TASTE MASKING OF BITTER DRUG BY USING ION EXCHANGE RESIN

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Abstract
Present study was aimed at taste masking of Ofloxacin using ion exchange resins as a taste masking agents. The Excipients used in the formulation was tested by drug-excipients compatibility study which showed no compatibility issues. For taste masking of Ofloxacin, ion-exchange resin method was used. The resins like Indion 204, Indion 214 and Tulsion 335 was tested at various ratios. Based on the results Tulsion 335 with the ratio 1:1.5 was selected for complexation. In vitro drug release studies showed more than 70% drug release at 20 minutes time point and complete drug release within 45 minutes.

Keywords :- Taste Masking, Ion Exchange Resin, Bitter drug, Drug Resin Complex, Batch Method etc.

INTRODUCTION
Taste masking of drug may be achieved by preventing the exposure of drug to the taste buds through processing or adding competing taste-masking agents. To achieve the goal of taste abatement of bitter or unpleasant taste of drug, various techniques reported in the literature are as follows:
➢ Ion-exchange resins
➢ Addition of flavouring and sweetening agents
➢ Microencapsulation
➢ Granulation
➢ Prodrug approach
➢ Solid dispersion system
➢ Bitterness inhibitor
➢ Gel formation
➢ Miscellaneous

Ion exchange resin
One of the popular approaches in the taste masking of bitter drugs is based Ion Exchange Resin (IER). IERs are solid and suitably insoluble high molecular weight polyelectrolyte that can exchange their mobile ions of equal charge with the surrounding medium.

Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of IER, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is an established unique advantage of IER due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites in their molecule,

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the resin’s charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7 and cation concentration of about 40meq/L in the saliva are not able to break the drug resin complex but it is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected \(2,3\).

**MATERIAL AND METHODS**

**Materials:** Ofloxacin was chosen as a model drug and was gifted by Shree Venkatesh International Ltd., Mumbai; Tulsion 335 (from Thermax India Ltd., Mumbai) was used as a taste masking agent.

**Methods:**

**Preparation of taste masked drug-resin (resinate) complex:**

Batch method was used to prepare drug-resin complex. Ofloxacin was mixed with different ion exchange resins i.e. Tulsion 335, Indion 204, and Indion 214 in the ratio of 1:1, 1:1.5, and 1:2. Fixed amount of resin was soaked in 500 ml of distilled water and allowed to swell for the definite period of time (30 min). Accurately weighed amount of Ofloxacin as per the ratio was added and stirred for 7 hours. Prepared complex kept overnight for the proper complexation. On the next day drug-resin complex was allowed to dry for the definite period of time in the tray dryer at a temperature of 60°C. The dried complex was sifted through sieve no. 30 and LOD was determined at a temperature of 105°C \(3,4\). The different trials were carried out as in table no. 1.

**Table No.3: Trials with ion exchange resin**

<table>
<thead>
<tr>
<th>S. N.</th>
<th>Resins</th>
<th>Batch</th>
<th>Drug: Resin Ratio</th>
<th>Swelling time (min)</th>
<th>Stirring time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Indion 204</td>
<td>F1</td>
<td>1:1</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>F2</td>
<td>1:1.5</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>F3</td>
<td>1:2</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Indion 214</td>
<td>F4</td>
<td>1:1</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>F5</td>
<td>1:1.5</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>F6</td>
<td>1:2</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>Tulsion 335</td>
<td>F7</td>
<td>1:1</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>F8</td>
<td>1:1.5</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>F9</td>
<td>1:2</td>
<td>30</td>
<td>7</td>
</tr>
</tbody>
</table>
Evaluation of Drug Resin Complex FT-IR Spectroscopy

The IR spectrum of pure Ofloxacin, Tulsion 335 and drug-resin complex was recorded using Fourier Transform Infra-Red spectrophotometer (Varian, 640 IR) with diffuse reflectance principle. The spectrum was scanned over a frequency range 4000 - 400 cm\(^{-1}\).

Differential Scanning Calorimetry

Phase transition of the untreated drug and the crystals were analyzed by DSC (Universal V2.4F TA Instruments, USA and Model: SDT 2960). The samples were heated in a hermetically sealed aluminium pans. Temperature range for each sample was set from 50 to 300\(^{0}\)C at a heating rate of 10\(^{0}\)C/min, using nitrogen as purging gas.

Evaluation of amount of non-complexed drug

The mixtures to be evaluated were kept aside to allow the particles to sediment and then filtered. From this filtrate, 1 ml was transferred in to 100 ml volumetric flask and the volume was made up to 100 ml and absorbance was noted, from which amount of non-complexed drug was calculated.

pH

The pH of Taste masked formulation was measured using Electroquip Digital pH meter at 25±1°C.

Drug content (By HPLC)

Taste masked formulation was dissolved in Buffer: Acetonitrile (80:20). An accurately weighed sample equivalent to 50 mg of Ofloxacin was taken in a stoppered volumetric flask (100 ml). The content was dissolved in Buffer: Acetonitrile (80:20) and the volume made up to 100 ml. This solution was filtered through Whatman filter paper no.41. The solution was diluted and the absorbance was measured at 315 nm. The drug content was calculated.

In vitro Dissolution Studies

Dissolution profile

Taste masked formulation of each batch was subjected to dissolution rate studies. In-vitro dissolution study was carried out to determine the drug release from various formulations. The release characteristic was determined by withdrawing aliquots of sample at the interval of 10, 20, 30 and 45 minutes.

RESULT AND DISCUSSION

![Figure No.1: FTIR Spectrum of Ofloxacin](image-url)
Figure No.2: FTIR Spectrum of Tulsion 335

Figure No.3: FTIR Spectrum of Ofloxacin - Tulsion 335 complex

Figure No.4: DSC graph of Ofloxacin
Figure No.5: DSC graph of Tulsion 335

Figure No.6: DSC graph of Ofloxacin-Tulsion 335 complex

Evaluation results of taste masked Ofloxacin-resin (resinate) complex
Complex was prepared by using different drug: resin ratio. Trials were carried out to obtained taste masked complex of drug with optimum drug loading efficiency. Depending upon the taste masking and % drug loading efficiency batch F8 i.e. with tulsion 335 in the ratio 1:1.5 was selected.
Table No.4: Evaluation results of taste masked Ofloxacin-resin (resinate) complex

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Resins</th>
<th>Batch</th>
<th>Drug: Resin Ratio</th>
<th>Taste</th>
<th>% Amount of non complexed drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Indion 204</td>
<td>F1</td>
<td>1:1</td>
<td>+</td>
<td>21.22</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>F2</td>
<td>1:1.5</td>
<td>++</td>
<td>19.55</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>F3</td>
<td>1:2</td>
<td>++</td>
<td>7.65</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>F4</td>
<td>1:1</td>
<td>+</td>
<td>32.73</td>
</tr>
<tr>
<td>5</td>
<td>Indion 214</td>
<td>F5</td>
<td>1:1.5</td>
<td>++</td>
<td>20.44</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>F6</td>
<td>1:2</td>
<td>+++</td>
<td>8.35</td>
</tr>
<tr>
<td>7</td>
<td>Tulsion 335</td>
<td>F7</td>
<td>1:1</td>
<td>+</td>
<td>14.80</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>F8</td>
<td>1:1.5</td>
<td>+++</td>
<td>1.75</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>F9</td>
<td>1:2</td>
<td>+++</td>
<td>1.68</td>
</tr>
</tbody>
</table>

Where,

+ = Slight taste masking
++ = moderate taste masking
+++ = complete taste masking

Selection of Drug-resin Complex

Using the batch method various drug-resinate complex was prepared with ion exchange resins in different ratio. Depending upon the taste masking and % drug loading efficiency batch F8 i.e. with Tulsion 335 in the ratio 1:1.5 was selected. The batch F8 has complete taste masking with 98.25% drug loading. Batch F9 also showed good taste masking with % drug loading but there is no significant difference when compared with batch F8. So batch F8 drug-resinate complex was used for the further study.

pH of Drug-resin Complex

The pH of the maximum stability of Ofloxacin in aqueous phase is in between 5 to 6. Therefore, the pH of the formulated Taste masked formulation was adjusted and maintained in between 5 to 6 with help of buffering agents such as citric acid and sodium citrate.

<table>
<thead>
<tr>
<th>Table No.5: pH of Drug-resin Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
</tr>
<tr>
<td>5.01 ± 0.05</td>
</tr>
</tbody>
</table>

Drug content of Drug-resin Complex

The drug content of Taste masked formulation of batches F1 to F9 was evaluated by HPLC method. The results are shown in the table.
Table No.6: Drug content of Drug-resin Complex

<table>
<thead>
<tr>
<th></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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>98.46%</td>
<td>99.36%</td>
<td>101.13%</td>
<td>100.35%</td>
<td>103.32%</td>
<td>96.65%</td>
<td>97.15%</td>
<td>100.30%</td>
<td>102.56%</td>
</tr>
</tbody>
</table>

The drug content of Ofloxacin found up to 100 % of formulation F8.

**In vitro drug release:**
In vitro dissolution was carried out using USP type II dissolution apparatus in 900 ml 0.1 N HCl dissolution medium at 75 RPM. Drug release was found to be more than 50 % of drug dissolved within 10 min.

![Figure no. 7 In vitro drug release profile of drug resin complex.](image)

**Taste evaluation of Drug-resin Complex**
The optimised formulation F8 was evaluated for taste using ten healthy, adult human volunteers. The grading system for the bitterness, aftertaste, sweetness, flavour, mouth feel given below the table:

Table No.7: Taste evaluation of Drug-resin Complex

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Volunteers</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitterness</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
</tr>
<tr>
<td>Aftertaste</td>
<td>NB</td>
<td>NB</td>
<td>BT</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
<td>NB</td>
</tr>
<tr>
<td>Sweetness</td>
<td>VS</td>
<td>SW</td>
<td>SW</td>
<td>VS</td>
<td>SW</td>
<td>VS</td>
<td>VS</td>
<td>VS</td>
<td>VS</td>
<td>VS</td>
<td>VS</td>
</tr>
<tr>
<td>Flavor</td>
<td>GD</td>
<td>MD</td>
<td>GD</td>
<td>GD</td>
<td>MD</td>
<td>GD</td>
<td>GD</td>
<td>GD</td>
<td>GD</td>
<td>GD</td>
<td>GD</td>
</tr>
<tr>
<td>Mouth feel</td>
<td>TS</td>
<td>TT</td>
<td>TT</td>
<td>TS</td>
<td>TS</td>
<td>TS</td>
<td>TS</td>
<td>TT</td>
<td>TS</td>
<td>TS</td>
<td>TS</td>
</tr>
</tbody>
</table>

Where,
**For Bitterness and Aftertaste:** non-bitter (NB), less bitter (LB), bitter (BT), very bitter (VB).

**For Sweetness:** less sweet (LS), sweet (SW), very sweet (VS).
For Flavour: less (LS), moderate (MD), good (GD).
For Mouth feel: less (TL), moderate (TT), good (TS).

From the table it indicates that overall taste response of ten volunteer it indicated that optimised formulation F8 having good taste.

**SUMMARY AND CONCLUSION**

The aim of the present study to taste masking of Ofloxacin. The Excipients used in the formulation was tested by drug-excipients compatibility study. All the excipients were compatible with Ofloxacin. For taste masking of Ofloxacin, ion-exchange resin method was used. The resins like Indion 204, Indion 214 and Tulsion 335 was tested at various ratios. Based on the results Tulsion 335 with the ratio 1:1.5 was selected for complexation. The dissolution studies of the Taste masked formulation for all the formulations show more than 70% drug release at 20 minutes time point and complete drug release within 45 minutes. The optimized formulation F8 evaluated for uniformity of dosage form and taste evaluation. It shows satisfactory results. Further this complex could be useful for the formulation of different taste masked dosage forms.

**REFERENCES**