



# **Disintegration, Hardness and Dissolution Profiles of Paracetamol Tablets Formulated using Sucrose and Formaldehyde Cross-Linked Starches**

**Ifeanyi Justin Okeke <sup>a,e</sup>, Angus Nnamdi Oli <sup>b\*</sup>, Zwanden Sule Yahaya <sup>c</sup>,  
Thaddeus Harrison Gugu <sup>d</sup> and Emmanuel Chinedum Ibezim <sup>e</sup>**

<sup>a</sup> *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.*

<sup>b</sup> *Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.*

<sup>c</sup> *Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Kaduna State, Nigeria.*

<sup>d</sup> *Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.*

<sup>e</sup> *Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.*

## **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors IJO and ECI designed all the experiments. Author IJO performed the experiment. Authors ANO, ZSY and GTH analyzed the data and wrote the manuscript draft. All authors read and approved the final manuscript.*

## **Article Information**

DOI: 10.9734/JPRI/2021/v33i60B34643

### **Open Peer Review History:**

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/74581>

**Original Research Article**

**Received 04 September 2021**

**Accepted 08 November 2021**

**Published 22 December 2021**

## **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 utilisability 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:** Sucrose and formaldehyde cross-linked starches obtained from *Zea mays*, *Triticum aestivum*, and *Oriza sativa* could serve as possible excipients for paracetamol tablets formulation.

**Keywords:** Cross-linked starch; polymer; sucrose; formaldehyde; binders; paracetamol; tableting.

## LIST OF ABBREVIATIONS

National Institute for Pharmaceutical Research and Development (NIPRID)

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

## 1. INTRODUCTION

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 obtain derivatives with desirable properties such as enhancement of adhesiveness, decrease retrogradation tendency by 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 utilisability of sucrose and formaldehyde cross-linked starches obtained from *Zea mays*, *Triticum aestivum*, and *Oriza sativa* as an excipient for paracetamol tablet formulation.

## 2. METHODS

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.

## 2.1 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.

## 2.2 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.

## 2.3 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  $37 \pm 2$  °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

## 2.4 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  $37 \pm 0.5$  °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  $\lambda_{max}$  of 283 nm using a spectrophotometer (UNICO UV – 2102 PC, USA). The dissolution experiment was conducted in triplicate.

## 2.5 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  $\pm$  standard deviation (SD). The differences between the data sets were determined using *T*-test and  $p < 0.05$  was considered statistically significant.

## 3. RESULTS

### 3.1 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.

### 3.2 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.

**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

**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

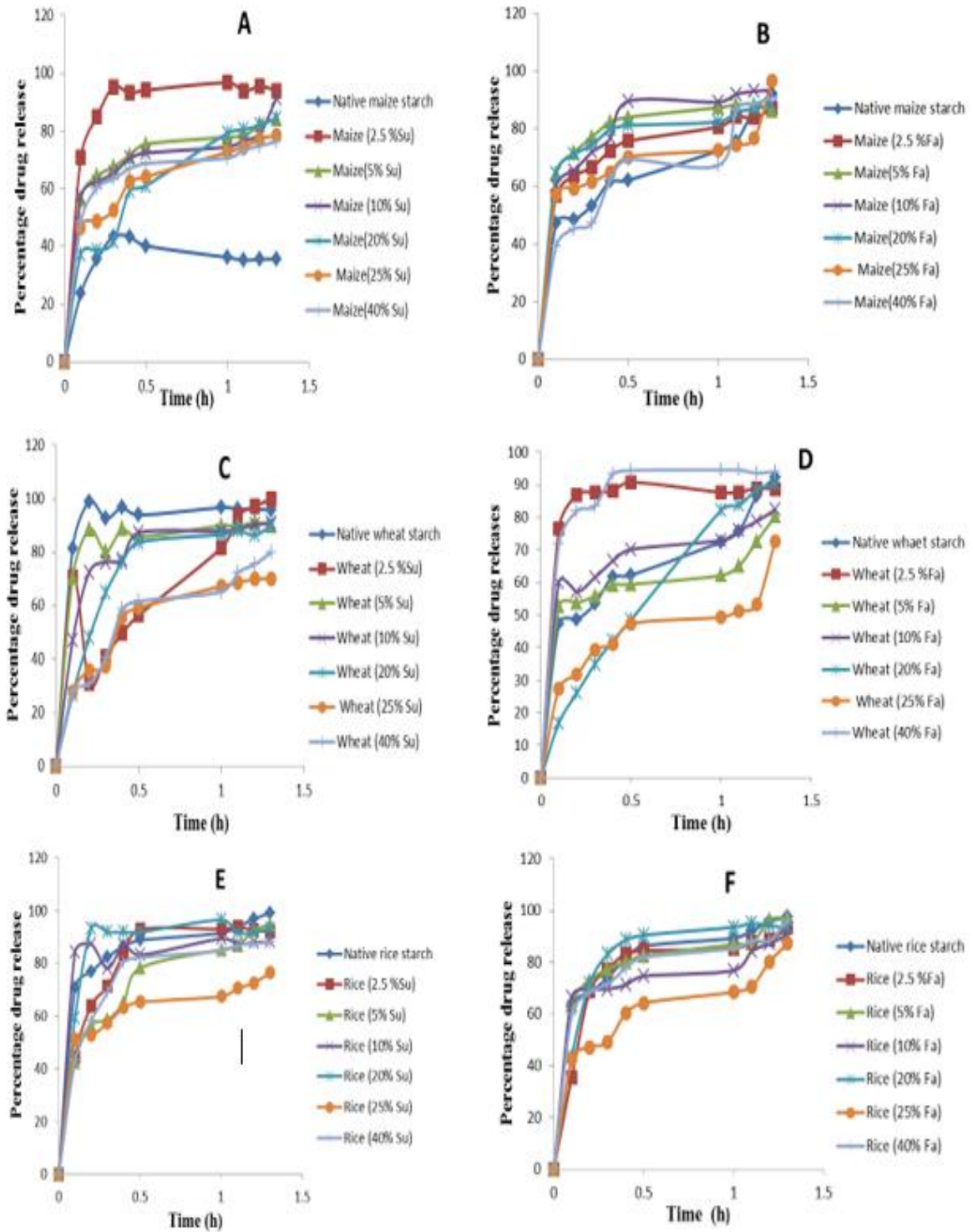


Fig. 1. Dissolution profile of paracetamol tablets prepared with native and cross-linked maize starch (A and B), native and cross-linked wheat starch (C and D) and native and cross-linked rice starch

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.

#### 4. DISSOLUTION TEST RESULTS

The dissolution profile of the tablets from the cross-linked maize, wheat and rice starch is shown in Fig. 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.

#### 5. 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. 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. The study also supports evidence of the usefulness of some Nigerian plant products as sources of pharmaceutical excipients [22].

## 6. 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.

## 7. 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.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICS APPROVAL

It is not applicable.

## ACKNOWLEDGMENTS

Authors wish to thank the managements of National Institute For Pharmaceutical Research and Development (NIPRID), Abuja and The National Agency for Food and Drug

Administration and Control (NAFDAC) laboratory, Agulu for providing space and equipment for the conduct of some of the investigations.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Jiang T, Duan Q, Zhu J, Liu H, Yu L. Starch-based biodegradable materials: Challenges and opportunities. *Advanced Industrial and Engineering Polymer Research*. 2020;3(1):8-18. Available: <https://doi.org/10.1016/j.aiepr.2019.11.002>
2. Lipsa R, Tudorachi N, Vasile C, Chiriac A, Grigoras A. Novel Environmentally Friendly Copolymers Carboxymethyl Starch Grafted Poly(Lactic Acid). *J Polym Environ*. 2013;21:461–471. Available: <https://doi.org/10.1007/s10924-012-0470-1>
3. Alcázar-Alay SC, Meireles MA. Physicochemical properties, modifications and applications of starches from different botanical sources. *Food Science and Technology*. 2015;35:215-36.
4. Koo SH, Lee KY, Lee HG. Effect of cross-linking on the physicochemical and physiological properties of corn starch. *Food Hydrocolloids*. 2010;24: 619 – 625.
5. Parhi R. Cross-Linked Hydrogel for Pharmaceutical Applications: A Review. *Adv Pharm Bull*. 2017;7(4):515-530. DOI: 10.15171/apb.2017.064. Epub 2017 Dec 31. PMID: 29399542; PMCID: PMC5788207.
6. Sun S, Liu P, Ji N, Hou H, Dong H. Effects of various cross-linking agents on the physicochemical properties of starch/PHA composite films produced by extrusion blowing. *Food Hydrocolloids*. 2018;77: 964-75.
7. Iken JE and Amusa NA. Maize research and production in Nigeria. *African Journal of Biotechnology*. 2004;3 (6): 302 – 307. DOI:10.5897/AJB2004.000-2056
8. Shewry PR. Wheat. *J Exp Bot*. 2009;60(6):1537-53. doi: 10.1093/jxb/erp058. PMID: 19386614.
9. Wani AA, Singh P, Shah MA, Schweiggert-Weisz U, Gul K and Wani IA. Rice Starch Diversity: Effects on Structural,

- Morphological, Thermal, and Physicochemical Properties - A Review. *Comprehensive reviews in food science and food safety*. 2012;11: 417-436. DOI.org/10.1111/j.1541-4337.2012.00193.x
10. Odeniyi MA and Ayorinde JO. Effects of modification and incorporation techniques on the disintegrants properties of wheat (*Triticum aestivum*) starch in metronidazole tablets formulations. *Polimers in Medicine*. 2014;44(3): 147 – 155.
  11. Builders PF, Arhewoh MI. Pharmaceutical applications of native starch in conventional drug delivery. *Starch-Stärke*. 2016;68(9-10):864-73.
  12. Tan X, Hu J. Investigation for the quality factors on the tablets containing medicated pellets. *Saudi Pharm J*. 2016;24(5): 507-514. DOI: 10.1016/j.jsps.2015.01.020.
  13. British Pharmacopoeia. Vol. III. The Pharmaceutical Press, Her Majesty's Stationery Office, London. 2009: 6578 - 6585.
  14. British Pharmacopoeia Vol. I and II. The Pharmaceutical Press, Her Majesty's Stationery Office, London; 2002.
  15. Markl D, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques. *Pharm Res*. 2017;34(5):890-917. DOI: 10.1007/s11095-017-2129-z.
  16. Xiao HX, Lin QL, Liu GQ, Yu FX. A comparative study of the characteristics of cross-linked, oxidized and dual-modified rice starches. *Molecules*. 2012;17(9): 10946-57. DOI: 10.3390/molecules170910946.
  17. Koo SH, Lee KY and Lee HG. Effect of cross-linking on the physicochemical and physiological properties of corn starch. *Food Hydrocolloids*. 2010;24:619 – 625.
  18. Jairoun AA, Al-Hemyari SS, Shahwan M, Zyoud SE, Ashames A. Hidden Formaldehyde Content in Cosmeceuticals Containing Preservatives that Release Formaldehyde and Their Compliance Behaviors: Bridging the Gap between Compliance and Local Regulation. *Cosmetics*. 2020;7(4):93.
  19. Asare-Donkor NK, Kusi Appiah J, Torve V, Voegborlo RB, Adimado AA. Formaldehyde Exposure and Its Potential Health Risk in Some Beauty Salons in Kumasi Metropolis. *J Toxicol*. 2020;2020: 8875167. DOI: 10.1155/2020/8875167. PMID: 33204257; PMCID: PMC7661109.
  20. Lin Z, Zhou D, Hoag S, Qiu Y. Influence of Drug Properties and Formulation on In Vitro Drug Release and Biowaiver Regulation of Oral Extended Release Dosage Forms. *AAPS J*. 2016;18(2): 333-45. DOI: 10.1208/s12248-015-9861-2.
  21. Fonteyne M, Vercruysse J, De Leersnyder F, Van Snick B, Vervaet C, Remon JP, De Beer T. Process Analytical Technology for Continuous Manufacturing of Solid-Dosage Forms. *Trends Anal. Chem*. 2015;67: 159 – 166.
  22. Ojiako CM, Okoye EI, Oli AN, Ike CJ, Esimone CO, Attama AA. Preliminary studies on the formulation of immune stimulating complexes using saponin from *Carica papaya* leaves. *Heliyon*. 2019;5(6):e01962. DOI: 10.1016/j.heliyon.2019.e01962.

© 2021 Okeke et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*  
The peer review history for this paper can be accessed here:  
<https://www.sdiarticle5.com/review-history/74581>