration time is defined as the time taken for FDT to completely dissolve and pass through the screen at the bottom of each tube of the disintegration tester, such that no solid residue remaining on the screen. A total of 6 FDTs were run for each formulation.[13]

6- Drug Content

The Drug Content was determined using the UV-Visible spectroscopy method. One FDT was dissolved in a 100 mL volumetric flask with methanol. The solution was subjected to sonication for 30 min. 1 mL of the stock solution was drawn out and was diluted with methanol to 10 mL in a volumetric flask and analysed using UV visible spectroscopy.[14]

7- In vitro drug release study:-

The dissolution studies were carried out on the optimum FDT formulation (30 mg Metaprolol tartarate). Drug dissolution study was carried out
in 900mL of 0.1M HCL (pH 1.0 ± 0.1) at 37.0 ± 0.5°C, using USP basket method at a stirring speed of 100 rpm at preset time intervals of 5, 10, 15, 20, 30, 45, 60, 90 and 120 min, 1 mL of samples were withdrawn and immediately replaced with an equal volume of fresh dissolution medium. The samples were filtered through 0.45 lm membrane filter and the amount of drug released was determined using the uv-visible spectroscopy. [14]

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (mm)</th>
<th>Thickness (mm)</th>
<th>% Friability</th>
<th>Disintegration time (Sec)std</th>
<th>Percentage drug content std</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.885±0.017</td>
<td>5.47±0.025</td>
<td>0.084±0.002</td>
<td>101±0.58</td>
<td>81.45±0.003</td>
</tr>
<tr>
<td>F2</td>
<td>1.24±0.015</td>
<td>5.99±0.036</td>
<td>0.091±0.006</td>
<td>124±0.69</td>
<td>86.21±0.089</td>
</tr>
<tr>
<td>F3</td>
<td>1.68±0.029</td>
<td>6.41±0.094</td>
<td>0.099±0.004</td>
<td>168±0.42</td>
<td>89.63±0.097</td>
</tr>
<tr>
<td>F4</td>
<td>0.101±0.081</td>
<td>3.65±0.014</td>
<td>0.028±0.008</td>
<td>19±0.35</td>
<td>94.15±0.095</td>
</tr>
<tr>
<td>F5</td>
<td>0.587±0.035</td>
<td>3.88±0.058</td>
<td>0.031±0.001</td>
<td>25±0.71</td>
<td>96.05±0.048</td>
</tr>
<tr>
<td>F6</td>
<td>0.648±0.049</td>
<td>4.1±0.019</td>
<td>0.038±0.005</td>
<td>31±0.05</td>
<td>98.37±0.046</td>
</tr>
<tr>
<td>F7</td>
<td>0.367±0.051</td>
<td>3.61±0.021</td>
<td>0.027±0.009</td>
<td>19±0.69</td>
<td>96.24±0.025</td>
</tr>
<tr>
<td>F8</td>
<td>0.489±0.084</td>
<td>3.97±0.025</td>
<td>0.036±0.008</td>
<td>38±0.5</td>
<td>96.88±0.07</td>
</tr>
<tr>
<td>F9</td>
<td>0.602±0.038</td>
<td>3.81±0.027</td>
<td>0.035±0.004</td>
<td>27±0.02</td>
<td>97.14±0.088</td>
</tr>
<tr>
<td>F10</td>
<td>0.514±0.05</td>
<td>4.04±0.011</td>
<td>0.038±0.001</td>
<td>29±0.038</td>
<td>96.02±0.066</td>
</tr>
</tbody>
</table>

The average weight of all tablet was found to be in a range of 250.14±0.61 to 251.69±0.41. [17] The hardness of lyophilized ODT of all batches was found to be in a range of 0.101±0.081 to 1.68±0.029. demonstrated that the tablet thickness of all formulation was uniform and it was found to be in the range of 3.61±0.021–5.99±0.036mm. revealed that % friability of all formulation was found to be less than 1% indicating that tablet have sufficient mechanical strength showed no cracked, cleaved, or broken after tumbling.

Increasing in polymers concentration increased the disintegration time. The hardness of ODT increased due to higher level of cross-linking polymer network formed which reduced the porosity of the tablet. As a result, the disintegration time prolonged. Disintegration time of all formulation was uniform and it was found to be in the range of 19±0.69–168±0.42 sec. percentage drug content of all formulation was found to be in a range of 81.45±0.003 to 98.37±0.046.

On the basis of above in vitro evaluation parameter formulation code F7 was selected for further evaluation.

The percentages of drug dissolved from FDTs F7 after 25 minutes were 98.21±1.23, indicate that the process used to prepare the FDTs greatly enhanced the extent and rate of dissolution of Metoprolol tartrate from the prepared tablets. [17]

**FT-IR spectral analysis**

FT-IR analysis measures the selective absorption of light by the vibration modes of specific chemical bonds in the sample. The FT-IR spectrum of Metoprolol tartrate is shown in Figure 13 and interpretation of data is given in Table 13.
The main infrared peaks of the Metoprolol tartrate are as follows: 3427.63 and 3253 cm\(^{-1}\), attributable to its vibrational stretching of O-H and functional N-H bond, respectively. Other peaks are C = C aromatic stretching vibration at 1510 cm\(^{-1}\); C-H stretching at 2817 cm\(^{-1}\). In formation these peaks were shifted and displayed with reduced intensity.

**Conclusion:**

On the basis of above in vitro evaluation parameters & different test like friability, hardness, thickness, percentage drug content, dissolution and disintegration time formulation code F7 was selected for further evaluation as well as formulation code F7 is show more activity and FDT action compare to other formulation. Thus the prepared FDTs greatly enhanced the extent and rate of activity of Metoprolol tartrate from the prepared tablets.

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