Masking the unpleasant taste of Etoricoxib by crosslinked acrylic polymer based ion-exchange resin complexation

Inderbir Singh*, Banveet Kaur, Pradeep Kumar, Sandeep Arora

Chitkara College of Pharmacy
Chandigarh-Patiala National Highway
Punjab, India

Summary

Etoricoxib is an antiinflammatory and analgesic agent in the treatment of arthritis, dysmenorrhoea, acute dental surgery pain and is having a bitter taste. The present study is designed to mask the bitter taste of etoricoxib by complexation with weak cation exchange resins (Indion 214, 234 and 414) in order to increase its compatibility and patient compliance. Drug resinate were characterized by FTIR and XRD analysis methods. Drug resinate were evaluated by sensory taste evaluation test. Indion 234 resin was showing good taste masking ability compared to Indion 214 and 414. The in vitro drug release (after 60 minutes) was found to be 95%, 90% and 82% for F 234 III, F 414 III and F 214 respectively.

Key words: Etoricoxib, Taste masking, Indion-214, Indion-234, Indion-414, resinate, bitter taste, characterization

INTRODUCTION

Majority of the orally administered drugs have a natural bitter taste that can create a burning feeling in the throat or in the mouth which can lead to patient non-compliance in taking medicines, especially for

Maskowanie nieprzyjemnego smaku preparatu Etoricoxib przez krzyżowe powiązanie z opartą na polimerze akryłowym jonowymienialną żywicą

Streszczenie

Etoricoxib jest środkiem przeciwdziałającym i przeciwbólowym stosowanym w leczeniu choroby zwyrodnieniowej stawów, w zaburzeniach miesiączkowania, w zwalczaniu ostrego bólu po zabiegach dentystycznych. Jest to środek o charakterystycznym gorzkim smaku. Prezentowane badanie ma na celu zamaskowania gorzkiego smaku etoricoxibu poprzez związywanie go z żywicą, mającą własność wymiany słabych kationów (Indion 214, 234 i 414), w celu zwiększenia kompatybilności leku i poprawy komfortu pacjentów.

Żywice dodawane do leku są opisane metodami analizy FTIR i XRD. Żywice te zostały także ocenione w oparciu o test oceanny smaku. Żywica Indion 234 wykazała dobry ability masking gorzkiego smaku w porównaniu do Indion 214 i 414. Uwalnianie leku in vitro (po 60 minutach) wykazano jak 95%, 90% i 82% dla odpowiednio F 234 III, F 414 III i F 214.

Słowa kluczowe: Etoricoxib, maskowanie smaku, Indion-214, Indion-234, Indion-414, żywica, gorzki smak, charakterystyka

INTRODUCTION

Majority of the orally administered drugs have a natural bitter taste that can create a burning feeling in the throat or in the mouth which can lead to patient non-compliance in taking medicines, especially for
children and elderly, thereby reducing the effectiveness of the pharmacotherapy. Therefore it is necessary to reduce the bitterness and to improve palatability so that it is acceptable to the patients readily. Various techniques are available to mask the bitter taste, such as use of ion-exchange resins [1], the use of inclusion complexes with cyclodextrins [2], viscosity modifications [3], melt granulation [4], microencapsulation techniques like spray-drying [5], spray-congealing [6], coacervation [7] and solvent evaporation method [8].

Ion exchange resins are solid and suitably insolubilized high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium reversibly. Typically, the ionised drug and the ion-exchanger form a stable complex for the relatively short period of exposure, making the drug unavailable for taste sensation. As the formulation passes to the further parts of the GI tract, the drug is released from the ion-exchanger into the surrounding media due to the low pH in the stomach, increased ionic concentration of the GI tract, larger volume of the surrounding media and/or increased gastric residence time and is, thus, available for absorption. Ion exchange resins have been widely used as a drug carrier in pharmaceutical dosage forms for their taste masking and controlled release applications [9].

Etoricoxib is a selective Cox-2 inhibitor. It is suitable for once-a-day treatment of osteo/rheumatoid/acute gouty arthritis, dysmenorrhoea, acute dental surgery pain, and similar conditions, without affecting platelet function or damaging gastric mucosa [10]. But this drug has the bitter taste which may lead to patient non-compliance.

The present study was aimed to prepare carboxylic acid functionalized crosslinked polyacrylic ion-exchange resins (Indion-214, 234 and 414) based drug resinate complexes for masking the bitter taste of etoricoxib. The drug resinate were evaluated for bitterness and drug loading. Micromeritic studies (bulk density, angle of repose, carr’s consolidation index and hausner ratio) were also performed on drug resinates. Characterization of the complexes was carried using FTIR and XRD analysis techniques. Drug resinates were formulated in tablets by direct compression and the prepared tablets were evaluated for various parametric tests (hardness, friability, disintegration time). Finally in vitro dissolution studies were carried out to study drug release pattern from the drug resinate complex tablet formulation.

**MATERIALS**

Etoricoxib was received as a gift sample from Helios Pharma, Baddi, India. Indion-214, Indion-234 and Indion-414 were kindly gifted by Ion Exchange (India) Ltd, Mumbai, India. Vivapur 102 was a generous gift from S. Zhaveri Pharmakem Pvt. Ltd, Mumbai, India. All other chemicals/reagents were of analytical grade and were used as such.

**METHODS**

**Preparation of Etoricoxib Resinates**

Batch method was used in the preparation of drug resinates. Etoricoxib was reacted with cation exchange resins (Indion 214, Indion-234 and Indion-414) in various stoichiometric ratios (0.5:1, 1:1 and 1:2 of Drug:Resin) for preparing drug resin complexes. The weighed amount of resin was added to distilled water (25ml) in a glass beaker and the suspension was stirred on magnetic stirrer for 30 minutes followed by the addition of the drug. The contents of the beaker were allowed to stir in ambient conditions until equilibrium was attained. The drug resinates were then separated from the filtrate by filtration and washed several times with methanol and distilled water to remove any unreacted drug and other ions, respectively. The resinates were dried overnight at 40°C and kept in a desiccator.

**Loading of Etoricoxib**

Dry resinate (50mg) was extracted with hydrochloric acid (0.1 N, 100ml) in a sonicating bath for 30 minutes. The flask was allowed to stand for 1 hour and then an aliquot (1ml) was diluted to 10 ml with water and filtered before analysis by UV spectrophotometry using a dual beam spectrophotometer (2202, Systronics, India) at 284 nm. A calibration curve was produced using standard solution of Etoricoxib (between 1 and 20mg/litre) in 0.1N hydrochloric acid. Three replicate extractions were carried out for each resinate type.

**Taste Evaluation**

All the batches of formulated drug resin complexes were subjected to gustatory sensory evaluation test performed by a panel of ten volunteers. Sample
equivalent to 50 mg was held in mouth for 15 seconds. The evaluation was performed by classifying bitter taste into five classes: 0 – No bitter taste, 1 – Very slightly bitter taste, 2 – Slightly bitter taste, 3 – Appreciably bitter taste, 4 – Very bitter. Significant differences among different drug resinates were analyzed using the student’s unpaired t-test; a value of P < 0.05 was accepted as index of a significant difference between samples.

**FTIR Spectroscopy**

The drug, resin and resinate were subjected to Fourier Transform Infrared (FTIR) studies to check drug resin interaction. FTIR spectra were recorded on samples prepared in KBr using FTIR-8400S with IR solution software (Shimadzu). Data were collected over a spectral region from 4000 to 650 cm⁻¹ with resolution 4 cm⁻¹ and 100 scans.

**X-ray Diffraction Analysis**

The samples were subjected to X-ray diffraction study for the confirmation of complex formation. X-ray powder diffraction patterns were recorded on an X-ray diffractometer (Model X’Pert, Philips, Netherlands) using Ni-filtered, Cu K radiation, voltage of 40 kV and 25 mA current. The scanning rate employed was 1° min⁻¹ over the 0–100° diffraction angle (2θ) range.

**Determination of micromeritic properties of resinate**

The drug resinate were evaluated for various micromeritic properties like angle of repose, bulk density, tapped density, carr’s compressibility index and hausner ratio.

**Physical Evaluation of Granules**

**a) Angle of Repose:** Angle of repose of granules was determined by fixed funnel method. The powder was allowed to flow through the funnel kept on a stand at a fixed height. The granules were carefully poured through the funnel on the piece of paper placed on the horizontal surface until the apex of conical pile just reached the tip of the funnel. The height of the pile and radius of the conical pile was noted and angle of response was calculated using the following formula.

\[
\tan (\alpha) = \frac{h}{r}
\]

Where, \( \alpha \) = angle of repose, \( h \) = height of pile and \( r \) = radius of pile.

**b) Bulk density, tapped density, Carr’s compressibility index and Hausner ratio:** An accurately weighed fifteen grams of the dried granules were introduced in to 100 ml-graduated cylinder. The volume occupied by the powder bed was \( V_b \). The graduated cylinder so filled was placed on mechanical tapping apparatus. The cylinder was tapped 100 times which resulted in minimum volume and the volume occupied after tapping i.e. the tapped volume (\( V_t \)) was noted. Using the tapped volume and bulk volume the bulk density, tapped density, Carr’s compressibility index and Hausner ratio were calculated as follows:

\[
\text{Bulk density} = \frac{M}{V_b}
\]

\[
\text{Tapped density} = \frac{M}{V_t}
\]

\[
\text{Compressibility index} = \frac{V_b - V_t}{V_b} \times 100
\]

\[
\text{Hausner ratio} = \frac{V_b}{V_t}
\]

Where, \( M \) = mass of test sample; \( V_b \) = bulk volume and \( V_t \) = tapped volume.

**c) Percentage of fines:** An accurately weighed fifteen-gram of the granules were placed on sieve no 60. Amount of granules, which passed through the sieve no 60, and amount of granules retained on the sieve were weighed and the percentages of fines were calculated.

**Tablet processing**

The tablets of taste masked resinates of etoricoxib were prepared by direct compression using single stroke mutipunch tableting machine (AK Industries, Nakodar, India). The tablet weight was kept 250 mg for all the batches consisting of resinate equivalent to 50 mg of drug, Vivapur 102 (q,s), PVP-K-30 (4% w/w), Talc (1% w/w), magnesium stearate (1% w/w). The formulated tablets were evaluated for hardness, friability and disintegration time.
Physical evaluation of tablets [11]

a) **Weight variation:** Twenty tablets were weighed individually and their mean weight, and percentage relative standard deviation was calculated.

b) **Hardness:** Six tablets of each formulation were tested for hardness using Monsanto hardness tester.

c) **Disintegration time:** Six tablets of each formulation were used to determine disintegration time. Water was used as a disintegration medium and temperature was maintained at 37 ± 0°C.

d) **Friability:** Twenty tablets of each batch were weighed and put into the friabilator drum. After 100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust and weighed. Friability was calculated from the following formula.

\[
\% \text{Friability} = \frac{W_1 - W_2}{W_1} \times 100,
\]

where, \(W_1\) and \(W_2\) are the weights of tablets before and after specified rotation in friability test apparatus.

**In vitro dissolution**

A USP 23 Dissolution Test Apparatus (paddle type) at 37 ± 0.5°C and 50 rpm using 900 mL 0.1 N HCl (pH 1.2) as dissolution medium (\(n = 3\)) was used to characterize the release of etoricoxib from the tablets formulated using drug resinates. Samples of dissolution medium (5 mL) were withdrawn at predetermined time intervals and an equal amount of fresh dissolution medium was added. Test samples were filtered through Whatman filter paper No. 41 (Whatman Paper Limited, UK), suitably diluted and assayed for etoricoxib at 284 nm using a blank solution as reference with a UV-Vis double-beam spectrophotometer (Systronics 2202, India). The cumulative percentage of etoricoxib dissolved was calculated using a regression equation generated from the standard data.

**RESULTS AND DISCUSSION**

Preparation of drug-resinate by batch method was preferred over elution method because of inefficient elution of drug solution from the column due to its small particle size. Batch method was also preferred because of its convenience. Equilibration time was determined by measuring the concentration of drug on the solution. Drug:resin ratio had a prominent effect on drug loading as shown in Table 1 with 1:1 showing the maximum drug loading. Increase in the amount of resin increases the amount of drug absorbed as number of sites increased in 1:1 ratio as compared to 0.5:1 ratio leading to a higher loading capacity, but the drug content per gram decreased in case of 1:2 ratio which might be due to exhaustion of the available complexation sites. Among the various resins, the % drug loading followed the sequence Indion 234 > Indion 214 > Indion 414.

**Taste evaluation**

A panel of 10 members using time intensity method were employed for discriminating (in terms of bitterness) various batches of resinates formulated using different ion exchange resins in different proportions. The taste masking potential of the selected resins was found to increase with increasing concentration of resin in the resinate. F 414 I was found to exhibit appreciable bitter taste compared to F 234 I and F 214 I. Very slight bitterness/no bitterness was exhibited by F 234 II and F234 II. The bitterness score of the resinates formulated using Indion 234 exhibited better taste masking ability when compared with Indion 214 and Indion 414. Compiled results of the taste evaluation study are depicted in Table I.

**FTIR**

The FTIR spectra of pure etoricoxib showed characteristic peaks at 1492.80, 1562.23 and 1596.95 cm\(^{-1}\) (C = N stretching vibration), 1431.08, 1296.08, 1137.92 and 1085.85 cm\(^{-1}\) (S = O stretching vibration) and 840.91, 775.33 and 727.11 cm\(^{-1}\) (C–Cl stretching vibration). Significant reduction in the intensity of distinctive peaks of drug at 727.11, 1085.85 and 1492.80 cm\(^{-1}\) demonstrates the formation of complex between drug and the resin molecule. The characteristic peaks in Indion 214 (1737.74/1701.10 and 1554.52 cm\(^{-1}\)), Indion 414 (1701.10/1647.10 and 1552.59 cm\(^{-1}\)) Indion 234 (1685.67 and 1633.59/1517.87 cm –1) corresponding to C = O stretching of aryl acids and aromatic C = C stretching respectively. The characteristic imine group a peak (1690 cm\(^{-1}\)) of drug was found to be suppressed upon complexation with the resins indicating the involvement of imine group in the formation of drug resinate.

**XRD**

Characteristic peaks appeared in the XRD pattern of the drug alone, suggesting that the drug is pres-
ent as a crystalline material. All the peaks of etoricoxib in the complex showed lower intensity compared to the pure drug and the drug resinate. The results indicated that the drug in the complex is completely amorphous compared to the pure drug as well as the resinate.

**Micromeritics**

The results of micromeritic properties viz. tapped density (0.54 – 0.71 g/cm³), bulk density (0.42 – 0.50 g/cm³), angle of repose (22.20 – 29.63), carr’s consolidation index (10.91 – 30.00), hausner ratio (1.12 – 1.48) clearly indicates good flow characteristics of the resinates (Tab. 2).

**Table 1. Drug loading and taste evaluation test on the formulated drug resinates**

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Drug : Resin</th>
<th>Drug loading (%)</th>
<th>Rating/Scoring</th>
<th>Remarks/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-214 I</td>
<td>1:0.5 (214)</td>
<td>27.75 ± 1.21</td>
<td>2</td>
<td>Slightly bitter taste</td>
</tr>
<tr>
<td>F-214 II</td>
<td>1:1 (214)</td>
<td>42.15 ± 1.36</td>
<td>2</td>
<td>Slightly bitter taste</td>
</tr>
<tr>
<td>F-214 III</td>
<td>1:2 (214)</td>
<td>35.11 ± 1.83</td>
<td>0</td>
<td>No bitter taste</td>
</tr>
<tr>
<td>F-234 I</td>
<td>1:0.5 (234)</td>
<td>29.22 ± 1.39</td>
<td>1</td>
<td>Very slightly bitter taste</td>
</tr>
<tr>
<td>F-234 II</td>
<td>1:1 (234)</td>
<td>43.50 ± 1.25</td>
<td>1</td>
<td>Very slightly bitter taste</td>
</tr>
<tr>
<td>F-234 III</td>
<td>1:2 (234)</td>
<td>35.14 ± 1.42</td>
<td>0</td>
<td>No bitter taste</td>
</tr>
<tr>
<td>F-414 I</td>
<td>1:0.5 (414)</td>
<td>18.24 ± 1.53</td>
<td>3</td>
<td>Appreciably bitter taste</td>
</tr>
<tr>
<td>F-414 II</td>
<td>1:1 (414)</td>
<td>38.48 ± 1.21</td>
<td>1</td>
<td>Slightly bitter taste</td>
</tr>
<tr>
<td>F-414 III</td>
<td>1:2 (414)</td>
<td>28.52 ± 1.32</td>
<td>0</td>
<td>No bitter taste</td>
</tr>
</tbody>
</table>

**Table 2: Micromeritic properties of the formulated batches of taste masked resinates of etoricoxib along with evaluation parameters of the prepared tablets**

<table>
<thead>
<tr>
<th>Batches</th>
<th>Micromeritic Properties of Resinate</th>
<th>Tablets Related Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bulk density (g/cm³)</td>
<td>Tapped density (g/cm³)</td>
</tr>
<tr>
<td>F-214 I</td>
<td>0.44</td>
<td>0.54</td>
</tr>
<tr>
<td>F-214 II</td>
<td>0.50</td>
<td>0.58</td>
</tr>
<tr>
<td>F-214 III</td>
<td>0.46</td>
<td>0.55</td>
</tr>
<tr>
<td>F-234 I</td>
<td>0.50</td>
<td>0.65</td>
</tr>
<tr>
<td>F-234 II</td>
<td>0.46</td>
<td>0.64</td>
</tr>
<tr>
<td>F-234 III</td>
<td>0.48</td>
<td>0.71</td>
</tr>
<tr>
<td>F-414 I</td>
<td>0.45</td>
<td>0.59</td>
</tr>
<tr>
<td>F-414 II</td>
<td>0.49</td>
<td>0.55</td>
</tr>
<tr>
<td>F-414 III</td>
<td>0.42</td>
<td>0.60</td>
</tr>
</tbody>
</table>

**Tablet properties**

Friability of the tablets was found to be ranging between 0.45 to 0.80 % indicating good mechanical resistance of the formulated tablets of the resinates. Hardness was found to be between 2.5 to 4.75 kg/cm². The disintegration time of tablets was found to be between 0.90 to 1.50 minutes. As no disintegrating agent was included for formulating tablets, the effective tablet disintegration was due to extensive swelling properties of the selected resins.
Release Profile

Figures 1 and 2 demonstrate the drug release studies of the etoricoxib resinate complexes (ERC). Even though the disintegration time of the ERC tablets is less than the conventional marketed tablets (CMT), the release of etoricoxib is modified as compared to the conventional marketed tablet. The retarded drug release from the ERC can be attributed to the bound form of the drug. Even so, all batches released more than 90 % in less than 2 hours. A suitable range for immediate-release dosage forms (in the Ph. Eur. or in the USP) would be the release of at least 80 % in 60 min. If this is applied to the release from the presented ERC tablets, all formulations comply and can therefore be described as immediate release dosage forms. Further, the $f_2$ values were calculated in accordance with the equation proposed by Moore and Flanner\textsuperscript{12} as follows:

$$f_2 = 50 \log \left(1 + \frac{1}{n} \sum_{i=1}^{n} w_i (R_i - T_i)^2 \right)^{-0.5} \times 100$$

where $f_2$ is similarity factor, $n$ is the number of observations, $w_i$ is optional weight, $R_i$ is percentage drug dissolved from reference formulation, and $T_i$ is percentage drug dissolved from test formulation. The results of similarity factor, $f_2$, revealed that the dissolution profile of batch F-214 II, F-414 II and F-234 II was found to be similar with that of F-214 III, F-414 III and F-234 III with $f_2$ values of 83.50, 79.86 and 73.16 % respectively (Fig. 3 and 4).

Fig. 1. *In vitro* drug release profile from F-214 III, F-414 III and F-234 III resinate tablet batches

Ryc. 1. Profil uwalniania leku z partii tabletek modyfikowanych żywicami F-214 III, F-414 III i F-234 III

Fig. 2. *In vitro* drug release profile from F-214 II, F-414 II and F-234 II resinate tablet batches

Ryc. 2. Profil uwalniania leku *in vitro* z partii tabletek modyfikowanych żywicami F-214 II, F-414 II i F-234 II
Fig. 3. FTIR spectra of (a) Etoricoxib (b) Indion 414 resin (c) Indion 214 resin (d) Indion 234 resin (e) F 414 I resinate (f) F 214 I resinate (g) F 234 I resinate

Ryc. 3. Spektra FTIR Etoricoxib (a), żywicy Indion 414 (b), żywicy Indion 214 (c), żywicy Indion 234 (d), żywicy F 414 I (e), żywicy F 214 I (f), żywicy F 234 I (g)

**CONCLUSION**

Complexation of etoricoxib with cation exchange resins (Indion 214, 234 and 414) was found to increase the acceptability and palatability of the drug. Moreover the 1:2 drug resin complex of Indion 234 was found to better taste masking properties compared to drug resinates of Indion 214 and 414. XRD and FTIR analysis were carried out for the characterization of resinates. The drug resinates were found showing good micromeritic properties.

**Acknowledgement**

The authors are grateful to Dr. Madhu Chitkara, Director, Chitkara Institute of Engineering and Technology, Rajpura, Patiala, India, Dr. Ashok Chitkara, Chairman, Chitkara Educational Trust, Chandigarh, India for support and institutional facilities.

**LITERATURE**


Author’s address
Inderbir Singh
Chitkara College of Pharmacy
Chandigarh-Patiala National Highway
Rajpura–140401, Patiala, Punjab, India
Corresponding author: inderbirsingh2906@gmail.com