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The Influence of Phosphate Modified and Pregelatinized Plantain (*Musa Paradisiaca,* Family*: Musaceae)* Starches as Disintegrants In Paracetamol Tablet Formulations

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Starch is the commonest disintegrant used in tablet formulation. The use of starch is however limited by its poor functional properties of flow, compressibility and compatibility. Hence, starches are chemically, physically or enzymatically modified to improve the aforementioned properties.

Objective: This study was aimed at investigating the disintegrant property of simultaneously phosphorylated and pregelatinized plantain starch (PPPS) obtained from *Musa paradisiaca* (Family: *Musaceae*) in directly compressed paracetamol tablet formulations in comparison with formulations containing natural plantain starch (PS) and sodium starch glycollate BP (SSG).

Method: The extracted plantain starch was purified to yield PS. A portion of PS was simultaneously modified by phosphorylation in 50% v/v monosodium phosphate medium and pregelatinized in the same medium to yield PPPS. The powdered PPPS was characterized using density measurements and Kawakita equations before incorporation as a disintegrant in directly compressed paracetamol tablet formulations at concentrations of 10, 15, 20 and 25 %w/w in comparison with PS and SSG. The tablets were evaluated for their mechanical and release properties. Statistical data was carried out using ANOVA at a significance level of p-values < 0.05.

Result: The yield of PS was 57.6 % w/w. The bulk and tapped densities are of the order PPPS (0.61±0.05 and 0.71±0.13) > PS (0.47±0.05 and 0.53±0.11) > SSG (0.38±0.01 and 0.50±0.01), while the angle of repose are of the order PS (57.10^0±0.14) > PPPS (35.60^0±0.01) > SSG (33.70^0±0.13). The ranking for friability values was PS Tablets>SSG tablets >PPPS tablets. Tensile strength values were of the reverse order for the tablets. Tablets containing PS had the highest disintegration time values at all concentrations, while onset of paracetamol release was fastest from PPPS tablets.

Conclusion: Modification of plantain starch by simultaneous phosphorylation and pregelatinization showed better disintegrant properties than unmodified plantain starch, but comparable with sodium starch glycollate BP.

Keywords: Pregelatinized plantain starch, Phosphate modification, Disintegrant, Paracetamol

INTRODUCTION

Solid medicaments may be administered orally as powders, pills, capsules or tablets, with tablets and capsules, accounting for well over two-thirds of the total number and cost of medicines produced all over the world (Sahoo, 2007), while the oral route is the most popular and preferred route of drug administration (Desai *et al*, 2016). According to

Gossop (2007), pharmaceutical tablets are solid, flat or biconvex, unit dosage form, prepared by compressing a drug or mixture of drugs and excipients.

Excipients not only aid in transporting the active drug to the part of the body where the drug is intended to exert its action, they also play a major role in the manufacturing process. (Apeji *et al*,2011). Over the last two decades, a lot of effort has been expended towards the development of locally produced starch as pharmaceutical excipients, especially as disintegrants, binders or bioadhesives (Adetunji *et al*, 2006; Odeniyi *et al*, 2011; Adeleye *et al*, 2015). Disintegrants are relatively the most important tablet excipient since a tablet is not useful until its active component is made available for absorption (Bakare and Jaiyeoba, 2009). Their main function is acting against the efficiency of the tablet binder and the physical forces that works under compression to form the tablet. Therefore, the more the binding ability of the binder, the more efficient must be the disintegrant in order for the tablet to readily release its active agent (Mohanachandran *et al*, 2011).

Starch is an odourless, fine white powder or irregular angular masses readily reducible to powder and insoluble in cold water and alcohol (British Pharmaceutical Codex, 1994). Apart from being a major food item, starch is a multifunctional excipient in tablet formulations as it can be employed as disintegrants, binders, glidants, lubricants or fillers as a result of its relative inertness and insolubility in cold water (Adedokun and Itiola, 2014). Starches obtained from different plant sources have been evaluated for use as pharmaceutical excipients (Adetunji *et* al, 2006; Musa *et al*, 2010; Ayorinde *et al*, 2013). Native starches have limited applications as a result of their low shear stress resistance and thermal decomposition, high retrogradation and solubility in common organic solvents. Thus, in order to satisfy the demanding technological needs of today, modifications are done to starches by a variety of methods to improve their functional properties. This is targeted at enhancing the versatility of starch and meeting consumer demand for formulations (Neelam *et al*, 2012).

Plantain starch is obtained from *Musa paradisiaca*, Family*: Musaceae*) and is available in abundance in Nigeria (Bamigbola *et al*, 2016). Alebiowu and Itiola (2001) reported the pregelatinization of plantain starch as an excipient in tablet formulation. However, little work has been done on the use of dually modified plantain starch as excipient in directly compressible tablets.

Justification of the Study:

Phosphorylation of starch enhances the rheological and pasting properties of starch, which is expected to improve the flowability of starch when used in tablet formulation. This is as a result of addition of phosphate groups to the C_6 position of the glycosyl group (Roznowski *et al*, 2015). Pregelatinized starches enhances the degree of bond strength of tablets (Alebiowu and Itiola, 2001). In this study, plantain starch obtained from *Musa paradisiaca* was simultaneously phosphorylated and pregelatinized, and the resulting modified starch was characterized and evaluated for its disintegrant properties at different concentrations (10.0 %w/w, 15.0 %w/w, 20.0 %w/w, 25.0 %w/w) in directly compressed paracetamol tablet formulations in comparison with sodium starch glycollate BP (SSG). The high disintegrant concentrations have been chosen based on preformulation studies that showed that at high levels, SSG is expected to form a viscous gel layer that will enhance rapid capillary activity (Chitral *et al*, 2008)

MATERIALS AND METHODS

The materials used include Paracetamol powder (Gift from Bond Chemicals Limited, Aawe, Oyo State), Corn starch BP (Lot 69833; gift from Bentos Pharmaceutical Products ,Podo-Ibadan, Oyo State, Nigeria), Lactose BP (Mitushi BioPharma Ltd, Ahmedalad, India), magnesium stearate powder (Fooding Group Limited, Shanxi, China) Ultrapure water (UPW) containing 50% v/v monosodium phosphate was prepared at the Centre for Drug Discovery, Development and Production, University of Ibadan, Nigeria, Plantain starch (from bunches of *Musa paradisiaca*) was obtained from the Botanical Garden, University of Ibadan, Ibadan. All the other reagents used were of analytical grade and their use were modified as described.

METHODS

Collection and Purification of *Musa paradisiaca* Starch

The starch used in the study was extracted from unripe plantain, *Musa paradisiaca* (Family: *Musaceae*), using standard procedures (Adetunji *et al*, 2006). The peel of the plantain was removed and the plantain was weighed. Distilled water and sodium metabisulphite were then added before it was pulped. The pulped plantain was soaked for 24 hours and sieved using muslin cloth. Distilled water was added to the pulped plantain filtrate and carefully decanted daily for 4 days for purification of the starch. The sludge was first air-dried in the sun under a net covering for about 3 days; it was then transferred into

the hot air oven (Gallenkamp BS oven 250 size 1, England) where it was dried at 40 °C for 24 hours. The dried sludge obtained was then milled and sieved through a sieve of mesh size 0.125 mm after which the resultant plantain starch (PS) powder was stored in an air-tight container in order to prevent re-absorption of moisture.

Test for starch

A drop of N/50 iodine solution was added to some powder of the PS on a microscope slide and examined under the optical microscope (Sofowora, 1993). About 1 g of PS powder was put in a test tube and an equal amount of UPW was added. The resultant paste was stirred with a glass rod and thereafter allowed to stand for a few minutes. Some of this paste was then transferred into another test tube via a pipette and a drop of Iodine solution was added. The resultant paste was then observed for any colour change.

Starch Modification

The modified thermal pregelatinization method was employed. Exactly 10 g of PS was soaked in 100 mL of ultrapure water containing 50 %v/v monosodium phosphate (UPWmsp) for 10 minutes. A slurry was thereafter made which was then heated at 85 °C using the water bath and consistently stirred with the glass stirrer for about 20 minutes. The resulting paste was then dried in hot air oven (Gallenkamp BS oven 250 size 1, England) at 60 °C for 48 hours. The dried mass was thereafter powdered using a laboratory mill (03200 Landers and Ciasa, Corona, USA) and then passed through a 250-µm sieve prior to storing the dried modified PS (PPPS) in an air-tight container. The PPPS was also tested for starch as already described (Sofowora, 1993)

Characterization of Starch Powder

Determination of volume reduction

Kawakita equations were used to determine the maximum volume reduction of the starch samples (Kawakita and Ludde, 1971), and is written as:

$$\frac{N}{C} = \frac{1}{a} x\, N + \frac{1}{ab} \quad (1)$$

The equation can be rearranged as (Alebiowu and Itiola, 2001):

$$C = V_0 - \frac{V_N}{V_\infty} \quad (2)$$

Where a and b are material specific constants, N is the number of taps, C is the degree of volume reduction, V_0 is the maximum bulk volume reduction, V_N is the bulk volume after N taps and Vα is the minimum bulk volume.

Determination of the particle, bulk and tapped density

The pycnometer method involving the use of xylene was used in determining the particle density of the starch samples. The loose bulk density (at zero pressure) of each sample was determined by pouring 10 g of each starch sample at an angle of 45 °C through a funnel into a graduated glass measuring cylinder of diameter 25 mm and 100 mL volume. The bulk volume was determined. Each starch sample was subjected to a number of taps reaching 100 taps according to British Standard 1460. The cylinders containing the starch samples were made to fall from a height of 2.54 cm at an interval of 2 secs. The corresponding volumes were then recorded. Values of the packing fraction, $P_{F,}$ (ratio of bulk density to particle density) for each starch sample was used in calculating the percentage porosity ($P_{\%}$) from the equation:

$$P\% = (1- P_F) \times 100\% \quad (3)$$

Swelling Capacity

The method of Iwuagwu and Onyekweli (2002) was adopted in determining the swelling capacity. Each starch sample (10 g) was poured in a 100 mL measuring cylinder. The volume occupied was noted (Vs). About 85 mL of UPW was added into the cylinder to make a suspension and the volume made up to 100 mL with UPW. The set-up was allowed to stand for 24 hrs and the final volume (Vt) was noted. The swelling capacity was calculated using the formula:

$$\text{Swelling capacity} = Vs - Vt \quad (4)$$

Confirmation of Modification

Morphological studies and Fourier Transform Infrared Spectroscopy (FTIR) were used to confirm that modification was due to simultaneous phosphorylation and pregelatinization of PS. Samples of the unmodified PS was placed on a slide,and mounted on an optical microscope (Olympus light microscope XSZ-107BN) and the photograph was taken. Samples of PPPS (modified PS) were also mounted on the microscope and the photograph was taken. The photomicrographs obtained from the two shots were compared for morphological differences. The FTIR spectroscopy for both the unmodified PS and PPPS were obtained using a Magna-IR, 760 spectrometer (Perkin Elmer, USA) attached to an OMNIC version 3.0 software. About 5 mg of each of the completely dried powdered samples was weighed and then dispersed in 200 mg potassium bromide (pellet procedure). Signal averages were obtained at a resolution of 4 cm^{-1}.

Preparation of Powder for Direct Compression
A basic formulation (400 mg) comprising paracetamol (50 %w/w), corn starch (20 %w/w) and magnesium stearate (0.5 %w/w) were triturated in a porcelain mortar and pestle. The mixture was thereafter mixed with appropriate amounts of each starch sample at concentrations of 10.0 %w/w, 15.0 %w/w, 20.0 %w/w, 25.0 %w/w and lactose at concentrations of 19.5 %w/w, 14.5 %w/w, 9.5 %w/w, 4.5 %w/w respectively in order to produce samples containing different concentrations of the disintegrant and filler.

Compression of Tablets
A Carver hydraulic hand press (Model C, Carver Inc., Menomonee Falls, Wisconsin, U.S.A.) fitted with a pressure gauge reading up to 2.5 metric tons was used. The prepared formulations were used in compressing 400 mg ± 5 mg tablets using a 10.5 mm diameter die in combination with flat-faced upper and lower punches. The punches and dies were lubricated with 2 %w/v dispersion of magnesium stearate in ethanol-ether (1:1) before each compression. The compressed tablets were kept in sealed containers for 24 hours to allow elastic recovery to occur prior to evaluation of the tablet properties.

Evaluation of Tablet Properties

Weight Uniformity of Tablets
Twenty tablets were selected randomly from each batch and weighed in triplicates. The percentage deviation from the average weight was recorded.

Tablet Diameter and Thickness
The diameter and thickness of 20 randomly selected tablets were accurately measured to within 0.01 mm using a micrometer screw gauge.

Tablet Hardness
The hardness of six (6) randomly selected tablets from each batch was determined using the hardness tester (DBK instruments, w400065, model-EH 01, Mumbai). The average hardness (N) was also determined and the standard error was recorded.

Friability Test
Twenty randomly selected tablets were weighed and placed in the friabilator (DBK friability apparatus, England) which was operated at 25 revolutions per minute for 4 minutes. The tablets were then collected, dusted and reweighed. The loss in weight and percentage loss in weight were subsequently calculated.

Disintegration Test
Disintegration tests were carried out using the disintegrating apparatus (DBK Tablet Disintegration Test Apparatus, England) containing distilled water at 37 ± 0.5 ^{0}C. A tablet from each batch was placed in the basket already fixed to the disintegration tester. The rotation speed of the device was set to 30 rpm. The time taken for each tablet to totally disintegrate and pass through the basket was recorded.

Dissolution Test
The dissolution profiles of the tablets were determined in freshly prepared phosphate buffer (pH 5.8) as the dissolution medium using the USP dissolution apparatus I (rotating basket) method. Each tablet was placed in a cylindrical basket of stainless wire mesh attached to a variable speed drive mechanism set to rotate at 100 rpm and suspended in a glass vessel containing 900 mL of phosphate buffer immersed in a water bath set at 37 ± 0.5 ^{0}C. Samples (5 Ml) of the dissolution medium was withdrawn at designated intervals and replaced with fresh samples. The withdrawn samples were appropriately diluted and then analyzed using the ultraviolet spectrometric method, their absorbances were measured using a UV visible spectrophotometer (Jenway UV-7804c print, England) at wavelength 243 nm.

Data and Statistical Analysis
Results were expressed as mean ± SD. Analysis of variance (ANOVA) was performed on the data sets generated using SPSS®16. Differences were considered significant for p-values < 0.05.

RESULTS AND DISCUSSION

The degree of volume reduction has been used to predict the behavior of powders on the application of pressure during the process of formulating the powder as a compact (Adetunji *et al*, 2006). The degree of volume reduction was of the order PPPS > SG > PS, thus suggesting that the simultaneously phosphorylated and pregelatinized plantain starch will be expected to provide more compacts as a result of die filling during the compression process. The flow properties of powdered mixtures are evaluated

using values obtained from the angle of repose, Hauner's ratio and Carr's Index. The angle of repose is a qualitative measure of the tendency of powdered materials to flow. The cohesive nature of a powdered material has a direct relationship with the angle of repose (Uzondu *et al*, 2014). Good flowability shows that the powders have less interparticulate attractions and so, they will not easily consolidate to block the hopper orifice during tableting (Rahim *et al*, 2014). Generally, angle of repose of 30° and below indicates a free-flowing powder, powders between 30°- 40° angles of repose are said to be passable, while powders with angles of flow greater than 40° are said to be highly resistant to flow (Apeji *et al*, 2013). The angle of repose for PPPS (35.60 ± 0.01^0) was comparable with that of SSG (33.70 ± 0.13^0) and both powders exhibited better flow properties than PS (57.10 ± 0.14^0). Carr's index is a measure of a powder flowability and compressibility. It provides intuitive logic and insight to how a powder is expected to behave during the process of manufacturing (Freeman and Price, 2009). Low Carr's index values give good flowability but poor compressibility. Values of 5-10, 12-16, 18-21, 23-35 represent excellent, good, fair to passable and poor flow properties respectively (Riley and Adebayo, 2010). The Hausner's ratio gives an indication of the degree of densification that could result from vibration of the feed hopper during tableting, higher values predicts significant densification of powders and lower values suggests enhanced flowability. The powdered PPPS gave the lowest Carr's index value (13.17±0.05), and also the lowest Hausner's ratio (1.15±0.11) thus implying having good flow properties, which will favour die filling during the process of compression.

Swelling Properties

The swelling capacity of a powdered material has been documented to determine to the disintegrant properties of the material (Apeji *et al*, 2013). The swelling capacity of the materials (Table 1) ranked in the order PS > PPPS > SSG. This result indicates that tablets containing PPPS as disintegrants are expected to disintegrate at a faster rate than tablets containing SSG as disintegrants (Jubril *et al*, 2012).

Tablet Properties

The preferred tablet manufacturing method used by the pharmaceutical industry is the direct compression method as it eliminates additional processing steps and avoids added equipment costs required for other compression methods . The uniformity of weight, thickness and diameter of the directly compressed tablets are presented in Table 2. Generally, there was no significant difference in thickness, weight and dimensions of the compressed tablets.

Table 2: Weight Uniformity, Thickness and Diameter of Tablets (n = 3 ±SD)

Concentration (% w/w)	Starch	Weight (g)	Thickness (mm)	Diameter (mm)
10.0	PPPS	0.413 ± 0.014	3.973 ± 0.082	10.779 ± 0.046
	PS	0.389 ± 0.021	3.912± 0.015	10.655± 0.014
	SSG	0.393 ± 0.009	3.783 ± 0.084	10.767 ± 0.042
15.0	PPPS	0.406 ± 0.009	3.923 ± 0.125	10.725 ± 0.022
	PS	0.383± 0.022	3.899± 0.003	10.623± 0.017
	SSG	0.388 ± 0.013	3.811 ± 0.418	10.737 ± 0.026
20.0	PPPS	0.399 ± 0.010	3.836 ± 0.100	10.721 ± 0.023
	PS	0.376± 0.014	3.891± 0.016	10.602± 0.011
	SSG	0.398 ± 0.011	3.832 ± 0.108	10.751 ± 0.039
25.0	PPPS	0.402 ± 0.009	3.871 ± 0.088	10.719 ± 0.036
	PS	0.371± 0.010	3.902± 0.012	10.613± 0.011
	SSG	0.400 ± 0.094	4.078 ± 0.110	10.886 ± 0.073

PPPS = Phosphorylated and Pregelatinized Plantain Starch. PS = Natural Plantain Starch SSG = Sodium Starch Glycollate BP

Mechanical and Release properties

Friability is an indication of how resistant a tablet is to external forces that cause abrasion during the process of packaging, shipping and handling, and also measures how weak a tablet is (Itiola and Pilpel, 1991), while hardness provides a quantitative estimate of the internal bonding strength of the powder compact, which is what gives the tablet sufficient mechanical strength to maintain its internal structure and geometry under applied external forces

(May *et al*, 2013). The Friability values of the tablets (Fig. 3) indicates that tablets containing PPPS as disintegrants were the least friable with the highest tensile strength (Fig. 4) across all the concentration ranges. Under such circumstances, it may be assumed that the tablets containing PPPS with the highest tensile strength would have the highest disintegration time based on the high internal bonding strength of PPPS tablets. However, the results obtained from the disintegration and dissolution times (Table 3) changed that perspective. This observation could be as a result of enhanced penetration of water due to the pregelatinized starch. The ultimate aim of tablet formulation is for the active ingredients to be released as fast as required, thus ensuring availability of the tablet for therapeutic activity (Adetunji *et al*, 2015). Tablets containing PS as disintegrants had the highest disintegration time values at all concentrations, while onset of paracetamol release was fastest from PPPS tablets (Table 3 and Fig.4). However, all the tablets disintegrated within the official limit of 15 minutes (USP, 2015), while tablets containing 10 %w/w of all the disintegrants could not release up to 80 % of paracetamol within 60 minutes (Fig. 5).

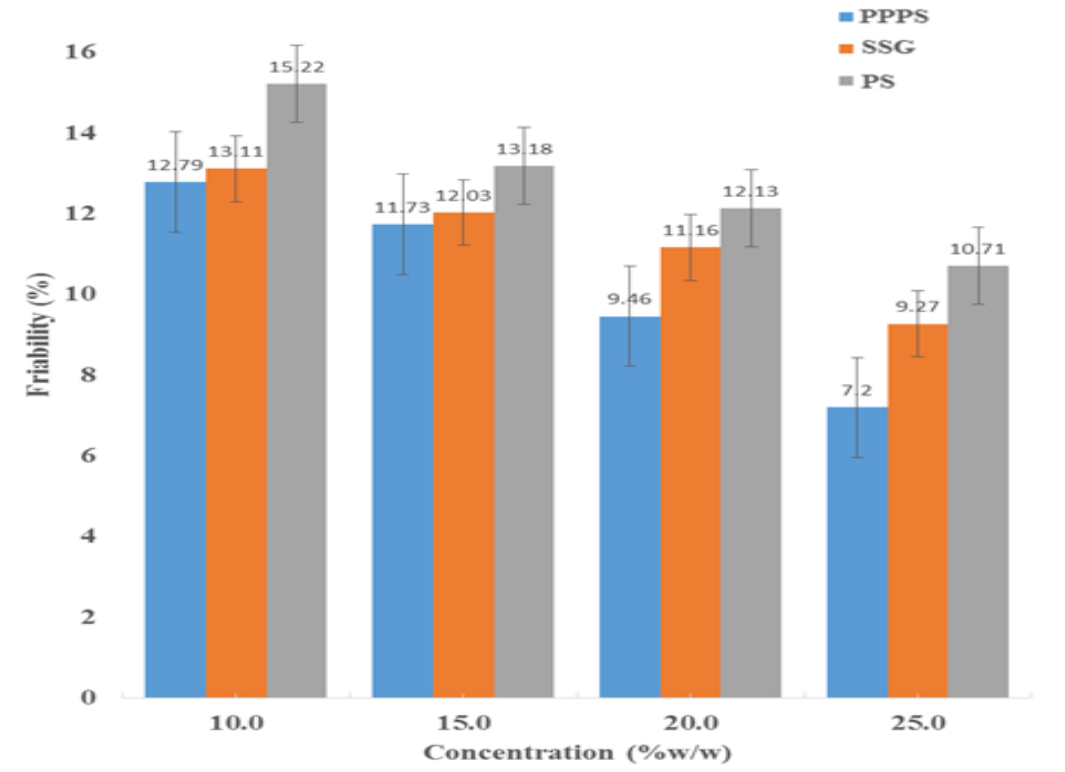

Fig. 3: Plot of Friability (%) against Concentration of Disintegrant (%w/w)

Table 3: Disintegration and dissolution characteristics of paracetamol tablets

Concentration (% w/w)	Starch	D (mins)	t_{50} (mins)	t_{80} (mins)
			(Total Time = 60 mins)	
10.0	PPPS	11.03 ±0.09	13.11 ±0.46	-
	PS	13.26 ±0.18	28.47 ±0.38	-
	SSG	10.11 ±0.11	29.53 ±0.09	-
15.0	PPPS	9.13 ±0.12	12.34 ±0.08	39.28 ±0.52
	PS	12.11 ±0.09	27.59 ±0.59	56.07±0.26
	SSG	8.37 ±0.08	21.43 ±0.21	40.11±0.29
20.0	PPPS	8.12 ±0.07	11.56 ±0.18	32.42 ±0.17
	PS	11.17 ±0.53	30.11 ±0.08	54.39±0.09
	SSG	8.08 ±0.45	17.28 ±0.29	38.57±0.25
25.0	PPPS	7.86 ±0.05	10.17 ±0.18	23.18 ±0.42
	PS	10.32 ±0.38	31.07 ±0.37	54.16±0.17
	SSG	7.63 ±0.17	16.01±0.42	36.48±0.29

PPPS = Phosphorylated and Pregelatinized Plantain Starch.
PS = Natural Plantain Starch
SSG = Sodium Starch Glycollate BP

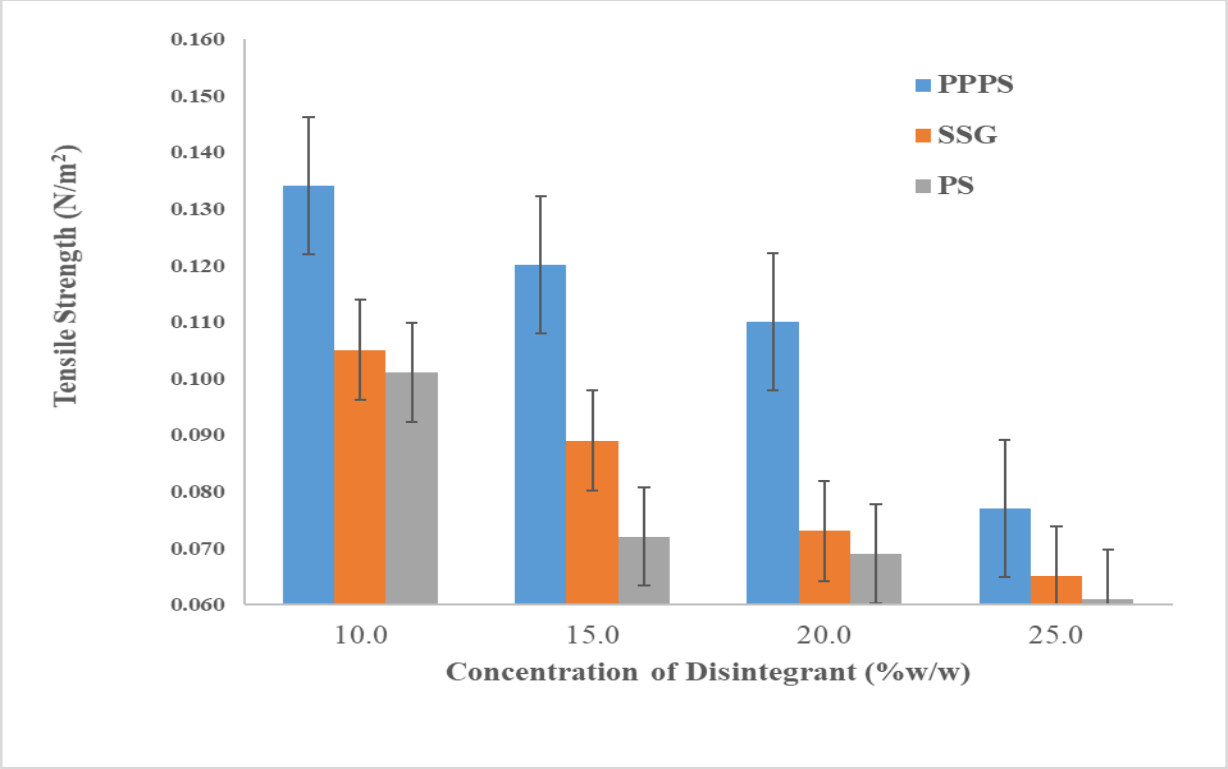

Fig. 4: Plot of Tensile Strength (N/m^2) against Concentration of Disintegrants (%w/w)

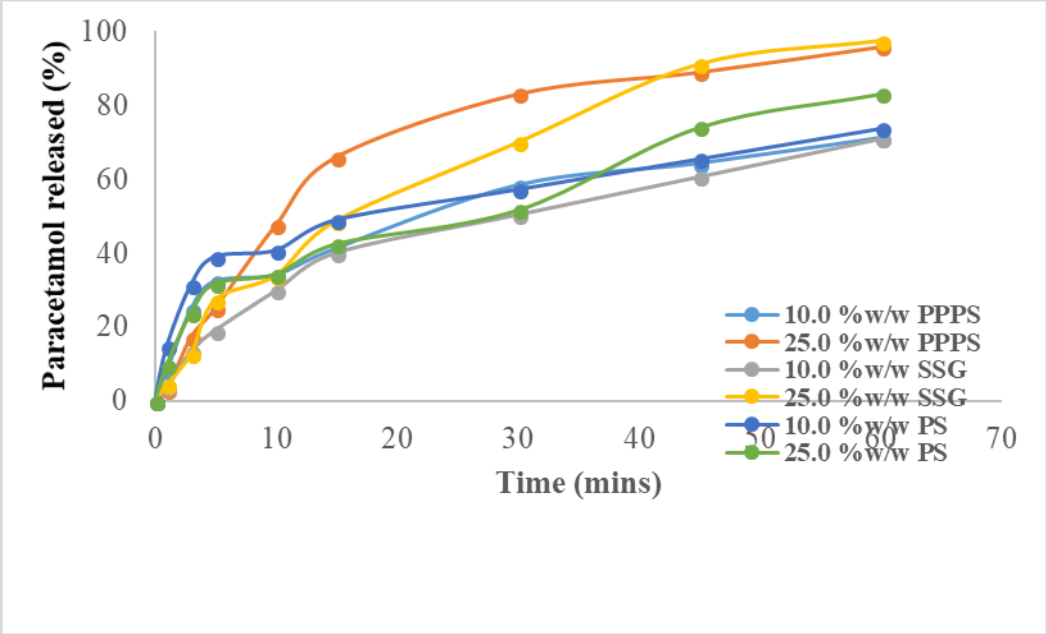

Fig. 5: Representative Dissolution profile of paracetamol tablet formulations containing 10.0 %w/w and 25.0% w/w starch as disintegrant.

Conclusion

Modification of plantain starch by simultaneous phosphorylation and pregelatinization showed better disintegrant properties than unmodified plantain starch. The disintegrant properties of the modified plantain starch are comparable with sodium starch glycollate BP. Further research studies will include the application of the modified starches as disintegrants in tablets formulated by wet granulation and to also exploit the potentials of the modified starches as binders in tablets.

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