# Disintegration, Hardness and Dissolution profiles of paracetamol tablets formulated using sucrose and formaldehyde cross-linked starches


## ABSTRACT

**Background**: Native starches have some limitations such as the inability to withstand some processing conditions, poor flow, packing and compressibility. Cross-linking of starch is one of the methods used to overcome these drawbacks to obtain derivatives with better and desirable properties. This study is aimed at assessing the utilisabilty of sucrose and formaldehyde cross-linked starches obtained from *Zea mays*, *Triticum aestivum***,** and *Oriza sativa* as an excipient for paracetamol tablet formulation. The formulated tablets were evaluated for hardness, disintegration and drug release rate.

**Results:** The formulated tablets had hardness in the range of 4.35 – 6.37 Kgf. Tablets produced from the native starches had significantly ($P < 0.05$) lower disintegration time compared to their respective cross-linked starches. The disintegration time of the tablets from the cross-linked starches was in the following order, modified rice starch tablets > modified maize starch tablets > modified wheat starch tablets. The optimal batches containing the modified starches released over 90% of the drug within 40 min.

**Conclusion**: The result from this study is a proof of concept that the cross-linked starches can be used as pharmaceutical excipients in tablet formulation, especially as a binder.



**Keywords**; Cross-linked Starch, Polymer, Sucrose, Formaldehyde, Binders, Paracetamol, Tableting


## BACKGROUND

Starch is readily available, affordable and also has a wide range of industrial applications [1]. It is also considered a nontoxic and polyfunctional polymer with high chemical reactivity [2]. The need for different novel properties with respect to those of native starches calls for a modification to obtained derivatives with desirable properties such as enhancement of adhesiveness, decrease retrogradation tendency for gel formation, adjustment of viscosity by changes of molecular weight, conferment of hydrophobic properties, increase hydrophilic properties, the introduction of ionic substituent, increasing of shear stability and improvement of film-forming ability [3]. Different chemical reactions such as esterification, oxidation, etherification, acid hydrolysis and cross-linking have all been employed in the chemical modification of starch[4]. Cross-linking is the formation of intermolecular bridges between adjacent molecules by using different chemicals referred to as cross-linking agents to make the polymer strong [5]. Cross-linking agents such as formaldehyde, sodium hexametaphosphate, monosodium phosphate, borax, sodium tripolyphosphate, zinc oxide, sodium trimetaphosphate, citric acid, phosphoryl chloride, glutaraldehyde, a mixture of succinic anhydride and vinyl acetate, a mixture of adipic and

acetic anhydrides and epichlorohydrin can form either ether or ester inter-molecular linkages between hydroxyl groups on starch molecules, hence, have all been used [2, 5, 6]. Cross-linking is one of the most widely used approaches in polysaccharide chemistry and is reported to be affected by factors such as cross-linking reagent concentration and composition, temperature, pH, the extent of substitution, reaction time and starch source. Cross-linking has been reported to improve the textural properties and viscosity of native starch and can withstand high temperature, low pH and higher shear [2, 5].

*Zea mays* is from the *Poaceae* family, the starch is obtained from the endosperm of the corn kernel [7]. Maize starch is a major ingredient in the manufacture of foodstuff; it is also extensively used as an adhesive, thickener, colloidal gelling agent and stabilizer [7]. *Triticum aestivum* referred to as wheat is a cereal grain cultivated worldwide [8]. For human food, wheat is the chief source of vegetable protein; it contains more proteins than other major cereals. It is used in making flour for bread, biscuits, and noodles and for fermentation to make alcoholic beverages [8]. Rice is the seed of the grass species *Oryza glaberrima* (African rice) or *Oryza sativa* (Asian rice) [9]. Rice provides more than one-fifth of the calories consumed worldwide by humans [9]. The starches from these cereals have all been reported to have several uses as pharmaceutical excipients. They have been employed in conventional dosage forms as binders, disintegrants, diluents, etc. [1, 10, 11].
This study is aimed at assessing the utilisabilty of sucrose and formaldehyde cross-linked starches obtained from *Zea mays, Triticum aestivum***,** and *Oriza sativa* as an excipient for paracetamol tablet formulation.

## METHOD

Paracetamol powder was obtained from Emzor Pharmaceutical limited, Lagos, Nigeria as a gift sample. Formaldehyde and sucrose were procured from Jenway, Bibby Scientific Limited, England. The starch of rice, wheat and maize were obtained from batches processed in our laboratory.

### Formulation

Starch from maize, wheat and rice were cross-linked with different concentrations (2.5, 5, 10, 20, 40%) of sucrose (Su) and formaldehyde (Fa) used as cross-linking agents. The cross-linked starches were used as an excipient to formulate different batches of paracetamol tablets. Fifty (50) tablets per batch were formulated using a single punch tableting machine (AR 400 Erweka Apparatus GmbH, Germany). The tablets formulae and formulation method are available from the lead author on reasonable request.

### Hardness testing

Three tablets selected at random from each batch were tested for hardness using a Monsanto hardness tester. Each tablet was positioned between the spindle and anvil of the tester. The knob was then screwed gradually and gently until the tablet was held in position. The reading on the pointer was adjusted to zero on the scale. The pressure was applied by turning the knob until the tablet was broken. The pointer was read and the force needed to break the tablet was noted. The hardness factor was taken as the average of three determinations per batch.

**Disintegration test**

The time needed for five tablets per batch to disintegrate was determined using Erweka disintegration tester (ZT Erweka, Germany) containing simulated gastric fluid (SGF) without pepsin thermostatically maintained at 37± 2 °C as the disintegration medium. The disintegration apparatus was set to run at thirty cycles per minute. The required time for the tablet or its fragment to cross the mesh into the disintegration medium was noted. The average of three determinations was computed to be the disintegration time

**Dissolution studies**

The dissolution study was carried out in 900 ml of SGF as the dissolution medium using USP XXI type II (Paddle method). In each case, a tablet from each batch was placed in the basket of the test apparatus set at an agitation speed of 50 rpm at 37 ± 0.5 °C. Then 5 mL aliquots were withdrawn at intervals of 10, 20, 30, 40, 50, 60, 70, 80, 90 min. The withdrawn sample was replaced with 5 ml of fresh dissolution medium each time and analyzed at λmax of 283 nm using a spectrophotometer (UNICO UV – 2102 PC, USA). The dissolution experiment was conducted in triplicate.

**Statistical analysis**

The data generated from the various determinations were analyzed using SPSS 23 software (SPSS, Chicago, IL, USA) and are presented as the mean ± standard deviation (SD). The differences between the data sets were determined using *T*-test and $p < 0.05$ was considered statistically significant.

**RESULTS**

**Hardness Testing**

Tablets prepared with modified rice starch (20%Fa) (rice starch modified with 20% formaldehyde) had the highest hardness of 6.37 Kgf while tablets prepared with maize starch (2.5%Fa) gave the lowest hardness of 4.35. The sucrose cross-linked wheat starches gave tablets with hardness in the range of 4.76 to 4.85, while the tablets formulated with formaldehyde cross-linked wheat starches exhibited hardness in the range of 4.87 to 5.61 Kgf. Maize starch cross-linked with both sucrose and formaldehyde gave tablets with

hardness between 4.35 and 5.20 Kgf. The result showed that the effect of concentration of cross-linking agent was very noticeable in maize and wheat starch. The results are as presented in Table 1.

**Table 1:** Hardness test for the formulated paracetamol tablets

| **Cross-linking Agent** | **Hardness with n = 3 (mean ± SD)** | | |
|---|---|---|---|
| | **Maize starch** | **Wheat starch** | **Rice starch** |
| **2.5% sucrose** | 5.07 ± 0.02 | 4.83 ± 0.10 | 5.31 ± 0.20 |
| **5% sucrose** | 5.12 ± 0.23 | 4.85 ± 0.11 | 5.33 ± 0.20 |
| **10% sucrose** | 4.88 ± 0.17 | 4.83 ± 0.12 | 5.10 ± 0.26 |
| **20% sucrose** | 5.13 ± 0.30 | 4.76 ± 0.30 | 5.22 ± 0.33 |
| **40% sucrose** | 5.11 ± 0.22 | 4.81 ± 0.15 | 5.42 ± 0.21 |
| **2.5% formaldehyde** | 4.35 ± 0.21 | 4.87 ± 0.11 | 5.42 ± 0.21 |
| **5% formaldehyde** | 5.05 ± 0.21 | 5.33 ± 0.19 | 5.44 ± 0.21 |
| **10% formaldehyde** | 4.97 ± 0.11 | 5.26 ± 0.19 | 5.43 ± 0.11 |
| **20% formaldehyde** | 5.14 ± 0.21 | 5.57 ± 0.22 | 6.37 ± 0.39 |
| **40% formaldehyde** | 5.20 ± 0.15 | 5.61 ± 0.15 | 5.45 ± 0.12 |

**Disintegration Testing**: The disintegration time results are given in Table 2. The results revealed that tablets produced from the unmodified wheat and rice starch had a significantly ($P < 0.05$) lower disintegration time compared to their respective cross-linked starches. The disintegration time between the native and cross-linked maize starch was however not significantly ($P > 0.05$) different. The disintegration time of the tablets produced from the native starches was in the range of 5.21 to 8.38 min.

The modified wheat starches yielded tablets with the least disintegration times of 8.49 to 8.93 min, followed by the tablets produced from the cross-linked maize starches with disintegration times of between 9.13 to 9.51 min, while the tablets produced from the modified rice starches exhibited the highest disintegration times of between 30.25 to 30.46 min, i.e., the disintegration time of the tablets from the cross-linked starches was in the following order, modified rice starch tablets > modified maize starch tablets > modified wheat starch tablets. The wheat and maize starches yielded Tablets with the British Pharmacopoeial specification as regards the disintegration time[13]

**Table 2:** The disintegration studies of cross-linked maize, wheat and rice starch tablets

| Cross-linking Agent | Disintegration time, in minutes, of tablets with n=5 (mean ± SD) | | |
|---|---|---|---|
| | Maize starch | Wheat starch | Rice starch |
| **Native Starch** | 5.23 ± 0.190 | 5.21 ± 0.10 | 8.38 ± 0. 09 |
| **2.5% sucrose** | 9.20 ± 0.30 | 8.58 ± 0.09 | 30.28 ± 0.14 |
| **5% sucrose** | 9.13 ± 0.09 | 8.55 ± 0.04 | 30.25 ± 0.09 |
| **10% sucrose** | 9.22 ± 5.35 | 8.49 ± 0.11 | 30.27 ± 0.02 |
| **20% sucrose** | 9.26 ± 0.10 | 8.69 ± 0.11 | 30.31 ± 0.02 |
| **40% sucrose** | 9.27 ± 0.19 | 8.72 ± 0.04 | 30.36 ± 0.02 |
| **2.5% formaldehyde** | 9.51 ± 0.15 | 8.71 ± 0.02 | 30.31 ± 0.06 |
| **5% formaldehyde** | 9.43 ± 0.18 | 8.78 ± 0.10 | 30.41 ± 0.02 |
| **10% formaldehyde** | 9.45 ± 0.06 | 8.83 ± 0.16 | 30.41 ± 0.01 |
| **20% formaldehyde** | 9.42 ± 0.02 | 8.84 ± 0.04 | 30.46 ± 0.00 |
| **40% formaldehyde** | 9.44 ± 0.07 | 8.93 ± 0.04 | 30.44 ± 0.00 |

**Dissolution test results**

The dissolution profile of the tablets from the cross-linked maize, wheat and rice starch is shown in Figure 1. Amongst the tablets containing cross-linked maize starch, the batch modified with 2.5% sucrose gave the highest release rate; while the batch containing wheat starch cross-linked 40% sucrose gave the least release rate. Tablets prepared with wheat starch modified with 40 % formaldehyde exhibited the highest release rate amongst all the batches prepared from the cross-linked wheat starch. For the batches prepared from the cross-linked rice starch, the batch made from rice starch modified with 20% sucrose had the highest release rate while the batch made with rice starch (25% Su) exhibited the least release rate.

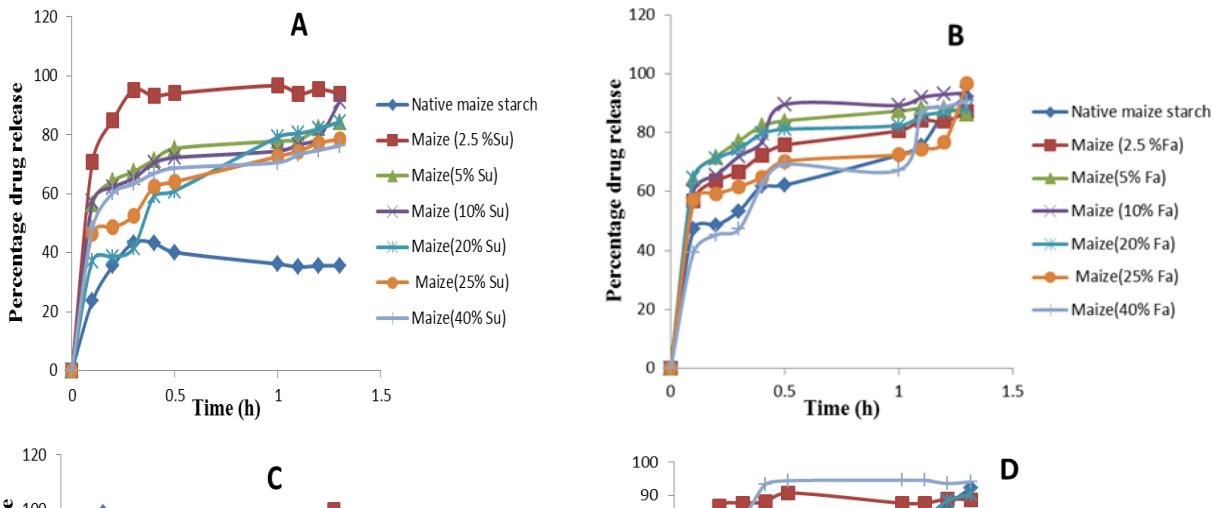

**Figure 1**: Dissolution profile of paracetamol tablets prepared with native and cross-linked maize starch (A and B), native and cross-linked wheat starch (C and D) and native and cross-linked rice starch.

**Figure 1**: Dissolution profile of paracetamol tablets prepared with native and cross-linked maize starch (A and B), native and cross-linked wheat starch (C and D) and native and cross-linked rice starch

## DISCUSSION

A hardness test is the assessment of the force needed to fracture a tablet on its diameter [12]. Tablets are expected to be hard enough to remain whole during their removal from a blister pack. According to the British Pharmacopoeia (BP) [13], for uncoated tablets, the acceptable hardness is in the range of 4 - 8 Kgf. The obtained results were within the British Pharmacopoeial specification indicating that all the batches had tablets with sufficient hardness which will ensure they remain intact during removal from blister packs.

For an active ingredient in a tablet to be available for absorption, such a tablet must first disintegrate and released the drug to the body fluids for dissolution. The disintegration of tablets yields drug particles with enlarged surface area for activity in the gastrointestinal tract [12]. The British Pharmacopoeia [14] specifies that uncoated tablets should disintegrate within 15 min. All the formulations passed this test except those containing cross-linked rice starch. The disintegration time of tablets prepared from the unmodified starches was significantly ($P < 0.05$) lower compared to those made from the modified starches. Starch is known to exert its disintegrant property by swelling; it swells and burst open causing tablet disintegration in the presence of water [15]. Cross-linked starches experienced granule

modification that decreased their hydration capacity, cross-linking is also reported to result in a high elastic contraction of the polymer network which counteracted the swelling process [16, 17]. The increase in disintegration time of tablets prepared from cross-linked starches may be a result of a reduction in hydration capacity and the swelling process of the modified starch consequent to cross-linking. Increasing cross-linking agent concentration, perhaps, increases the number of cross-links which in turn confer greater stability on the starch granule. This may be the reason for the observed increase in disintegration time in tablets prepared from starch modified with a higher concentration of cross-linking agent compared with those made with a lower cross-linking agent concentration. It can also be inferred that formaldehyde may be more effective as a cross-linking agent compared to sucrose, because tablets prepared from the starches modified using formaldehyde exhibited a higher disintegration time than those prepared from starches modified with sucrose. However, it should also be verified the residual formaldehyde content in the formulation to ensure that is not above a maximum of 0.1% w/w allowable for oral products [18-19].

*In vitro* dissolution testing provides a way of determining drug release from a solid dosage form over a period of time and describes the overall rate of all the procedures involved in the release of the drug into a bioavailable form [20]. Evaluation of the release profiles showed that the best formulations (with regards to dissolution test), which are, maize (2.5 %Su), wheat (40%Fa), and rice (20%Su) from the modified maize, wheat, and rice starch respectively all released over 90% of the drug within 40 min, fulfilling the requirements for immediate-release tablets [21]. All the batches containing the modified starches gave a higher release rate than the batches with their respective native starches.

## CONCLUSION

Sucrose and formaldehyde cross-linked starches obtained from *Zea mays, Triticum aestivum,* and *Oriza sativa* were successfully used as an excipient for paracetamol tablets formulation. Tablets formulated from maize starch cross-linked with 2.5% sucrose, wheat starch cross-linked with 40 % formaldehyde and rice starch cross-linked with 20% sucrose gave the best release rate, with over 90% of the drug released within 40 min. The result from this study is a proof of concept that the cross-linked starches can be used as pharmaceutical excipients in tablet formulation, especially as a binder.

**Limitation:** The safety profile of the formaldehyde formulation was not tested and so the use cannot be guaranteed. The manuscript merely reported a proof of concept requiring further studies.

## List of abbreviations

National Institute for Pharmaceutical Research and Development (NIPRID)

The National Agency for Food and Drug Administration and Control (NAFDAC)

**Declarations**

- **Ethics approval and consent to participate:** "Not applicable"
- **Consent for publication: "Not Applicable"**
- **Availability of data and material:** "Not applicable"
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- **Local, national or international guidelines and legislation:** Not applicable for starches from maize, wheat and rice

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