Formulation and Evaluation of Diclofenac Sodium Tablet using Isolated starch from Unripe Papaya Fruits as Disintegrant.

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ABSTRACT
The main objective of this research was to introduce and evaluate the disintegrant property of natural excipient like starch from unripe fruits of Papaya when used in tablet formulation. Pharmaceutical excipients developed from natural sources are economic. The unripe fruit of Papaya has high level of starch content and hence can be used as a raw material for starch isolation. Starch was isolated from green unripe papaya fruits using 0.5 N NaOH as Lye solution. Isolated starch was evaluated and used as a disintegrant in formulation of tablet using diclofenac sodium as model drug by wet granulation method. Studies indicate that starch so obtained is qualitatively and quantitatively comparable to Corn starch. The disintegration time of formulated tablet was evaluated as per Indian Pharmacopoeia and was compared with marketed tablets. These tablets also conformed to the disintegration and dissolution specifications of Indian Pharmacopoeia. Results from various evaluations suggested that Carica papaya starch showed adequate disintegrating characteristics and could be used as disintegrant in tablet formulation.

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INTRODUCTION
Starch is a relatively cheap raw material with physical and chemical properties that impart multiple uses in pharmaceutical industry. Starch can be extracted using different processes, depending on the plant source and end use of the starch. Starch from various sources has been widely used for various reasons in pharmaceutical formulations. Besides the yield of isolated starch, in order to make it economically viable, it must be accomplished without any significant modification to the starch granules [1]. Carica papaya Linn. (C.P) (Caricaceae) is a fast-growing, semi woody tropical herb reaching 3-10 m in height. The fleshy stem is single, straight and hollow and contains prominent leaf scars. Papaya exhibits strong apical dominance rarely branching unless the apical meristem is removed, or damaged. Carica papaya contains many biologically active compounds. Since, each part of papaya tree possesses economic value; it is grown on commercial scale [2]. Unripe pulp of Carica papaya can be ranked as carbohydrate rich fruit due to its high carbohydrate and starch contents. Unripe Carica papaya fruit contains about 43% of starch [3]. Starch is used as multifunctional excipients in the field of pharmaceutical sciences. Swelling property of the starch is responsible for its disintegration activity. Disintegrating agents are the hydrophilic substances which when come in contact with saliva or gastric fluid absorb water, swell and cause disintegration of tablets [4]. Starch is one of the most widely used excipient as filler, binder, and disintegrant in the manufacture of solid dosage forms. Although Corn starch is one of the most widely used starches in pharmaceutical formulations, starches from other botanical sources have shown difference in functional properties such as gelling, swelling and water binding capacity which influence their capacity to function effectively as binding and disintegrating agent. Due to their effect as powerful disintegrant, starches have been found useful in preparation of insoluble drug substances.[5] In the present study starch was isolated from the unripened papaya pulp and the isolated starch was used as disintegrant for the preparation of tablets using diclofenac sodium as a model drug. Wet granulation method was used for the preparation of tablets. The tablets were then evaluated as per Indian Pharmacopoeia and compared with marketed tablets.

MATERIALS AND METHODS
Materials
Unripe papaya was obtained from local market and starch was isolated in laboratory. Diclofenac (Korten Pharma Pvt Ltd.), Corn starch and all other chemicals were of analytical grade which were obtained from Loba chemicals Pvt Ltd Mumbai.

Isolation of starch
Extraction of starch from unripe papaya was carried by alkaline extraction method using sodium hydroxide as Lye solution. The pulp of unripe papaya was isolated and dried, powdered and mixed with 0.5 N NaOH solution to prepare a slurry in ratio 1:3 (Papaya: Lye solution). The slurry was held for 2-3 hrs, then diluted with water in ratio 1:5 (Slurry: Water). The mass was then strained through muslin cloth and washed with saline solution several times to remove soluble substances, sugar and mucilage present. The mass obtained was then washed repeatedly until the supernatant solution was clear. This residue was further filtered and centrifuged at 5000 rpm for 45 min. The sedimented starch was collected and washed with ethanol followed by water until the pH was neutral. It was then sieved, dried at room temperature and milled to fine powder [6].

Figure 1a-1b: Carica papaya starch grains in microns.

Pharmaceutical characterization of Starch.
Identification test (Iodine Test).
1 g of papaya starch and corn starch was boiled with 50 ml of water separately. After cooling to 1 ml of the mucilage, 2 drops of 0.1 N iodine solutions were added and the color change was noted [7].

Particle size determination (Light Microscopy).
A small amount of starch was mixed with glycerol and mounted onto a microscope slide with a cover slip and examined by polarized light microscopy. The mean particle size of samples of starch was determined microscopically with the aid of a calibrated eyepiece. The particle size of each sample dispersed in glycerol was determined [8].
Paste clarity.
The clarity (transmittance % at 650 nm) of papaya starch paste was measured. A 1% aqueous suspension of starch near neutral pH was heated in a boiling water bath for 30 min with intermittent shaking. After the suspension was cooled for 1 hr at 25° C, the light transmittance at 650 nm was read against water blank [9].

Moisture content
A 3 g weight each of corn and papaya starch was heated at 135° C using moisture analyzer and the reading was recorded.

Swelling capacity.
The tapped volume occupied by 10 g of each corn powder and papaya starch (Vd) in a 100 ml measuring cylinder was noted. This powder was then dispersed in 85 ml of distilled water and volume was made up to 100 ml with distilled water. After 18 hrs of standing, the volume of the sediment, (Vw) was estimated and the swelling capacity was determined as: [10]

Swelling capacity = Vw – Vd

Ash Value of starch.
Total 2 g quantity of starch was weighed into a silica crucible and incinerated. Determination of ash value was done by measurement of the residue left after complete combustion in a muffle furnace at 550° C [11].

Table 1: Formulation of tablet by wet granulation:-

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>F1 Corn Starch</th>
<th>F2 *C.P. Starch</th>
<th>F3 *C.P. Starch</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diclofenac sodium (mg)</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2.</td>
<td>Lactose (mg)</td>
<td>145.75</td>
<td>145.75</td>
<td>152.5</td>
</tr>
<tr>
<td>3.</td>
<td>Starch (mg)</td>
<td>22.50</td>
<td>22.50</td>
<td>11.25</td>
</tr>
<tr>
<td>4.</td>
<td>Talc (mg)</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>5.</td>
<td>Magnesium stearate (mg)</td>
<td>2.25</td>
<td>2.25</td>
<td>2.25 μ</td>
</tr>
<tr>
<td>6.</td>
<td>Isopropyl alcohol (ml)</td>
<td>QS</td>
<td>QS</td>
<td>QS</td>
</tr>
</tbody>
</table>

Table 2: Pharmaceutical characterization of starch.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Characterization of Starch</th>
<th>*C.P. Starch</th>
<th>Corn Starch</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Iodine test</td>
<td>+ Ve</td>
<td>+ Ve</td>
</tr>
<tr>
<td>2.</td>
<td>Paste clarity (%)</td>
<td>14.9</td>
<td>9.67</td>
</tr>
<tr>
<td>3.</td>
<td>Average Grain size (µ)</td>
<td>12.23</td>
<td>27.3</td>
</tr>
<tr>
<td>4.</td>
<td>Ash Value(% w/w)</td>
<td>16.2 ± 0.8</td>
<td>15.3 ± 0.2</td>
</tr>
<tr>
<td>5.</td>
<td>Moisture Content</td>
<td>5.93 ± 0.3</td>
<td>6.24 ± 0.4</td>
</tr>
<tr>
<td>6.</td>
<td>Swelling capacity</td>
<td>2.147 ± 0.86</td>
<td>2.037 ± 0.52</td>
</tr>
<tr>
<td>7.</td>
<td>Angle of repose</td>
<td>27.35° ± 1.45</td>
<td>24.43° ± 1.34</td>
</tr>
<tr>
<td>8.</td>
<td>Bulk Density(g/ml)</td>
<td>0.43 ± 0.38</td>
<td>0.44 ± 0.47</td>
</tr>
<tr>
<td>9.</td>
<td>Tapped Density(g/ml)</td>
<td>0.53 ± 0.28</td>
<td>0.50 ± 0.62</td>
</tr>
<tr>
<td>10.</td>
<td>Carr’s Index (%)</td>
<td>18.86 ± 1.12</td>
<td>12.00 ± 1.44</td>
</tr>
<tr>
<td>11.</td>
<td>Hausner’s ratio</td>
<td>1.23 ± 0.29</td>
<td>1.13 ± 0.66</td>
</tr>
</tbody>
</table>

Table 3: Evaluation of granules.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Batch</th>
<th>Tapped Density (g/ml)</th>
<th>Bulk Density (g/ml)</th>
<th>Carr’s Index (%)</th>
<th>Angle of repose</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>1.0 ± 0.01</td>
<td>0.90 ± 0.005</td>
<td>10.0 ± 0.057</td>
<td>18.25°</td>
<td>1.17 ± 0.14</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>0.8 ± 0.05</td>
<td>0.75 ± 0.002</td>
<td>6.25 ± 0.005</td>
<td>21°</td>
<td>1.15 ± 0.12</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>0.7 ± 0.01</td>
<td>0.62 ± 0.005</td>
<td>11.42 ± 0.020</td>
<td>16.23°</td>
<td>1.14 ± 0.15</td>
</tr>
</tbody>
</table>
Table 4: Friability test and Hardness Test

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Batch</th>
<th>Friability (%)</th>
<th>Hardness (kg / cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>0.8 ± 0.012</td>
<td>4.7</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>0.7 ± 0.013</td>
<td>4.1</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>0.7 ± 0.025</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Table 5: Disintegration Test

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Diclofenac Sodium Tablet</th>
<th>Disintegration time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Marketed Tablet</td>
<td>5.50</td>
</tr>
<tr>
<td>2.</td>
<td>Batch F1</td>
<td>3.18</td>
</tr>
<tr>
<td>3.</td>
<td>Batch F2</td>
<td>2.80</td>
</tr>
<tr>
<td>4.</td>
<td>Batch F3</td>
<td>4.32</td>
</tr>
</tbody>
</table>

Table 6: Dissolution study of batch F1, F2 and F3.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>10</td>
<td>38.8</td>
</tr>
<tr>
<td>20</td>
<td>47.3</td>
</tr>
<tr>
<td>30</td>
<td>64.2</td>
</tr>
<tr>
<td>40</td>
<td>71.6</td>
</tr>
<tr>
<td>50</td>
<td>78.2</td>
</tr>
<tr>
<td>60</td>
<td>82.5</td>
</tr>
</tbody>
</table>

Flow properties of starch [12].

Angle of repose
It was determined by allowing powder to flow through a funnel and fall freely on to a surface. Further addition of powder was stopped as soon as the pile has touched the tip of the funnel. A circle was drawn around the pile without disturbing it. The height and diameter of the resulting cone was measured. The same procedure was repeated three times and the average value was taken. Angle of repose was calculated by using the following equation: \( \tan \theta = \frac{h}{r} \)

Where, \( h \) = height of the powder cone; \( r \) = radius of the powder.

Bulk density
A quantity of material sufficient was passed through a 1.00 mm (no.18) screen to break up agglomerates that may have been formed during storage to complete the test. Into a dry 250 ml cylinder approximately 100 g of the test sample (M) was introduced. The cylinder was filled carefully and level of powder was adjusted without compacting and the unsettled apparent volume (Vo) was noted. Bulk density was calculated, in g/ml.

Using the formula: \( \text{Bulk density} = \frac{M}{Vo} \)

Tapped density
Accurately weighed quantity of powder was introduced into a measuring cylinder. Mechanically the cylinder containing the sample was tapped by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester at a nominal rate of 300 drops/min. The cylinder was tapped 500 times and the tapped volume (Va) was measured. Procedure was repeated for an additional 750 tapings and again the tapped volume was measured as (Vb). If the difference between Va and Vb was <2%, Vb was the final tapped volume (Vf). If the difference was higher, the tapings were repeated for an additional 1,250 times, and then the tapped density was calculated using the following formula:

\( \text{Tapped density} = \frac{M}{Vf} \)

Where, \( M \) = weight of the sample taken; \( Vf \) = final tapped volume

Carr’s index
The compressibility index of granules was determined using Carr’s compressibility index, as follows:
(Tapped density –Bulk density) 

\[
\text{Carr’s index} = \frac{\text{Tapped density}}{\text{Tapped density}} \times 100
\]

**Hausner’s ratio**

The Hausner’s ratio was determined using the following formula:

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

**Formulation of tablet by wet granulation.**

Tablets were prepared by wet granulation process using isopropyl alcohol as granulating fluid. Granules were prepared using formula in (Table1). Prepared granules were evaluated for following parameters Bulk density, Tapped density, Carr’s index, Angle of repose, Hausner’s ratio.\(^{11}\) Tablet of 225 mg was prepared by compressing evaluated granules using single punch tablet compression machine. Three batches F1 (10% Corn starch), F2 (10% Papaya starch), F3 (5% Papaya starch) were prepared [13].

**Evaluation of Tablets [14, 15].**

**Hardness Test**

Monsanto hardness tester was used for measuring the hardness of the formulated tablets. From each batch five tablets were taken at random and subjected to test. The mean of these five tablets is given in the table.

**Friability**

It is a measure of tablet strength. The friability was determined by using Roche friabilator. 10 tablets were taken and the weight was determined. Then they were placed in the friabilator and allowed to make 100 revolutions at 25 rpm. The tablets were then dusted and reweighed. The percentage weight loss was calculated.

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![Figure 2: Dissolution study of batch F1, F2 and F3.](image)

**Weight variation**

The weight variation test of the tablets was performed as per I.P. Twenty tablets of each type were weighed and average weights were calculated.

**In-vitro disintegration time**

The *in-vitro* disintegration time was determined using disintegration test apparatus. Six tablets were taken in disintegration apparatus. A tablet was placed in each of the six tubes of the apparatus with 3 inches long opened at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test the disintegration time one tablet was placed in each tube, and the basket rack was positioned in a 1 litre beaker of water at 37º C ± 2º C such that the tablets remain 2.5 cm from the bottom of the beaker. A standard motor driver device was used to move the basket assembly up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minute. To meet the IP standard all particles of tablet must pass through 10 mesh screen in the time specified.

**Dissolution studies**

Dissolution was carried out using IP dissolution apparatus I (paddle apparatus). Dissolution of tablets was carried out in 900 ml-dissolution medium. The dissolution medium for diclofenac tablet was phosphate buffer pH 6.8. The temperature of dissolution medium was maintained at 37º C ± 2º C. The agitation intensity was 100 rpm. The samples of dissolution medium were withdrawn at every interval of 10 min for 1 hr. Equal volume of fresh medium having same temperature was replaced at each time. The samples were suitably diluted and the amount of active ingredient was determined spectrophotometry with respect to the reported methods.
RESULTS AND DISCUSSION
Starch extracted from Carica papaya had a light yellowish tinge hence bleaching was carried out with ethanol. On dry basis 32.5% starch was obtained. Grains of Carica papaya starch were found to be smaller in size compared to Corn starch (Fig. 1a) and (Fig. 1b). They were round and oval in shape. Not much difference was observed in loss on drying, acidity, ash value, pH values of Carica papaya starch and Corn Starch. The loss on drying and acidity values was well within official limit. The bulk density, angle of repose and compressibility index of both starches were comparable. In all the cases the values of angle of response were ≤30°, which indicate that both the starches were free flowing (Table 2). Evaluation of formulated granules showed significant increase in bulk and tapped density with increase in concentration of starch and the good correlation was observed between the concentrations of disintegrant. The bulk and tapped densities (0.75 ± 0.002, 0.62 ± 0.005 g/ml) exhibited by Carica papaya granules was lower compare to corn starch granules (0.90 ± 0.005 g/ml) (Table 3). It was observed that diclofenac tablets prepared with papaya and corn starch passes the friability test and was found to be within acceptable limits for all the formulation. The friability test showed that the Corn starch had slightly less binding strength than that of Carica papaya starch (Table 4). Disintegration time observed was less with papaya starch at all the concentrations employed compared to those of corn starch which may be due to higher swelling capacity subjected to good disintegration property of Carica papaya. The study of disintegrating property of all the formulations showed that the disintegration time for the tablets prepared with Carica papaya was less than that of Corn starch (Table 5) reflecting its good disintegrating characteristic. Weight variation test carried showed no tablet deviated from average weight by 7.5%. Thus all tablets pass the weight variation test as per official limit. One point dissolution data of all the tablets prepared with both the starch conform to dissolution specifications of I.P. (Table 6). The result of in vitro drug release study for F1 tablet formulated with corn starch shows slow drug release profile in comparison to other papaya starch tablet. While in case of formulation (F2) and (F3) the drug release observed was 91.3 and 83.9 % respectively with (Carica papaya starch was used in concentration of 10% and 5%). Thus it can be concluded that the starch isolated from unripe papaya fruit possesses significant disintegrating properties in range of 5 to 10 % concentration which is an acceptable range of starch incorporation in tablet formulation as a disintegrating agent (Fig 2).

CONCLUSION
The results of the present study provide some insights into the relative effectiveness of papaya starch as disintegrating agent over corn starch In addition to this it is observed that it maintains mechanical strength of a tablet in terms of friability and hardness. The dissolution studies suggest that tablets (batch F3) containing 5% Carica papaya starch gives 79.6 % of drug release after specified dissolution test time. Thus it can be concluded that the starch isolated from unripe papaya fruit possesses significant disintegrating properties and has excellent scope as disintegrant in pharmaceutical formulations. Papaya starch could be used as a promising pharmaceutical excipient in tablet technology as, it showed adequate physicochemical and disintegrating properties.

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