Tablet disintegrant activities of new starch from immature pepino fruits

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A new starch powder isolated by steeping process from pepino fruits (Solanum muricatum Aiton) as tablet disintegrant was compared with maize starch BP (MS) in paracetamol tablets prepared via wet granulation method. Increasing concentration resulted in slight increase in hardness and decrease in friability for MS, whereas hardness slightly decreased and friability marginally increased for PS. PS absorbed least moisture followed by MS. PS formulations showed longer disintegration time than MS. However disintegration time was comparable at 10% w/w concentration: PS, 4.7; and MS, 5.0 min. PS is likely to initiate disintegration by swelling and capillary action. Drug dissolution (70%) was within 30 min. Thus PS powder appears to be a suitable substitute for MS as internal disintegrant in paracetamol tablet formulations.

Key words: Paracetamol, Solanum muricatum, Pepino, Fruits, Starch and Disintegrant, Maize Starch.

Introduction

Disintegrant aids in breakup of tablets into smaller fragments in a fluid environment prior to dissolution of active drug and its absorption from gastrointestinal tract1. Starch as disintegrant is rated among top 10 pharmaceutical ingredients2. Although various studies have been carried out on the use of starches as disintegrants in tabletting3, information on pepino (Solanum muricatum Aiton, Family: Solanaceae) starch as disintegrant appears to be scanty. Factors that affect action of disintegrants in tablets4 include porosity and capillary action (wicking)5, swelling of disintegrant particles and force development6,7, release of gases, enzymatic action, evolution of heat of wetting and expansion of entrapped air8, deformation and lysis of physico-chemical bonds. Porosity, intrinsic moisture sorption, hydration and swelling capacity provide qualitative assessments of potential disintegrating agents9,10. Pepino is a small herbaceous perennial herb native to South America11. Whole plant extract inhibit growth of various solid tumour cell lines (prostrate, stomach, liver, breast, ovarian, colon and lung), but lower toxicity to normal cells.

This study presents mechanism of disintegration and disintegrant profile of pepino starch (PS) in paracetamol (PC) tablets and disintegrant profile was compared with maize starch BP (MS).

Experimental Section

Materials

PC (Paxmy specialty chemicals, Chennai) was used as model drug. MS, magnesium stearate and gelatin were purchased from SD Fine chemicals, Mumbai. Aerosil was purchased from Degussa, Mumbai. All other solvents and chemicals were of pharmaceutical grade. Pepino fruits were purchased from local sellers, Ootacamund and authenticated in Medicinal Plant Collection unit, Government Arts College, Ootacamund.

Isolation of Starch

Washed fruits were cut into small pieces and steeped in water containing dilute sulphur dioxide (0.1-0.2%) for > 2 h at 48-52°C to break starch from protein bonds and release starch12. Softened fruits were then blended with 1% NaCl to free starch from cells. Then milky liquid was filtered through fine muslin with several washes, coarse and fine fibres and part of protein were removed during filtration. On standing, starch granules settle at the bottom and supernatant was then decanted. Wet
starch was purified to separate trace amount of proteins
and soluble materials (gluten if any), by washing with
1% NaCl solution (3 times, once with 0.01 M NaOH).
Finally, settled starch sediment was washed with water
and dried at 30-40°C for ½ h in a tray drier. Dried product
was stored in dessicator for further studies.

Characterization of Starch

Limit Tests, Microbial Count and Microscopy

In limit tests13, opalescence, turbidity or colour is
compared with fixed standards as prescribed in Indian
Pharmacopoeia, 1996. Microbial count of starch was
examined by Plate count method14. Surface
characteristics of pepino starch (Fig. 1) were observed
using Digital Microscope attached to the computer
system (Motis instruments, Bangalore).

pH, Viscosity and Angle of Repose (AR)

Each starch (1 g) was made into mucilage with
distilled water (100 ml) and pH was determined using a
digital pH meter15 (Merck, Mumbai). Brookfield
Viscometer (Engineering labs, INC, Middlebord, USA)
was used to determine viscosity of starch mucilage (5%
w/v) at 28°C16.

Flow property of starch powder was investigated
by measuring AR17, which was calculated from an open
ended cylinder (diam, 2.5 cm) placed on a base of similar
diameter. Starch powder (30 g) was allowed to flow
through a funnel under force of gravity to form a conical
heap. AR was calculated as a mean of four
determinations as Tan Ø=h/r where, h is height of cone
and r is radius of base of the cone. Mean AR was
calculated after three determinations.

Particle Size, Bulk Density and Compressibility (Carr’s index)
and Hausner’s Ratio

Particle size distribution was determined by sieve
analysis using test material (100 g) and series of US
standard sieves range in screen opening from 1000 µm to
180 µm. Test material was placed on the top sieve and
mechanically shaken for 10 min on a shaker (Rota C 30,
Germany). Fraction retained on each screen was weighed
and average particle size was calculated accordingly18.

For bulk and tapped densities, samples (30 g each)
were carefully poured into a cylinder (100 ml) and initial
volume was noted. Bulk density was calculated as the
ratio of sample weight to initial sample volume19.
Measuring cylinder was then tapped by Tapped density
tester (Erweka, SVM101, Heusenstamm, Germany) till
constant volume was achieved. Tapped density was
calculated as the ratio of sample weight to final (constant)
sample volume. Compressibility (%) was calculated from
difference between tapped and bulk densities divided by
tapped density20. Hausner’s ratio is the ratio between
tapped and bulk density.

Moisture Content

Weight loss on drying was determined using a
Sartorius moisture balance. Each granulation (5 g) was
put on pan of the balance. Heating temperature was set
at 100°C and time mode was set at 30 s, giving continuous
heating to sample after removal of free water content
for 30 s. Moisture content (%) was directly read. Test
was carried out on all granules and mean values were
calculated.

Mechanism of Disintegrant Action

Swelling Capacity

Swelling capacity was determined using method of
Leach, McCowen and Schoch (1959). Starch (1 g) was
dissolved in distilled water (10 ml) in a centrifuge tube
and heated for 30 min with continuous shaking at 80°C.
Thereafter, suspension was centrifuged at 1000 x g for
15 min, supernatant was decanted and paste weight was
noted. Swelling power was calculated by the ratio between
weight of paste and weight of dry starch.

Water Retention Capacity

Water retention capacity (hydration capacity) was
determined using method of Ring. Starch powder (1 g)
was dissolved in water (10 ml) in a centrifuge tube and
kept aside for 30 min after shaking for 2 h. Thereafter,
centrifuged for 10 min at 3000 rpm and supernatant were
decanted. Weight of starch powder after water uptake
and centrifugation was determined. Hydration capacity
= x/y, where x is weight of moist powder after
centrifugation and y is weight of dry powder.
**Powder Porosity**

Porosity was computed from bulk density values and granule density of powders as $E = (1 - \frac{\rho_b}{\rho_g}) \times 100$, where $\rho_b$ and $\rho_g$ are bulk and granular densities and $E$ is powder porosity to be determined. Granular density of powder was determined using specific gravity bottle method. Purified water was liquid of known density. In general, disintegrant particles with low cohesiveness and compressibility act to enhance porosity which provides pathways for penetration of fluid into tablets.

**Moisture Sorption Capacity**

Samples (2 g each) previously dried at 60°C for 5 h (moisture level <1%) were evenly distributed in a tarred petri dish and then placed in a desiccator containing distilled water in its reservoir at room temperature. Moisture (%) adsorbed was determined from the weight gained by exposed samples at the end of a 5 day period and weight difference.

**Compatibility Studies**

Infrared (IR) spectra were matched for detection of any possible chemical interaction between drug and polymer. A physical mixture (1:1) of drug and PS was prepared and mixed with suitable quantity of potassium bromide. Mixture (100 mg) was compressed to form a transparent pellet using a hydraulic press at 15 tons pressure. It was scanned from 4000 to 400 cm$^{-1}$ in a Perkin Elmer FTIR series (model 1615) spectrophotometer. IR spectrum of physical mixture was compared with those of pure drug and PS and matching was done to detect any appearance or disappearance of peaks.

**Preparation of Granules**

PC tablet formulation contains: PC, 275; gelatin (7.5% w/w), 28.12; PS and MS as disintegrants (2.5-10.0% w/w), 9.37-37.50; microcrystalline cellulose, 44.25-72.50; and aerosil (0.5% w/w), 1.80 mg. Granules were prepared by wet granulation method using PC as drug. Required quantities of PC and other excipients were mixed thoroughly and a sufficient volume of granulating agent (starch in water) was added slowly. Coherent mass obtained was passed through 10 mesh sieve and then dried at 60°C for 5 h (to moisture level <1%) and size fraction (250-1000 µm) were collected and used for tablet preparation. Aerosil and magnesium stearate were finally added.

**Compression and Evaluation of Tablets**

Rotary tablet compression machine (10 stations, Rimek, karavati Eng. Ltd., Ahmedabad, India) was used to prepare tablets (diam, 10 mm), using standard concave punches. Tablets (400 mg) contain microcrystalline cellulose as diluent, magnesium stearate as lubricant, aerosol as glidant and gelatin as binder. Batch size contained 100 tablets. Totally, 4 batches (2.5, 5.0, 7.5 and 10.0% w/w) were prepared to evaluate disintegrant properties.

Tablets were evaluated with regard to content uniformity, weight variation, thickness and hardness, friability and disintegration time. For content uniformity test, representative samples of 30 tablets were selected and 10 were assayed individually. At least 9 must assay within ± 15% of declared potency, none may exceed ± 25%. Procedure involves assay of active ingredient in individual tablet. For determination of content uniformity, assay procedure in Indian Pharmacopoeia 1996 was used. Tablets (20) from each batch were selected randomly and weighed using an electronic balance and average weight was calculated. Tablet thickness was measured by a Vernier caliper (Nippon Sokutei, Japan), which provides accurate measurements and information of variation between tablets. Tablet thickness should be controlled within a ± 5 variation between tablets. Force required to break each tablet in lesion was determined at room temperature by diametric compression using a Monsanto hardness tester (Cadmach machineries, Ahmedabad). Hardness is an indication of strength of tablet reported in kilogram. Minimum of 6 tablets were measured and mean value was considered.

Friability assessed ability of tablet to withstand abrasion in packing, handling and transport. Friability (1%) of tablets was determined using Roche friability tester (EF2 model, ElectroLab, Mumbai) operated at 25 rpm for 4 min. Tablets were weighed before and after the test and loss in weight (%) was calculated. Disintegration test was used to determine time required for complete disintegration of tablets into small particles (size, >10 mesh). Tablets (6) were tested in USP Disintegration test apparatus (ED2 model, ElectroLab, Mumbai) using distilled water as test medium.

**In vitro Drug Release of Paracetamol**

For dissolution study, a randomly selected tablet was weighed and placed in phosphate buffer (900 ml) at pH 5.8 in paddle type apparatus, model TDT-06T (Electro lab, Mumbai, India) operated at 50 rpm. Test temperature.
Table 1—Physicochemical properties of pepino starch and maize starch BP

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pepino starch (PS)</th>
<th>Maize starch BP (MS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.39</td>
<td>5.82</td>
</tr>
<tr>
<td>Viscosity, cp</td>
<td>2.167</td>
<td>2.192</td>
</tr>
<tr>
<td>Particle size analysis, µm</td>
<td>11.5 ± 4.1</td>
<td>10.6 ± 4.3</td>
</tr>
<tr>
<td>Angle of repose (AR), Ø</td>
<td>28°49'</td>
<td>28°91'</td>
</tr>
<tr>
<td>Bulk density, g/cm³</td>
<td>0.465 ± 0.032</td>
<td>0.454 ± 0.034</td>
</tr>
<tr>
<td>Tapped density, g/cm³</td>
<td>0.571 ± 0.021</td>
<td>0.555 ± 0.026</td>
</tr>
<tr>
<td>Carr's index, %</td>
<td>18.60 ± 1.01</td>
<td>18.19 ± 1.17</td>
</tr>
<tr>
<td>Hausner's ratio</td>
<td>1.222</td>
<td>1.222</td>
</tr>
<tr>
<td>Moisture content, %</td>
<td>0.82</td>
<td>0.91</td>
</tr>
<tr>
<td>Swelling capacity</td>
<td>8.1</td>
<td>7.4</td>
</tr>
<tr>
<td>Water retention capacity</td>
<td>3.86</td>
<td>1.45</td>
</tr>
<tr>
<td>Powder porosity, %</td>
<td>32.72</td>
<td>31.94</td>
</tr>
<tr>
<td>Moisture sorption capacity, %</td>
<td>1.91</td>
<td>2.23</td>
</tr>
</tbody>
</table>

was maintained at 37 ± 0.5°C. Samples (5 ml) were withdrawn at pre-determined time intervals and immediately replaced with fresh buffer (5 ml) at same temperature. Absorbance reading on solutions was taken on a Shimadzu 160A UV-Vis spectrophotometer at absorption maximum of 249 nm for PC. Amount of drug in solution was determined from a prepared calibration curve. A stock solution (100 mg) of PC in phosphate buffer (100 ml) was prepared and absorbance of all dilutions was measured using water as a blank. A plot of absorbance (A) against concentration (C) was made and calibration curve was determined from the slope of graph.

Results and Discussion

For PS (8 ± 2.0% w/w), limit tests were well within official limits. Microbial and fungal counts were absent, however it has to be confirmed on long term storage conditions. pH of MS was 5.82 while that of PS was 7.39. Since, pH value of extracted starch is near to neutral, it may be less irritating in gastrointestinal tract and hence was suitable for uncoated tablets. Both starches had low viscosity and high swelling factors (Table 1). Particles of PS are larger (11.5 ± 4.1) than those of MS (10.6 ± 4.3), indicating that PS may have a higher porosity than MS.

AR of MS was found more than that of PS. PS, being less cohesive, has good flow property, which assures efficient mixing and acceptable weight uniformity for compressed tablets. Both starches have similar bulk and tapped densities. Compressibility index and AR indicated that powder is having good flow with moderate compressibility. Moisture content of different granulations was less than 1%. Most common mechanism of action for tablet disintegration is penetration of liquid medium into tablet and replacement of air adsorbed on particles, which weakens intermolecular bond and breaks tablet into fine particles. Swelling capacity and water retention capacity of PS were found to be more than those of MS, suggesting that PS may be used as a better and alternative disintegrant to MS.

Porosity of PS (32.72%) and MS (31.94%) indicates that granules are loosely packed and confirming that particles are not of greatly different sizes. PS absorbed least moisture followed by MS. Physicochemical parameters observed support applicability of selected excipient as tablet disintegrant. There was no appearance or disappearance of FTIR peaks in PS-drug mixture, which confirmed absence of any chemical interaction between drug and selected starch (Fig. 2). Preformulation study indicates that drug and PS are compatible.

All tablets (wt, 393-403 mg) showed uniform thickness. Average percentage deviation of 20 tablets of each formula was less than ±5 % and hence formulations passed test for uniformity of weight (Table 2). Increasing concentration resulted in slight increase in hardness (Fig. 3a) and decrease in friability (Fig. 3b) for MS. Increase in concentration of disintegrant may lead to a better balance between binding and disintegrant properties of a tablet. Internally added starch may increase hardness of tablets since penetration of liquid may wetted starch turning it into mucilage and would acted as a binder. In case of PS, hardness slightly decreased and friability marginally increased as concentration of disintegrant increased.
Fig. 2—FTIR spectrum of: a) pepino starch; b) paracetamol; and c) pepino starch & paracetamol mixture.
A decrease was observed in disintegration time with increase in disintegrant concentration for all formulations (Fig. 3c). Incorporation of PS to tablets has short disintegration time (4.7 min) and comparable with that of MS (5.0 min) at optimum concentration (10% w/w), may be due to increased swelling and hydration capacity, which suggested that increasing in swelling force by increasing amount of PS had more pronounce effect on disintegration time than did increased tablet hardness. It is possible that upon an initial contact between PS and water, particles swell thereby generating enough pressure to initiate disintegration well before gel is formed. Considering mechanisms of disintegrant action and results of this investigation, extracted PS is likely to initiate disintegration by swelling and capillary action. However, all tablets formulated with starch powders passed British Pharmacopoeia (BP) specifications for disintegration time of uncoated tablets within 15 min.

### Table 2—Some tablet properties of paracetamol prepared with different concentrations of disintegrants

<table>
<thead>
<tr>
<th>Disintegrant</th>
<th>Concentration (%) w/w</th>
<th>Average weight (weight variation) mg</th>
<th>Thickness mm</th>
<th>Content uniformity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepino starch (PS)</td>
<td>2.5</td>
<td>398.23 (1.67)</td>
<td>3.99</td>
<td>97.78</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>394.32 (1.25)</td>
<td>3.98</td>
<td>98.24</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>399.18 (1.52)</td>
<td>3.96</td>
<td>99.12</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>403.18 (1.52)</td>
<td>3.97</td>
<td>99.48</td>
</tr>
<tr>
<td>Maize starch BP (MS)</td>
<td>2.5</td>
<td>398.12 (0.74)</td>
<td>3.98</td>
<td>99.06</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>394.32 (1.25)</td>
<td>3.97</td>
<td>97.65</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>399.18 (1.52)</td>
<td>3.98</td>
<td>98.21</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>403.34 (1.87)</td>
<td>4.01</td>
<td>99.94</td>
</tr>
</tbody>
</table>

**Fig. 3—** Effect of disintegrant type and concentration of paracetamol tablets prepared with pepino starch and maize starch BP on: a) hardness; b) friability; and c) disintegration time

**Fig. 4—** Dissolution rate of paracetamol from tablets as a function of disintegrant type and 10% w/w concentration prepared with pepino starch and maize starch BP

A decrease was observed in disintegration time with increase in disintegrant concentration for all formulations (Fig. 3c). Incorporation of PS to tablets has short disintegration time (4.7 min) and comparable with that of MS (5.0 min) at optimum concentration (10% w/w), may be due to increased swelling and hydration capacity, which suggested that increasing in swelling force by increasing amount of PS had more pronounce effect on disintegration time than did increased tablet hardness. It is possible that upon an initial contact between PS and water, particles swell thereby generating enough pressure to initiate disintegration well before gel is formed. Considering mechanisms of disintegrant action and results of this investigation, extracted PS is likely to initiate disintegration by swelling and capillary action. However, all tablets formulated with starch powders passed British Pharmacopoeia (BP) specifications for disintegration time of uncoated tablets within 15 min.
All tablets passed BP dissolution test for tablets, specifying that at least 70% of drug should be in solution after 30 min (Fig. 4). There was no significant difference between dissolution rates of PC from tablets containing 10% of disintegrants. Release of PC from tablets was generally concentration dependent, with faster release occurring as disintegrant concentration was increased.

Conclusions
Physical characteristics of PC tablets produced via wet granulation method with PS and MS as disintegrants were pharmaceutically acceptable. There was no significant difference between PS and MS in terms of disintegration time. PS and MS showed comparative effectiveness as disintegrant in PC tablets and drug release from tablet (disintegrant, 10% w/w) was 70-90% in 1 h.

References
11 Yoga Narasimhan S N, Medicinal Plants of India, 2nd edn (Cyber Media, Bangalore) 2000, 205.
16 Subramaniam C V S, Textbook of Physical Pharmaceutics (Vallabh Prakashan, New Delhi) 2000, 236.