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Research Paper

Comparing the Diluent Properties of Dual-Modified *ManihotEsculenta* and *ManihotTristis* Starches in Folic Acid Tablet Formulation.

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ABSTRACT: *Properties of starchesvary among sources and within species of same source. The aim of this study is to compare the diluent properties ofManihotesculenta and Manihottristisstarches.For this study, folic acid, a low drug-load active, was used as the active pharmaceutical ingredient, and corn starchwas used as control diluent. The test starches were dual-modified using acid hydrolysis and oxidation techniques. The swelling ratio, moisture content and gelatinization temperature of the starches were determined. Compatibility of folic acid with the starches was determined using FTIR analysis.Folic acid was granulated with the starches. The granules wereanalysedand tableted. Thephysicochemical properties of the tablets were evaluatedand theresults analysed.Dual-modifiedManihottristis showed moisture content< 10.31 %, swelling ratio< 1.32 %, and gelatinization temperature > 68.70 ˚Cin comparison with swelling ratio 1.51 %, moisture content 11.06 % and gelatinization temperature67.40 ˚C of dual-modifiedManihotesculentastarch. FTIR result showed no drug-starch interaction. The tablets had friabilities< 0.75 %, disintegration times<1.18 min, and tensile strengths> 1 Kgf.Tablets containing dual-modifiedManihottristis starchreleased>75.00 %drug after 60 min,compared to< 70.00 % drug release after 60 min from tablets containingdual-modifiedManihotesculenta starch.Dual-modifiedManihottristis starch showed better (p > 0.05) diluent properties that is closer to the diluent properties of conventional corn starch in comparison with dual-modifiedManihotesculenta starch.*

KEYWORDS*: acid hydrolysis; oxidation;low drug-load; gelatinization; swelling-ratio.*

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I. INTRODUCTION

Diluents are inert, physically stable, high carrying capacity, cost-effective, low hygroscopicity, and processable non-functional or functional excipients used in dosage design [1] and [2]. Functional diluents are used to bulk, ease ingestion, ease dispensing, add structure, improve mouthfeel, impact appearance, extend the activity of API and modify drug releaseof dosage forms [3].Non-functional diluents are used mainly for diluting drug active to measurable unit dosing sizes for effective production, packing and dispensing.

Starch is one of the most commonly used pharmaceutical diluent[4]. Native starch from different sources have been applied as diluents in different dosage forms in either as natural, modified or co-processed starch, or in different combinations of natural, modified, and co-processed starches[3],[5],[6], [7] and [8]. Starch modification can be by genetic, enzymatic, physical and chemical processes [3]. The extent and effectiveness of modification of native starch is dependent on its source and inherentproperties [9]. It is more efficient and effective to modify starch that already have a sort-after character in its native starch form [8], [9], [10], [11] and [12].Chemical modification degradesand depolymerizesthe amorphousunit of starch polymerto leave a more crystalline granule associates and arrangements [13], [14] and [15].Dual-modification of starch further refines and fine-tunes its functional properties [16].

The aim of this study is to modify starches from *Manihotultilissima* and *Manihottristis* cassava plants using dual chemical modification techniques. The objective is to compare the effect ofdual-modification on the diluent properties of starches from different species of cassava plant.Folic acid, ahaemopoietic drug, was used

asthe active pharmaceutical ingredient in this study because it is a low-dose drug (about 4.0 – 5.0 mg per tablet of 90.0 – 120.0 mg weight) that requires high concentration of diluent[17], [18], [19] and [20].

II. MATERIAL AND METHODS

2.1 Sample Collection

The materials used in this study include: *Manihotultilissima* and *Manihottristis* starches (Agricultural Development Project, ADP, Farm, Ibusa, Delta State), Folic acid (Shandong Xinfa Pharmaceutical Company Limited, China), Corn starch (Norbright Industry limited, China), Magnesium stearate (Takehara, Kagaku Kogy Company Limited, Japan), Gelatin (Jiangsu Guo Tai International Group Huatai Import and Export Company Limited, China), and Microcrystalline cellulose (VijlakPharma Limited, India). The other reagents used were of analytical grade.

2.2 Preparation of Dual-modifiedStarch

The Xing *et al* [16] concept of dual-modification was adapted in combining the modified methods ofZilli*et al*. [21]for acid hydrolysis and Attama*et al.* [22] for oxidation of starch. A 350.0 g dried starch powder was passed through a 0.35 mm sieve, and made to 1.0 L with water in a 2.0 L volumetric flask. A 10.0 ml of 0.3 M hydrochloric acid was added to the flask mix, kept at 40.0 ℃ in a hot air oven (Kottermanns Company, Germany). The flask was removed every 6 h, stirred for 2 min and replaced three times during 24 h period, and then filtered. The wet mass was then washed with 10.0 ml of 0.1 M sodium hydroxide three times, and with 500.0 ml water three times to obtain a neutral starch with litmus paper. The wet starch was pressed to a solid mass by squeezing in a muslin cloth, and dried at 70.0 ℃ in a hot air oven (Kottermanns Company, Germany) for 36 h.A 200.0 g of the dried mass was mixed with 500 ml sodium hydroxide. The filtrate of calcium hypochlorite, from a mixture of 10.0 g calcium chloride in 25.0 ml sodium hydroxide,was added to the dry mass mixture and left to stand for 1 h with intermittent 10 min stirring. The supernatant was decanted and the wet mass dried in the hot air oven at 45.0℃ for 12 h. The dried starch was milled, passed through a 1.7 mm stainless sieve, and packed in sealed container.

2.3 Evaluation of Dual-modified starch

The starches wereeach evaluated to determine theirmoisture absorption, swelling ratio, viscosity, gelatinization temperature, paste clarity, bulk and tapped densities, Hausner ratio and Carr's index.

The method of Akpa*et al.* [23] for moisture content determination was adopted. A clean petri dish was dried in a hot air oven (Model DHG-9053A, Ocean Medical, England) at 110.0 ℃ for 15 min., removed and allowed to cool in a desiccator for 10 min. A 5.0 g starch sample, weighed out after screening though a 0.22 mm stainless steel sieve, was poured on the petri dish, weighed and recorded as initial weight. The petri dish was placed in the hot air oven and heated for 2h at 110.0 ℃, removed from the oven, and allowed to cool in a dessicator for 30 min. The petri dish was removed and weighed to record the final weight. The test was repeated three times, and the average reported. The percent moisture content was calculated using Equation 1.

$$\% \text{ moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100 \quad \text{.....1}$$

Swelling ratio was determined using the modified method of Daramola and Osanyinlusi [24]. A 2.00 g was mixed with 1.0 ml ethanol. The mixture was made up to 25.0 ml with water in a test-tube and placed in a HS – S8 Digital Thermostatic water bath (Erweka-GmBH, Germany) at 60.0℃, shaken vigorously intermittently every 10 min in for 1 h. The test tube was then allowed to stand for 3 h, and centrifuged using Centaur 2 MSE Centrifuge (DJB Labcare Limited, United Kingdom) at 1200 r.p.m for 15 min to separate the mixture. After centrifuging, the swollen starch volume was obtained by reading the volume of the swollen sediment in the test-tube. The resultant supernatant was removed, and the sediment was put in a metal dish and weighed. The weight of the precipitated gel was noted as the weight of swollen gel. The swollen gel was then dried at 105.0℃ for 1 h, and weighed. The dried weight was noted as the weight of dry gel. The test was repeated three times, and the average reported. The swelling ratio of starch was determined using the in Gupta and Shivakumar [25] Equation 2.

$$\text{Swelling ratio} = \frac{\text{weig ht of swollen gel}}{\text{weight of dry gel}} \quad \text{.....2}$$

The viscosity and gelatinization temperatures of the starches were obtained from the viscoelastic reading of their stirred dispersions at different temperatures in a test viscometer (LvDv 1+, Brookfield) using the method of Ascheri*et al.* [26]. A 9 % $^{w}/_{w}$ dispersion of starch in cold water was prepared and gently stirred at

960 r.p.m. for 2 seconds, then at 160 r.p.m. for a minute in the operating viscometer. The dispersion was allowed to equilibrate at 50 ℃ for 1 min., heated to 95.0℃ at the rate of 5.0℃ / min., and kept at this temperature for 2 min. At the rate of 5.0℃ / min., the dispersion was cooled to 50.0℃ with extra 2 min at the end. A viscosity curve obtained from a plot of viscosity readingsat different temperatures against their temperatures, and was use to interpret the peak viscosity, trough viscosity, final viscosity and final gelatinization temperature (G.T).

Paste clarity determination was done using the method reported by Xiao *et al.* [27]. A 1 % $^{w}/_{v}$ aqueous dispersion of sieved starch sample was prepared in a beaker, and heated with constant stirring to 95.0℃ for 30 min in an Accuplate Hotplate stirrer (Model D0420, Labnet International, United Kingdom) to form paste. The paste was left to stand at room temperature for 3 h, and then at 4.0℃ for 24 h in Bosch Economic-20 refrigerator (BSH Home Appliances Limited, United Kingdom). The transmittance of the starch paste was then measured using a UV Spectrophotometer (Model 23D, Uniscope, England) at 650 nm wavelength and compared with the transmittance of blank water. The test was repeated three times, and the average reported.

Bulk and tapped density were determined using cylinder and tap method.A 10.0 g powder at 45.0 ° through a funnel into a 50.0 ml measuring cylinder and the volume occupied noted as bulk volume (bv). The cylinder was tapped on a padded wooden base from a height of 2.5 cm until a fixed tap volume is reached and recorded as tv. The bulk density was calculated from 10 / bv. The tapped density was calculated from 10 / tv. The test was independently repeated in triplicates.

The Hausner ratios and Carr's indices of the starch were derived from their bulk and tapped densities using equations 3 and 4.

$$\text{Carr's index} = \frac{Tapped\ \ density\ \ - Bulk\ \ density}{Tapped\ \ density} \quad \ldots\ldots\ldots\ldots 3$$

$$\text{Hausner ratio} = \frac{Bulk\ \ density}{Tapped\ \ density} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 4$$

2.4 Chemical Compatibility Test

Fusion method was used to determine the chemical compatibility of the starches with folic acid. Using the fusion method reported by Leuner and Dressman [28] and a Schimadzu FTIR-8400S Fourier transmission Infrared Spectrophotometer, the FT - IR absorbances of a 1.00 % solid dispersion of 1:1 of API / starch in KBr, and of a 1.00 % pure API in KBr mixture were obtained at different wavelength. The FT - IR readings obtained were analysed and used to determine chemical compatibility of starch with folic acid.

2.5 Granulation

Using the formula in Table 1, a mixture of 3.0 g folic acid and 0.2 g methyl paraben was made to 5.0 ml with water and stirred at 50 r.p.m in a Kenwood Equipment Company (England) planetary mixer for 10 min. The dispersion obtained was then gradually poured onto 76.0 g sample diluent for formulations F6, F7, F8, F9 and F10 respectively, and mixed at 30 r.p.m. in a planetary mixer (Kenwood Equipment Company, England) for 10 min. Then 5 % $^{w}/_{v}$ gelatin was prepared by heating 4.5 g gelatin in 90.0 ml water at 80.0℃ in a water bath for 2 min slurry. This cold slurry was added to the dispersion and blended for 5 min. The wet mass formed was screened through a 1.7 mm stainless steel sieve, and dried at 60.0℃ in a hot air oven (Kotternmanns Company, Germany) for 6 h, and allowed to cool for 30 min. Microcrystalline cellulose (1.0 g) and 1.0 g of magnesium stearate were added to the mix, and blended for 5 min at 50 r.p.m in the dried rotor mixer. The dried granules were stored in granule bottles for compression and evaluation of tablets.

Table 1.Formula for preparing 100 folic acid tablets with modified starch as diluent

	Quantity (g)				
Component	F6	F7	F8	F9	F10
Folic acid	3.0	3.0	3.0	3.0	3.0
Corn starch	76.0	-	-	-	-
Manihottristis starch	-	76.0	-	-	-
Manihotesculenta starch	-	-	76.0	-	-
Dual-modified*manihottristis* starch	-	-	-	76.0	-
Dual-modified*manihotesculenta* starch	-	-	-	-	76.0
Gelatin	4.5	4.5	4.5	4.5	4.5
Microcrystalline cellulose	4.0	4.0	4.0	4.0	4.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0
Methyl paraben	0.2	0.2	0.2	0.2	0.2

Total	88.7	88.7	88.7	88.7	88.7

Note: 1 tablet of 120 mg contains 4 mg folic acid active drug.

2.6 Compression of Granules

The granules were compressed to tablets using type F8 single punch machine (Manesty machines limited, England) with a 7.0 mm die cavity at a set of upper and lower punches. The machine was adjusted to produce 120.0 mg weight, and operated at 12 Nm pressure at a speed of 25 rpm. The compressed tablets were collected, de-dusted, packed in an air tight dry container, labelled and stored.

2.7 Evaluation of Tablet Properties

The weight variation, content uniformity, hardness, percent friability, disintegration time and dissolution rate properties of the tablets were evaluated.

Using the International Pharmacopoeia [19] method, 20 tablets from each batch were randomly selected and each of the 20 tablets in a batch was weighed individually using the electronic balance (Mettler, Switzerland), and recorded. The entire 20 tablets in the batch were weighed, and the average weight of each 20 tablets was calculated. The variation of each tablet weight from this average weight, and the deviation was calculated. The test for all the batches was repeated three times, and the average reported.

Content uniformity test was determined by weighing and pulverizedten tablets from each batch. A 435.0 mg of the pulverized powder, which is equivalent to 14.5 mg of folic acid, was dissolved in 1000.0 ml of water and filtered through a Whatman number 1 filter paper. Then 10 ml of this solution was made up to 100.0 ml with 0.1 M sodium hydroxide solution. The absorbance reading was taken at 256 nm and applied on the folic acid Beer's Lambert plot.

Ten tablets randomly selected from a batch were used for hardness test withMosanto tablet hardness tester (Model MHT-20, Thermonik, Campbell Electronics, India). From the selected 10 tablets, a tablet was measured for thickness and diameter and placed between the moving jaw and the fixed jaw of the Mosanto tablet hardness tester (Model MHT-20, Thermonik, Campbell Electronics, India). Pressure was applied on the tablet through screwing the lead, until the tablet brake. The pressure at which the tablet broke was recorded as F. Using the thickness, diameter and F of each tablet, the tablet tensile strength was determined using Equation 5. The test for all the batches was repeated three times, and the average reported.

$$\delta = \frac{2F}{\pi dT} \ldots\ldots\ldots 5$$

Using a single drum friabilator (PTF 10E, Pharma Test Instruments India Pvt. Limited, India), 10 tablets from a batch were weighed and placed inside the friabilator for friability testing. The friabilator was operated at 25 r.p.mfor 4 min (100 revolutions), after which the tablets were removed, dusted, and weighed. The percentage weight loss was calculated and recorded as % friability. The test for all the batches was repeated three times, and the average % friability recorded.

Disintegration time test was determined by selecting and analysing six tablets from a batch using a disintegration tester (Model MK4, Manesty Machine Limited, England) with its beaker filled with disintegration medium 1000.0 ml of 0.1 N HCl.A tablet was placed in each of the six tubes in the disintegration tester, and held down by the guide. The basket was then immersed into the disintegration medium set at 37.0± 1.0 ℃ and the disintegration tester was operated at 30 cycles/ min. The time taken for fragments of the tablets to completely pass through all the tubes meshes was recorded. The test for all the batches were done in triplicates, and the averages reported.

Dissolution test was determined using the USP-NF (2006) method, a dissolution medium of 1000.0 ml of 0.1 N HC1 was placed in a 1.1L dissolution flask set at 37.0± 1.0 ℃ in the Dissolution Apparatus II (Caleva Company Limited, England). The speed was set at 100 r.p.m. One tablet from each batch was placed in the basket of this machine. The basket was immersed in the dissolution medium and the machine was operate. A 5.0 ml of the dissolution medium was withdrawn, at 5, 10, 15, 20, 25, 30, 45 and 60 min intervals, with a syringe and filtered. Every 5.0 ml dissolution medium removed was replaced with a fresh dissolution medium kept at the same temperature of 37.0±0.5 ℃. The absorbance of the filtered solution was measured in a UV spectrophotometer (Model 23D, Uniscope, England) at 256 nm wavelength. The amount of drug released was determined from the Beer's Lambert plot generated from pure folic acid active. The percent of the drug released against the actual drug in the tablet was plotted against time to obtain a dissolution profile for each drug containing the modified starch samples. The percentage drug release at time intervals (D_T) was calculated from the Equation 6. The test for all the batches was repeated three times, and the average reported.

$$D_T = \frac{Wd}{Wt} \times 100 \ldots\ldots\ldots\ldots\ldots 6$$

Where D_T is the drug released after time, Wd is weight of drug dissolved into the dissolution medium, and Wtis the original weight of drug in the tablet.

III. RESULT AND DISCUSSION

3.1 Properties of Starch Powders

The swelling ratio, viscosity, gelatinization temperature and paste clarity of the starches are presented in Table 2, while the Hausner ratios and Carr's indices of the starches are presented in Table 3. There was reductions in moisture contents, swelling rates and paste clarity with increase in gelatinization temperatures and compression properties of the modified starches which consistent with reports by Mishra and Rai [29]; NapapornandSaiyavit [30], and Karlsson*et al*. [31] on the effect of starch modification on starch moisture properties.

The moisture contents of *manihottristis* and *manihotesculenta* reduced from 12.46 % to 10.01 % and from 12.38 % to 10.36 % respectively on modification of the starches. These moisture contents are close to the moisture content of control corn starch (10.78 %) within the acceptable moisture content (< 14 %) for diluent starch of Ashogbon and Akintayo [32]**.** Reduction in moisture content reduces hydrolytic degradation and improves the stability of solid dosage formulation, as reported by Roy *et al.* [33] and Maclean *et al*. [34].

The swelling ratio of starches reduced with modification, with the modified *manihottristis* starch showing a swelling ratio of 1.32 which is closer to the 1.15 swelling ratio of corn starch than the 1.52 swelling ration of *manihotesculenta* starch. The reduced swelling ratio of modified starch may be as a result of increased hydrogen bonds in interlinking depolymerized starch molecules which leads to reduction in available starch chain for interaction with water as reported by earlier works on swelling of granules such as Balamurugan&Anbuselvi [35]. Reduction in swelling ratio of diluent is important in reducing the interfering and competing effect of diluent with surrounding solvents.

The high viscosity of the native *manihottristis* and*manihotesculenta* starch dispersions (225 and 269 R.V.U) decreased with chemical modification to 151 and 168 R.V.U respectively which is closer to the 156 R.V.U viscosity of corn starch. This reduction can be as a result of collapse of depolymerized starch granules from modification, and conforms to reports by Xiao *et al*. [27] and Ashogbon and Akintayo [32] that depolymerized starches do not easily swell nor distend to affect the viscosity of water in drug formulation or release.

The gelatinization temperature of *manihottristis* starch gelatinization temperature increased withmodification from 64.2˚C to 68.7˚C, was higher than the increase in gelatinization temperature of *manihotesculenta* starch with modification from 62.44˚C to 67.40˚C, and nearerto the 66.26˚C gelatinization temperature of corn starch. The higher gelatinization temperature of dual-modified*manihottristis* starches can be attributed to more compactnessand more pronounced retrogradation of its modified starch granules. This result is consistent with earlier reports by Reeve [36], BeMiller [37], and Mishra and Rai [29] on starch gelatinization.This high gelatinization temperature of dual-modified starch reduces the tendency of the starch to gel and interfere with formulation and drug release properties.

Dual-modified starches showed increase in absorbance above the 3.31 absorbance of corn starch, with the light absorbance of dual-modified*manihottristis*anddual-modified*manihotesculenta* starches increasing on modification from 3.1 to 6.64 and 2.8 to 5.76 respectively. The higher absorbance ofdual-modified*manihottristis* starch can be attributed to better depolymerisation of starch leading to increased compactness of starch granules resulting in increased whiteness and reduced in paste clarity in line with reports by Craig *et al*. [38] and Garrido*et al*. [39].

Table 2.Moisture properties of native and modified starches

Starch	RVU	G.T. (˚C)	% T_{650}	% MC	SR
MT	225.00	64.26	3.10 ± 0.20	12.46 ±0.32	1.37 ± 0.17
ME	269.00	62.44	2.83 ± 0.10	12.38 ±0.28	1.52 ± 0.17
DMT	151.00	68.70	6.64 ± 0.80	10.01 ±0.63	1.32 ± 1.19
DME	168.00	67.40	5.76 ± 0.70	10.36 ±0.48	1.51 ± 0.38
Corn starch	156.00	66.26	3.91 ± 0.20	10.78 ±0.27	1.15 ± 0.39

Key: MT = *Manihottristis*, DMT= dual-modified*manihottristis*, ME= *Manihotesculenta*, DME = dual-modified*manihotesculenta***.**

The flow and compression properties of starches are presented in Table 2. The Hausner ratios of dual-modified*manihottristis*, dual-modified*manihotesculenta* and corn starches were < 1.6 and meet the interpretation of good powder flow of Wells [40]. The lower Hausner ratio (1.36) ofdual-modified*manihottristis* starch in

comparison to the Hausner ratio (1.46) of dual-modified*manihotesculenta* starch is indicative of better flow and granule shape of dual-modified*manihottristis* starch, and is closer to the Hausner ratio (1.35) and flowability of corn starch. The percent Carr's index ofdual-modified*manihottristis*(26.00) is similar to the Carr's index of corn star, better pronounced than the Carr's index ofdual-modified*manihotesculenta* (31.00) starches meet Zhou and Qiu [41] indication for fluid and cohesive powders, and.

Table 3. Flow and compression properties of starches

Starch	Pb (g/ml ± SD)	Pt (g/ml± SD)	Hausner ratio ± SD	Carr's Index (% ± SD)
MT	0.36 ± 0.01	0.50 ± 0.01	1.39 ± 0.02	28.00 ± 1.09
DMT	0.53 ± 0.00	0.71 ± 0.01	1.36 ± 0.03	26.00 ± 1.12
ME	0.33 ± 0.00	0.49 ± 0.01	1.48 ± 0.01	32.00 ± 1.16
DME	0.65 ± 0.00	0.95 ± 0.01	1.46 ± 0.01	31.00 ± 1.09
Corn	0.40 ± 0.01	0.54 ± 0.01	1.35 ± 0.01	26.00 ± 1.08

Key: MT = *Manihottristis*, DMT = dual-modified*manihottristis*, ME= *Manihotesculenta*, DME = dual-modified*manihotesculenta*, ρb = bulk density, and ρt = tapped density

3.2 Chemical Compatibility of API and Modified Starches

The FT - IR absorption frequencies and spectra is presented in Table 4. Using the Jacox [42] interpretation, the FT-IR reading showed that the functional amide, carboxyl, aliphatic alkyl, and imine groups of folic acid were all unaffected by preparations with dual-modified starches. This shows that none of the APIs was denatured and no new chemical entity was formed by these formulations. This indicates that modified starches are chemical compatible with their respective preparation APIs.

Table 4: FT - IR stretching vibrations absorption frequency of folic acid and folic acid dispersion

		Absorption band		
Functional group	Vibration mode	Fa	Fa+ DMT	Fa+ DME
Amide	N-H stretch	3550	3400	3400
Carboxyl group	O-H stretch (carboxylic acid dimer)	3364	3400	3400
Alkyl aliphatic group	C-H stretch (saturated)	2914	2926	2928
Imine	C=N stretch	2265	2200	2250
Amide	C=O stretch	1644	1638	1647

Key

Fa = FT - IR absorption band of pure folic acid sample

Fa+DMT = FT - IR absorption band of folic acid in the ratio 1:1 solid dispersion with dual-modified*manihottristis* starch
Fa+DME = FT - IR absorption band of folic acid in the ratio 1:1 solid dispersion with dual-modified*manihotesculenta* starch

Table 5: Properties of folic acid tablets formulated with dual-modified starch diluent

Formulation ↓	Weight (mg) ± SD	Friability (%) ± SD	TS (Kg/cm^2) ± SD	D.T. (min) ± SD	D_{10} (%) ± SD
F1	121.3 ± 1.7	0.70 ± 0.03	4.58 ± 0.15	0.47 ± 0.07	75.40 ± 2.90
F2	120.7 ± 1.0	0.60 ± 0.04	4.79 ± 0.17	1.18 ± 0.09	55.50 ± 1.80
F3	120.5 ± 1.3	0.75 ± 0.06	4.67 ± 0.11	0.97 ± 0.07	15.75 ± 1.25
F4	120.3 ± 1.0	0.75 ± 0.02	4.62 ± 0.13	0.69 ± 0.05	78.60 ± 3.30
F5	119.2 ± 1.1	0.70 ± 0.03	4.62 ± 0.11	0.76 ± 0.08	70.45 ± 2.55

Key:
TS = tensile strength

D.T = disintegration time

D_{60} = drug released after 60 min

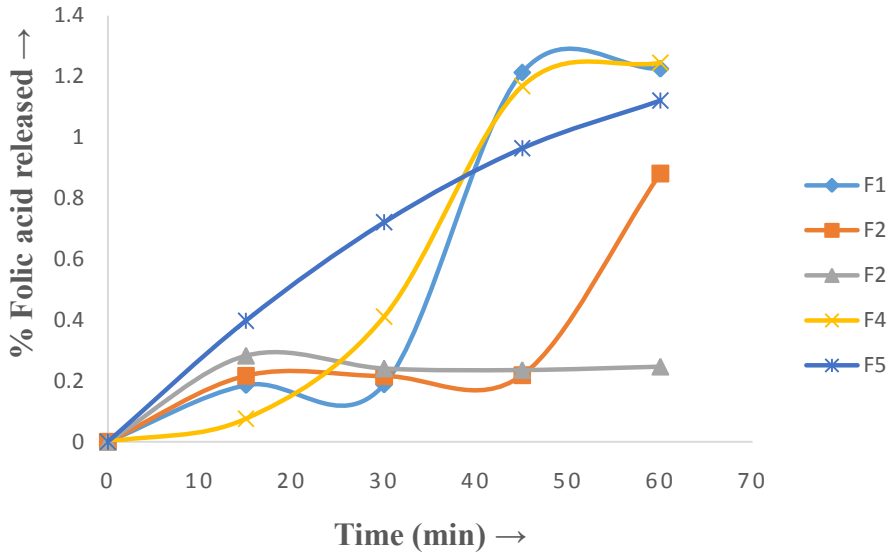
F1 = folic acid granules prepared with corn starch as diluents

F2 = folic acid granules prepared with native *manihottristis* starch as diluents

F3 = folic acid granules prepared with native *manihotesculenta* starch as diluents

F4 = folic acid granules prepared with dual-modified*manihottristis* starch as diluents

F5 = folic acid granules prepared with dual-modified*manihotesculenta* starch as diluents



Key:

F1 = folic acid granules prepared with corn starch as diluents

F2 = folic acid granules prepared with native *manihottristis* starch as diluents

F3 = folic acid granules prepared with native *manihotesculenta* starch as diluents

F4 = folic acid granules prepared with dual-modified*manihottristis* starch as diluents

F5 = folic acid granules prepared with dual-modified*manihotesculenta* starch as diluents

Figure 1: Dissolution Profiles of Folic Acid Tablets in 0.1 N Hydrochloric Acid at 37 ℃

3.3 Tablet Properties

The physicochemical properties of folic acid tablets are presented in Table 5. Folic acid formulated with dual-modified cassava starches showed near similar physical properties as folic acid tablets formulated with corn starches. All the tablets showed strong tensile strength above 1 Kgf for their 120 mg tablet in conformity with properties of mini-tablets stated by Lura*et al*. [43] and folic acid tablets [20]. Folic acid tablets formulated with dual-modified*manihottristis* starch had shorter disintegration time (0.69 min), closer to the disintegration time of 0.47 min. of tablets formulated with corn starch, and better than the 0.76 min disitengration time of tablets formulated with dual-modified*manihotesculenta* starch.The dissolution efficiency (D.E.) after 15, 30, 45 and 60 min, and $T_{50\ \%}$are shown in showed Table 5 and Figure 1 respectively. Tablets formulated with native*manihotesculenta* starch gave the least dissolution after 60 min (15 %), while the tablets formulated with corn ordual-modified*manihottristis* (F1 and F4) showed higher folic acid release after 60 min (78 and 75 %) respectively, than the 70 % drug release from folic acid tablet of formulation F5 withdual-modified*manihotesculenta*.

3.4 Statistical Analysis

The effect of dual-modification of native starch on their diluent properties in folic acid tablets was significant ($p > 0.05$) and dependent on the specie of the native starch.

IV. CONCLUSION

The*Manihottristis* (Mull. Arg.) starch is more responsive, than*Manihotesculenta* (Crantz) starch to dual-modification of enhancing starch diluent properties.Dual-modified*Manihottristis* starch, in comparison withdual-modified*Manihotesculenta* starch, had less hygroscopicity, reduced swelling ratio, and better flow and compaction properties.Folic acid tablets formulated withdual-modified*Manihottristis*starch produced better tablet properties, oflower friability, high tensile strength, lower disintegration time and better dissolution rate, than the tablet properties of folic acid tablets formulated with dual-modified*Manihotesculenta* starch, and closer tablet properties to folic acid tablets formulated with corn starch. This diluent properties of dual-modified*manihottristis* starch can be improved further using dry heat treatment method described by Habitante*et al.* [44] for modification of starch.

Conflict of interest

There are no conflicts of interest.

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