Dissolution studies on tablets of ibuprofen using chitosan

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An attempt has been made to study the release retardant behaviour of chitosan in ibuprofen tablets. Three different ibuprofen tablets were prepared by using 1,3 and 5% chitosan paste. In vitro evaluations were carried out by using dissolution testing apparatus U.S.P (XXI). The dissolution pattern indicated the role of chitosan in sustained release. Bioavailability studies in male beagle dogs clearly showed the sustained nature of release from chitosan based ibuprofen tablet as compared to conventional ibuprofen marketed formulation. Potential use of chitosan as a new matrix forming material for sustained release preparation has been examined. Chitosan, a natural polysaccharide, has structural characteristics similar to glycosaminoglycans. Chitosan has been shown to be non-toxic and biodegradable. It is inexpensive and has been explored in the present investigation as a release retarding agent in ibuprofen tablets.

Chitosan is (1,4)-2-amino-β-d-glucan. Crustaceans shells are the usual raw material of chitin. Earlier workers reported LD₅₀ and oral toxicity of chitosan in mice and rats. Lack of acute oral toxicity of chitosan was noticed as evidenced by an oral LD₅₀ of 10g/kg in mice. Controlled release of drug through chitosan has been achieved. For the present study ibuprofen is selected as a model drug. Ibuprofen[2-(4-isobutyl phenyl) propionic acid] a non-steroidal anti-inflammatory agent is widely used in the treatment of several acute and chronic conditions. The drug when administered as a conventional dosage form has a very short half life and causes gastrointestinal irritation. A controlled release formulation of ibuprofen could provide sustained plasma levels of drug for a prolonged period and also minimise gastric distress.

The investigation reports the design of sustained release tablets containing 300 mg of ibuprofen per unit. The tablet matrices were fabricated using chitosan paste in different concentrations. The formulations were tested for in vitro release profile. The selected formulations which showed sustained in vitro release pattern commensurate with pharmacokinetic characteristics of the drug were tested for stability and in vivo plasma levels of the drug in dogs.

Ibuprofen, talc, magnesium stearate and lactose of I.P grade were used. Chitosan was obtained from Central Institute of Fisheries Technology, Cochin. All other reagents were of analar grade. Digital three stage dissolution testing apparatus, UV-vis spectrophotometer (Systronics 118 model) and centrifuge were the instruments used.

Ibuprofen was triturated thoroughly with lactose and passed through a fine mesh. The collected material was granulated using 3 and 5% chitosan paste which was prepared with 10% acetic acid solution. When enough cohesion obtained the mass was passed through sieve No. 14 and the granules were dried at 150°C for 2 hr.

The dried mass was passed through a sieve No. 20. The 16/20 fraction was mixed with 5% of its weight with starch and lubricated with talc and magnesium stearate. The lubricated granules were then taken for compression.

The tablets were punched in cadmach single punch tablet compression machine using concave punches under constant pressure.

Tablet pressure such as weight variation, hardness and percent friability were determined by standard methods. The drug content of the tablet was determined by spectrophotometry.

Physical stability and effect of ageing on the drug release were studied in ibuprofen matrix tablets containing 1, 3 and 5% Chitosan.

Physical stability and effect of ageing on the drug release were studied for the following preparations. Ibuprofen control tablets and ibuprofen tablets
prepared with Chitosan. Tablets were kept in small air tight glass containers and stored at 37°C in an incubator and 45°C in an oven and at relative humidities of 82.5, 57 and 17.5% for eight weeks. The tablets were observed every two weeks for the following changes, if any (i) change of colour (ii) change in tablet characteristics (iii) effect of ageing on the release characteristics were studied (Table 1 & 2).

The in vitro drug release profile of each formulation was determined on U.S.P. XXI dissolution testing apparatus. The medium used was pH 7.2 buffer and the speed of rotation of the basket was maintained at 150 rpm.

Samples of 5 ml were withdrawn at 30 min intervals for a period of 8 hr. After each withdrawal, the dissolution medium was replenished with 5 ml of the same fresh medium. The amount of drug released was estimated spectrophotometrically at 221 nm. The minimum sensitivity of assay procedure is 1 µg/ml.

In vivo availability—Standard conventional marketed ibuprofen tablet, formulated and selected matrix tablet each containing 300 mg of ibuprofen were administered by intubation to three anaesthetised male dogs weighing between 10 and 15 kg, according to randomized cross over design. Dogs were anaesthetised by intraperitoneal administration of pentobarbitone sodium (May & Baker) 40 mg/kg. Blood samples (5 ml) were withdrawn before administration of the product and at 1, 2, 4, 6, 8, and 10 hr after dosing. Butterfly cannula was used for sample collection from femoral vein. Plasma was separated by centrifuging the heparinised blood samples immediately after withdrawal. To 1 ml of plasma sample, 0.1 ml of perchloric acid was added

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<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density g/ml</th>
<th>True density g/ml</th>
<th>Total Porosity</th>
<th>Angle of repose</th>
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</thead>
<tbody>
<tr>
<td>Control tablet</td>
<td>0.300 ± 0.030</td>
<td>0.836 ± 0.04</td>
<td>64.5 ± 2.6</td>
<td>36.45 ± 0.25</td>
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<tr>
<td>Ibuprofen</td>
<td>0.325 ± 0.020</td>
<td>1.052 ± 0.072</td>
<td>68.5 ± 0.072</td>
<td>30.15 ± 0.22</td>
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<td>Ibuprofen Matrix Tablet (1% Chitosan)</td>
<td>0.355 ± 0.050</td>
<td>1.126 ± 0.22</td>
<td>70.11 ± 4.8</td>
<td>36.15 ± 0.15</td>
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<tr>
<td>Ibuprofen Matrix Tablet (3% Chitosan)</td>
<td>0.045 ± 0.0250</td>
<td>1.184 ± 0.072</td>
<td>72.75 ± 3.3</td>
<td>36.16 ± 0.14</td>
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<tr>
<td>Ibuprofen Matrix Tablet (5% Chitosan)</td>
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Table 1—Characteristics of granules in various tablets
(Values are mean ± SD)

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![Graph](image_url)

Fig. 1—In vitro dissolution studies of Ibuprofen matrix tablets in buffer 7.2 pH. Each data point is the mean of 8 determinations.
and the drug was extracted into 5 ml of hexane. The drug was determined spectrophotometrically at 221 nm. Non-interference of pentobarbitone sodium in the assay of ibuprofen in plasma was confirmed by UV spectrum.

There was no interaction between chitosan and ibuprofen which was confirmed by infrared spectrum of physical mixture of chitosan and ibuprofen. The dissolution decreases with increase in concentration of chitosan. The rate of dissolution was more faster in the case of control tablets. 10% for 1, 3 and 5% chitosan matrix tablets were 45, 90 and 240 min respectively. The release of ibuprofen from the matrix tablet may be diffusion controlled, obeying the Higuchi equation. The dissolution data indicate that the matrix containing 5% chitosan has more sustained action than the other two formulations. Chitosan formed hydrophilic matrices and dissolution of chitosan formed matrix tablets are diffusion controlled (Fig. 1).

In vivo study in dogs with matrix tablets showed no drug dumping. Matrix formulation provided an extended availability of the drug for a period of 11 hr (Fig. 2). In comparison the conventional formulation showed a quick rise and decline in plasma levels. The in vitro release pattern of two of the formulations was reflected by a sustained in vivo performance in dogs. Thus it is possible to formulate suitable oral sustained release ibuprofen for better drug delivery system.

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<table>
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<tr>
<th>Formulation</th>
<th>Hardness kg/cm²</th>
<th>Friability loss (%)</th>
<th>Disintegration time (min)</th>
<th>Av. weight mg</th>
<th>Diam. of tablet (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control tablet</td>
<td>1.18 ± 0.05</td>
<td>0.38 ± 0.02</td>
<td>5</td>
<td>250 ± 0.12</td>
<td>3/8</td>
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<td>Ibuprofen</td>
<td>1.85 ± 0.05</td>
<td>0.036 ± 0.05</td>
<td>10</td>
<td>250 ± 0.08</td>
<td>3/8</td>
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<td>Ibuprofen Matrix Tablet (1% Chitosan)</td>
<td>1.92 ± 0.06</td>
<td>0.34 ± 0.15</td>
<td>15</td>
<td>250 ± 0.02</td>
<td>3/8</td>
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<td>Ibuprofen Matrix Tablet (3% Chitosan)</td>
<td>1.98 ± 0.20</td>
<td>0.30 ± 0.20</td>
<td>22</td>
<td>250 ± 0.05</td>
<td>3/8</td>
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Fig. 2—In vivo release studies of ibuprofen tablets prepared using 5% concentration of chitosan in comparison with starch paste as binding agent in male beagle dogs. Each data point is mean of 6 determination.
References