ABSTRACT

This work was aimed at masking the bitter taste of ondansetron HCl using Ionotropic gelation technique. Ondansetron HCl is 5HT3 receptor antagonist commonly used in treatment of emesis. Oral administration of ondansetron HCl faces major problem due to its bitter taste. In this work taste masking was done by formulating tasteless beads of ondansetron HCl using varied concentration of xyloglucan polymer by ionic orifice gelation technique. beads were evaluated for various parameter like drug content, particle size, entrapment efficiency, in vitro taste evaluation and drug release. Use of 3% polymer concentration shows 98 % practical yield of beads having 90.60 % entrapment efficiency, particle size 630 µm. SEM study reveals spherical shape with rough surface of beads, in vitro taste evaluation of beads shows that satisfactory taste masking was achieved. Drug release from beads was found to be 84.34 % within 20 min. These beads were compressed into fast disintegrating tablet which rapidly disintegrated in oral cavity. Crospovidone was used as a superdisintegrant. 4 batches of tablets were prepared by varying concentration of crospovidone from 2-5 %.tablets were subsequently evaluated for various pharmacopoeial tests, drug release and disintegration time. The results were found to be satisfactory.

Keywords – Ondansetron HCl, xyloglucan, Taste masking, beads.
1. INTRODUCTION

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers.\textsuperscript{1}

The bitterness of pharmaceutical medicines plays critical role in patient compliance, as the oral administration of bitter drugs is often hampered by their unpleasant taste which leads to non-compliance and further worseness of diseased condition.

Taste perception is associated with taste buds so taste masking can be achieved by preventing contact of drug with taste buds. By the process of micro encapsulation, very tiny droplets for particles of liquid or solid materials are surrounded or coated with a continuous film of polymeric material.

Here is one attempt to mask the taste of bitter drug by encapsulating it in the polymer coat by ionotropic orifice gelation technique.

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form gel beads. Which are spherical crosslinked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through beads is controlled by polymer relaxation. Hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuses into the drug-loaded polymeric drops, forming a three dimensional lattice of ionically crosslinked moiety.\textsuperscript{3}

There has been a growing interest in the use of natural polymers as drug carriers due to their biocompatibility and biodegradability. The natural or semisynthetic polymers i.e. Alginites, gellan gum, chitosan, pectin and carboxymethyl cellulose are widely use for the encapsulation of drug by this technique. These natural polymers contain certain anions/cations on their chemical structure, these anions/cations forms meshwork structure by combining with the counter ions and induce gelation by cross linking. \textsuperscript{3}
Xyloglucan is a natural polysaccharide isolated from the seed kernel of Tamarindus indica. It possesses properties like high viscosity, broad pH tolerance, and adhesivity. This led to its application as a stabilizer, thickener, gelling agent, and binder in the pharmaceutical industry. In addition to this, other important properties of xyloglucan have been identified recently. They include noncarcinogenicity, biocompatibility, high drug loading capacity, and high thermal stability.

Ondansetron HCl is a 5HT3 receptor antagonist commonly used as an anti-emetic. But it is very bitter in taste; so an attempt was made in this work to use xyloglucan polymer to form taste masked beads of ondansetron HCl by ionotropic gelation. Calcium chloride is used as a crosslinking agent. This taste masked beads was then compressed in the form of fast disintegrating tablets.

2. MATERIALS AND METHOD

2.1 Materials
Ondansetron HCl obtained as a gift sample from Pranami drugs Pvt.Ltd, Ankleshwar; Xyloglucan was a kind gift of Encore polymer Pvt.Ltd, Ahmadabad; Calcium chloride was purchased from Sisco research Pvt.Ltd, Andheri. Other chemicals used were of analytical reagent grade and procured from the local suppliers.

2.2 Methods

2.2.1 Method of analysis
The drug was estimated spectrophotometrically at 248 nm using UV spectroscopy.

Table 1- Composition of ondansetron beads

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Drug : polymer Ratio</th>
<th>Calcium chloride Concentration (%)</th>
<th>Curing time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1</td>
<td>1:1</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>X2</td>
<td>1:2</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>X3</td>
<td>1:3</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

2.2.2 Preparation of Ondansetron HCl loaded Beads
The beads were prepared by ionotropic gelation technique. At first, xyloglucan (1%, 2%, 3% w/v) was dispersed uniformly in 2 N NaOH by stirring so that the homogeneous solution of xyloglucan was obtained. Ondansetron HCl was added to this polymer solution slowly and stirred for about 5 minutes, to disperse the drug uniformly. The Polymer- drug dispersion was added dropwise via a needle fitted with a 10ml syringe into 50ml of 10% calcium chloride.
solution stirring at 300 rpm after incubating for a 30 min, the gelled beads were separated by filtration and washed with distilled water. Then the microparticles were dried at the room temperature. (Table-1)

2.2.3 Evaluation of beads

1) Percentage Practical Yield:
The % practical yield of microbeads was determined by comparing the whole weight of microbeads obtained against the combined weight of the polymer and drug.

\[
\% \text{ Practical yield} = \frac{\text{Total weight of beads obtained}}{\text{Total weight of drug and polymer}} \times 100 \ldots \ldots \ldots \ldots (I)
\]

2) Drug content & entrapment efficiency
The drug content was determined by UV-Visible spectrophotometer. The 100 mg of beads were powdered in mortar and transferred to 100 ml 0.1N HCl, stirred for 2 hours to ensure complete elution of drug. The drug concentration was determined at 248 nm after suitable dilution. The readings were taken in triplicate.

\[
\% \text{ Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \ldots \ldots \ldots \ldots (II)
\]

Among these beads with 3% polymer concentration show satisfactory result with compactness, spherical shape and rough surface so this batch was selected for further studies.

3) Particle Size Analysis: The sample of prepared microbeads was randomly selected and their size was determined using an optical microscope.

4) Infrared Spectroscopy
Infrared (IR) spectroscopy was conducted using a FTIR Spectrophotometer and the spectrum was recorded over the region 400-4000 cm\(^{-1}\) for the ondansetron HCl, xyloglucan and drug loaded beads.

5) Differential scanning calorimetry study (DSC)
A Mettler Toledo Differential Scanning Calorimeter (DSC) 821 (Mettler Toledo, Greifensee, Switzerland) equipped with an intracooler and a refrigerated cooling system was used to analyze the thermal behavior of ondansetron HCl, xyloglucan and ondansetron HCl loaded beads, in hermetically sealed flat aluminium crucibles, with temperature range from 30 to 300ºC. Nitrogen was purged at 40 ml/min and 100 ml/min through cooling unit.
6) Scanning electron microscopy
SEM photographs were taken with a scanning electron microscope at the required magnification at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the microparticles.

7) Taste Evaluation
Evaluation of taste was done in two parts

A) Determination of Threshold Bitterness Concentration of ondansetron HCl
A panel of ten healthy human volunteers (age 20-25) was selected. A series of solutions of ondansetron HCl in phosphate buffer of pH 6.8 of concentrations 10, 20, 30, 40 and 50µg/ml were prepared. The volunteers were asked to hold 10 ml of each solution in oral cavity for 30 second and rate the taste as per scale. (Table 2)

Table 2: Ranking scheme for bitterness

<table>
<thead>
<tr>
<th>Taste</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bitterness</td>
<td>0</td>
</tr>
<tr>
<td>Threshold bitterness</td>
<td>1</td>
</tr>
<tr>
<td>Bitter</td>
<td>2</td>
</tr>
<tr>
<td>Moderate bitter</td>
<td>3</td>
</tr>
<tr>
<td>Strong bitter</td>
<td>4</td>
</tr>
</tbody>
</table>

Rinsing the mouth by distilled water and a gap of 30 min were applied between successive tests. Based on the opinion of the volunteers, threshold bitterness concentration of ondansetron HCl was judged.

B) In vitro taste evaluation
A quantity of beads equivalent to normal dose of ondansetron HCl was added to each of the three volumetric flasks containing 10 ml of phosphate buffer of pH 6.8. The mixtures were vortexed for 20, 40 and 60 seconds and filtered. Content of ondansetron HCl in each filtrate was determined. For satisfactory taste masking, the amount of drug dissolved should not be more than the threshold bitterness concentration of the drug.

8) In Vitro Release Profile of Drug loaded beads
In vitro drug release studies of drug loaded beads were performed in 0.1N hydrochloric acid using USP Type II Dissolution Test apparatus. Drug loaded beads equivalent to normal dose of drug was placed in dissolution jar. The dissolution medium was maintained at 37ºC ± 0.5ºC. The paddle was rotated at 50 rpm. The sample 5 ml was withdrawn after every 5 min
and absorbance was measured at 248 nm. The quantity of drug released was determined periodically.

9) Micromeritic Properties Of beads
Evaluation parameters like bulk density, tapped density, angle of repose and Carr’s index of beads were determined using methods reported.

2.2.4 Formulation of fast disintegrating tablets of taste masked beads of Ondansetron

Table 3- Composition of fast disintegrating tablets of beads

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Beads</td>
<td>44.15 mg</td>
<td>44.15 mg</td>
<td>44.15 mg</td>
<td>44.15 mg</td>
</tr>
<tr>
<td>2</td>
<td>Crospovidone</td>
<td>2 mg</td>
<td>3 mg</td>
<td>4 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>3</td>
<td>Magnesium Stearate</td>
<td>0.5 mg</td>
<td>0.5 mg</td>
<td>0.5 mg</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>4</td>
<td>Lactose</td>
<td>29 mg</td>
<td>28 mg</td>
<td>27 mg</td>
<td>26 mg</td>
</tr>
<tr>
<td>5</td>
<td>Aerosil</td>
<td>1 mg</td>
<td>1 mg</td>
<td>1 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>6</td>
<td>Mannitol</td>
<td>23.35 mg</td>
<td>23.35 mg</td>
<td>23.35 mg</td>
<td>23.35 mg</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100 mg</td>
<td>100 mg</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

Formulation of tablet was accomplished by compressing the mixture of beads (equivalent to dose of drug) along with other excipients as per the formula. (Table 3) Concentration of crospovidone was varied from 2-5 %. Tablets were compressed using 6 mm concave punch on Minipres II MT Rimek 8 station compression machine. Weight was maintained at 100 mg.

2.2.5 Evaluation of fast disintegrating tablets

Hardness
Five tablets from each batch were selected and hardness was measured using Monsanto hardness tester to find the average tablet hardness.

Friability
Twenty tablets were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability

\[ \% \text{ Friability} = \left( \frac{\text{Loss in weight}}{\text{Initial weight}} \right) \times 100 \]

Weight variation
Tablets were subjected to weight variation test I.P.20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2
of tablets differ by more than the percentage as per standards and no tablets differ in weight by more than double that percentage.

**Drug content of Tablets**

Five tablets were selected randomly and powdered. A quantity of this powder corresponding to normal dose of ondansetron HCl was dissolved in 100 ml of 0.1 N HCl, stirred for 60 min and filtered. 1 ml of the filtrate was diluted to 100 ml with 0.1 N HCl. Content of ondansetron HCl was estimated spectrophotometrically.

**Disintegration time (DT)**

The conventional DT apparatus may not give correct values of DT for FDTs. The amount of saliva available in the oral cavity is very limited (usually less than 6 ml) whereas the conventional DT apparatus uses a large amount of water with very rapid up and down movements. FDT is required to disintegrate in such small amount of saliva within a minute without chewing the tablet. In a simplest method to overcome this problem, 6 ml of phosphate buffer of pH 6.8 was taken in a 25 ml measuring cylinder. Temperature was maintained at 37±2°C. A FDT was put into it and time required for complete disintegration of the tablet was noted.

**Wetting time**

A Petri dish containing 6 ml of distilled water was used. A tissue paper folded twice was kept in the dish and a tablet was placed on it. Small drop of amaranth red solution was added at upper surface (middle portion) of the tablet. Time required for the upper surface of the tablet to become red was noted as the wetting time of the tablet.

**Dissolution studies**

Dissolution test was carried out using USP Type II Dissolution Test Apparatus at 37±2°C and 50 rpm speed. 900 ml of 0.1 N HCl was used as dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time intervals and amount of Ondansetron HCl released from tablets was determined.

3. **RESULT AND DISCUSSIONS**

3.1 Evaluation of beads

1) % Percentage practical yield
% practical yield was increased with increase in polymer concentration. Batch with 3% polymer show best yield while 1% polymer concentration and found difficulty to separate out the beads.

Table 4- % Practical yield and % entrapment efficiency

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>% yield</th>
<th>% E.E</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1</td>
<td>43.4±1.4</td>
<td>41.38±0.10</td>
</tr>
<tr>
<td>X2</td>
<td>55.86±1.05</td>
<td>53.16±0.11</td>
</tr>
<tr>
<td>X3</td>
<td>98.01±1.07</td>
<td>90.60±0.70</td>
</tr>
</tbody>
</table>

2) Drug content & Entrapment efficiency
It was observed that the drug entrapment efficiencies increased progressively with increasing the concentration of polymer. Increase in polymer concentration resulting in the formation of more compact beads entrapping the greater amount of the drug this may be attributed to the greater availability of active calcium binding sites in the polymeric chains and, consequently, the greater degree of cross-linking as the amount of polymer increased. Increase in polymer concentration may also reduce loss of drug in the curing medium due to the formation of dense matrix structure. Beads with 3% polymer concentration show % entrapment efficiency 90.6 much higher than other and therefore selected for further study. (Table-4)

3) Particle size analysis
The mean particle size of drug loaded beads was determined by Optical microscopy, and mean particle size of the beads was found to be 630μm.
4) Infrared spectroscopy

From the FT-IR spectra, it was observed that similar characteristic peaks appear with minor differences for the drug and drug loaded beads. Hence, it appears that there was no chemical interaction between the drug and the polymer used. It can be concluded that characteristic band of pure drug were not affected by successful loading. (Fig 1)

5) DSC study of beads

The endothermic peak of Ondansetron HCl appeared at 183.96°C which is its melting point. This endothermic peak was not observed in the DSC plots of the Ondansetron HCl loaded beads. It indicates that Ondansetron get entrapped in the polymeric matrix of beads. (Fig 2)
Figure 2 - DSC of 1) Ondansetron HCl, 2) Xyloglucan, 3) Drug loaded beads

6) Scanning electron microscopy
Morphological examination of beads by SEM shows spherical shape with rough surface.

Figure 3 - SEM of beads

7) Taste evaluation
A) Threshold Bitterness Concentration of ondansetron HCl
Threshold bitterness concentration of Ondansetron HCl was determined by 10 healthy human volunteers which was found 30 µg/ml. (Table 5)

Table 5 - Threshold Bitterness Concentration of ondansetron

<table>
<thead>
<tr>
<th>Volunteer No.</th>
<th>Rating on the scale of bitterness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10µg/ml</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>
Scale: 0= No bitter, 1=Threshold bitter, 2= bitter, 3= Moderate bitter, 4= Strong bitter

B) In vitro taste evaluation
The drug release from drug loaded beads in phosphate buffer pH 6.8 was less than the threshold bitterness value i.e. 30µg/ml. (Table 6) so it can be conclude that satisfactory taste masking was done.

Table 6 – In vitro taste evaluation of beads.

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Time (sec)</th>
<th>Concentration(µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>11.45±0.17</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>16.24±0.24</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>19.66±0.18</td>
</tr>
</tbody>
</table>

(n=3)

8) In vitro drug release profile of beads
In vitro release profile of beads shows drug release of 84.34 % within 20 min. (Figure 4)

Figure 4-In vitro drug release profile of beads

9) Micromeritic Properties Of beads
Micromeritic properties of drug loaded beads were evaluated such as bulk density, Carr’s index, angle of repose. It was observed that flow and compressibility were satisfactory.
3.2 Evaluation of fast disintegrating tablets

Hardness was found to be 3.0-3.3 kg/cm². Friability of FDTs was 0.44-0.54%. Disintegration time was decreasing with increase concentration of crospovidone, batch 3 with 4% crospovidone disintegrate within 44 sec. Wetting time was observed between 32-40 seconds. Batch 3 with 4% crospovidone was selected on the basis of less disintegration time than other and subjected for In vitro drug release study. All tablets passes weight variation test. (Table 8)

Batch 3 with 4% crospovidone was selected on the basis of less disintegration time than other and subjected for In vitro drug release study. In vitro release profile of FDT shows drug release of 77.48% within 20 min. (Figure 5)
4. CONCLUSION
Taste masking of bitter drug ondansetron HCl was successfully done by formation of tasteless beads using ionotropic gelation technique. Varying concentrations of xyloglucan polymers were used among them 3% concentration shows satisfactory result. (Figure 6)
It can also be concluded from above work that xyloglucan polymer can effectively use for ionotropic gelation technique and proves simple and easy method of taste masking.

REFERENCES


