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CHARACTERISATION OF SILICIFIED DIOSCOREA DUMETORUM STARCH MODIFIED BY ADDITION OF CHARGED AMINO ACIDS AT VARIOUS PH LEVELS

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ABSTRACT

Introduction: The use of starches as excipients in drug delivery has led to the modification of starch to improve its functional properties. This study involved two step modification of Dioscorea dumetorum Pax starch (Family: Dioscoreacea) by silicification and co-blending with charged amino acids at various pH levels. The modified starch was characterized and evaluated for its flow and functional properties in comparison with unmodified Dioscorea dumetorum starch (DDS). **Methods:** DDS was modified by thermal blending with silicon dioxide to yield sDDS. Buffer solutions of pH4 (acetate 0.1M), pH7 (phosphate 0.5M) and pH10 (carbonate 0.05M) were prepared. 20g of sDDS was added into a beaker containing lysine (or aspartic acid) and buffer solution of pH4, pH7 or pH10. The mixture was stirred and dried in the oven at 300C. The dried samples (A-G) were granulated (A=sDDS/lysine/pH4; B=sDDS/lysine/pH7; C=sDDS/lysine/pH10; D=sDDS/aspartic-acid/pH4; E=sDDS/aspartic-acid/pH7, F=sDDS/aspartic-acid/pH10, G=DDS). All samples were characterized using density measurements, flow properties, morphology, Fourier-transform infra-red (FTIR) spectroscopy and pasting properties. The results were analyzed using mean and standard deviation. **Results:** Bulk and tapped density measurements ranked D>E>F>C>B>A>G and G>B>A>C>D>E>F, respectively, thus indicating that the modification led to a reduction in the spatial volume of the granules. Angles of repose ranked G>C>A>B>D>E>F. Spherical granules were formed by samples A,B,D and E, while others formed irregular shaped granules. FTIR spectra of DDS showed prominent peaks that were retained after modification, but with introduction of more functional groups due to the silicification and amino-acid blending. The peak and breakdown viscosities was ranked D>B>E>F>C>A>G, while the trough viscosity was the reverse. **Conclusion:** The two-step modification of DDS led to enhanced functional properties of the starch. Granules C and E had better flow and pasting properties respectively, than other granules. Further studies involving modification of the starch using uncharged non-polar amino acids may be carried out.

KEYWORDS: Dioscorea dumetorum starch, Modification, Silicification, Amino acids, Functional properties.

INTRODUCTION

Starch is one of the most widely used as fillers, binders, and disintegrants in the manufacture of solid dosage forms. Although corn starch is one of the most widely used starches in pharmaceutical formulations, starches from other botanical sources have shown different functional properties such as gelling, Swelling, and water binding capacity, which are related to their capacity to function effectively as binders and disintegrants in solid dosage forms.[1] Trifoliate yam starch obtained from the tubers of *Dioscorea dumetorum* Pax (Family: *Dioscoreaceae*), the second most important root and tuber crop in Africa[1] has been evaluated for its mechanical, compressional and release properties when incorporated as a binder in chloroquine tablet formulations.[2] When incorporated as a directly compressible excipient, trifoliate yam starch did not form intact tablets except at high compression pressures.[3] Such disadvantages of native *Dioscorea dumetorum* Pax starch, exemplified by low shear stress resistance, thermal decomposition and high retrogradation[4], have led to research into ways of enhancing the functional characteristics of the starch. Modification of native starches to improve functional properties either by physical, such as heat or moisture treatments, or chemical means through etherification, esterification, cross-linking and grafting of starch[5] has led to the increase in the application of starches as excipients in the pharmaceutical industry. Functional characteristics relate to the behavior of a starch product when subjected to various processing treatments, and are important indicators of final product quality.[6] Incorporation of charged amino acids (such as lycine or aspartic acid) to native starch (such as potato starch) has been demonstrated to alter starch functional properties leading to reduction in water binding capacity, lower pasting viscosities,[7] retrogation potentials[8] and reduction in gelatinization temperature of native starch.[9] This study is aimed at two-step modification of *Dioscorea dumetorum* Pax starch, formation of granules from the

modified starch blends and characterization of the granules using density measurements, flow properties, morphology, Fourier-transform infra-red (FTIR) spectroscopy and pasting properties as the assessment criteria, in comparison with native *Dioscorea dumetorum* Pax starch. The first modification step involves the addition of silicon dioxide by physical blending, while the second step involves the addition of charged amino acids (lysine and aspartic acid) to the silicified starch at three different pH levels (4, 7 and 10) in a controlled thermal environment. The flowability of granules is of critical importance in the production of pharmaceutical dosage forms and processes such as uniform feed from the bulk storage containers or hoppers into the feed mechanisms of tabletting or capsule-filling equipment, reproducible filling of tablet dies and capsule dosators and reduction of particle die-wall friction, amongst others. The first modification step (silicification) is aimed at enhancing the flow of the granules based on previous work done,[10,11] while the second modification (co-blending with charged amino acids at different pH) is aimed at investigating the alteration of different functional properties (such as shear resistance, viscosity etc) of the silicified starch granules.

MATERIALS AND METHODS

Materials

Dioscorea dumetorum Pax starch (DDS) was obtained from the tubers of *Dioscorea dumetorum* (Family: *Dioscoreacea*) and authenticated at the herbarium of the Department of Pharmacognosy, University of Ibadan, Nigeria. Silicon dioxide (Batch 0571900100, Loba Reagents and Chemicals, Italy) and ethanol were obtained as gifts from BASF Company, Lagos, Nigeria. Distilled and ultra-pure water (UPW) were obtained from the research laboratories of the Department of Pharmaceutics and Industrial Pharmacy, and Centre for Drug Discovery, Development and Production, both of the Faculty of Pharmacy, University of Ibadan, Nigeria. The lysine and aspartic acid powders were purchased online (www.herbsng.com) and authenticated at the central laboratory, University of Ibadan, Nigeria. The buffers were prepared in the research laboratory of the department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ibadan, Nigeria. All the other reagents used were of analytical grade.

Method

Starch isolation

Tubers of *Dioscorea dumetorum* Pax (Family: *Dioscoreacea*) were weighed, peeled, cut into smaller pieces, washed and wet-milled. The resulting slurry was sieved, allowed to stand for 6 h before decanting to leave a wet mass which was oven dried at 40 ^{0}C until a constant weight was obtained. The resulting dry mass was dry-milled and sieved to obtain the dried starch powder (DDS), which was further granulated and packed in an airtight container.

Silicification of Starch

Slurry containing 150 g of DDS and 375 mL of UPW was prepared and 3.20 g of silicon dioxide was added with continuous stirring for 5 min before heating on a water bath at 50 ^{0}C for 15 min. After cooling, 100 mL of 99% ethanol was added in aliquots with continuous stirring over a period of 10 min., and the mixture was allowed to stand for 24 h. The supernatant was decanted and the wet mass was oven dried at 40 ^{0}C for 3 h. The resultant dried silicified DDS (sDDS) was milled, sieved and packaged in an air-tight container.

Co-blending of silicified Dioscorea dumetorum starch with amino acids at various pH levels

A predetermined quantity of sDDS was weighed into a 50 mL beaker and an equal amount of lysine was added. The 0.1M acetate buffer (pH 4) was added to overflow the powder level. The mixture was stirred continuously for 30 min. and left to stand for 24 h. The supernatant was decanted and the wet mass was oven dried at 30 ^{0}C for 3 h. The dried sample was manually milled using a mortar and pestle, granulated to obtain silicified *Discorea dumetorum* starch/lysine blend at pH4 **(**sDDS/lysine/pH4). The procedure was repeated to obtain other samples: sDDS/lysine/pH7, sDDS/lysine/pH10, sDDS/aspartic-acid/pH4, sDDS/aspartic-acid/pH7 and sDDS/aspartic-acid/pH10. All the granulated samples were packed in air-tight containers.

The dried samples were granulated (A= sDDS/lysine/pH4; B=; C=; D=; E=, F=; G=DDS)

Density Measurements

Bulk Density: Exactly 10 g of each sample was poured at an angle of 45^0 through a funnel into a 100 mL measuring cylinder. The bulk density (g/mL) of each sample was calculated as a mean of three determinations using the following formula:

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Volume}} \qquad \text{Eqn. (i)}$$

Tapped Density: The tapped density (g/mL) for each sample, which was determined by applying 100 taps to the measuring cylinder containing 10 g of each sample that was poured at an angle of 45^0 through a funnel, was calculated as a mean of three determinations using the following formula:

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Volume}} \qquad \text{Eqn. (ii)}$$

Carr's Compressibility Index: The Carr's Compressibility Index was calculated for each sample from values obtained from the bulk and tapped densities using the formula:

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100 \qquad \text{Eqn. (iii)}$$

Hausner's Ratio: Hausner's ratio for each of the samples was calculated using the formula:

$$\text{Hauner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \quad \textbf{Eqn. (iv)}$$

Flow Properties

Angle of repose*:* About 10 g of each sample was poured through a funnel clamped on a retort stand onto a flat surface under the funnel to form a cone. The values obtained for the height (h) of the conical powder heap and radius (r) of the circular base of the cone formed was used in calculating the angle of repose as a mean of three determinations using the formula:

$$\text{Angle of repose}, \theta = \tan^{-1}\left(\frac{h}{r}\right) \quad \textbf{Eqn. (v)}$$

Morphological Studies

Each sample was placed on a glass slide and stained with 0.2 % iodine solution. Images (photomicrographs) of each sample were taken using an optical microscope (Olympus model 312545, Japan) to examine the shapes.

Determination of Pasting Properties

The pasting properties of each sample were evaluated using a Rapid Visco-Analyzer with a RVA-4 machine (RVA-4, Newport Scientific Pty. Ltd., Warriewood NSW, Australia). Sample (modified or unmodified starch)-water suspensions based on the dry sample weight of 2.60 g were used in monitoring the viscograms of the samples under similar temperature and time conditions at a final speed of 160 rpm. The pasting temperature (PT), peak viscosity (PV), minimum viscosity (MV), final viscosity (FV), and peak time (PTime) were measured by the RVA with the Thermocline for Windows v.3 (TCW3) software. Total setback (TSB) and Breakdown (BD) were calculated as the difference between FV and MV, and PV and MV, respectively Determinations were carried out in triplicates.

RESULTS AND DISCUSSION

Assessment of the density of powders and granules is a useful pathway for meeting quality control standards of pharmaceuticals.[12] Values obtained from the bulk and tapped densities for the different granules are presented in Table 1. The bulk and tapped densities give an idea of how well granules will compress to make a tablet due to forces of cohesion and adhesion within the bed of granules.[13] The bulk and tapped density measurements ranked D>E>F>C>B>A>G and G>B>A>C>D>E>F respectively, thus indicating that modification led to a reduction in the spatial volume of the granules after the application of pressure. Furthermore, the functional groups associated with lysine and aspartic acid may be responsible for the ranking observed after tapping the bulk of powder. Lysine, an amino acid associated with side chains containing basic groups has a higher density than aspartic acid,[14] and this may be responsible for the ranking noticed with the tapped density where samples A, B and C had higher values than samples D, E and F.

Many industrial processes require the movement of granules from one location to another. These processes are achieved by various methods such as gravity feeding, mechanically assisted feeding and pneumatic transfer.[15] In each of these processes, granules are required to flow. Angle of repose is defined a constant three dimensional angle measured relative to the horizontal base, assumed by a cone-like pile of material formed when the powder is passed through a funnel-like container. This measurement gives a quick qualitative assessment of the internal cohesive and frictional effects under low levels of external loading as applicable to powder or granule mixing or tablet die or capsule shell filling. Carr's index and Hausner's ratio suggests the compressibility of a material as an indicator of the tendency of the material to flow. The results obtained from the study showed that the angle of repose ranked G>C>A>B>D>E>F, thus indicating that the unmodified *Disocorea dumetorum* starch (DDS) had the highest resistance to flow, while silicified *Disocorea dumetorum* starch blended with aspartic acid (pH10) had the lowest resistance to flow. Generally, silicification enhanced the flow properties of the DDS with silicified DDS containing lysine showing higher resistance to flow (angles of repose > 40^0) than silicified DDS containing aspartic acid. This suggests that granules containing aspartic acid are less cohesive than granules containing lysine. Carr's index is a measure of the potential granule arch or bridge strength and stability, and usually describes the compressibility of a material.[16] Values of 5-10, 12-16, 18-21, 23-35 represent excellent, good, fair to passable and poor flow properties respectively.[17] 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 results of the Carr's indices and Hausner's ratio indicate that samples A, B and C had values greater than samples D, E and F. DDS had the highest values. This implies that samples containing lysine had higher compressibility values and poorer flow properties when compared with samples containing aspartic acid.

The ability of a material to flow sometimes depends on the size and shape of the material.

The morphological characterization of the samples (Fig. 2) indicates that samples A, B, D and E were spherically shaped, while other samples formed irregular shapes. It was also observed that only amino acids that were co-blended with silicified DDS at pH 4 and 7 were spherically shaped. Amino acids bear at least two ionizable weak acid groups, a –COOH and an $–NH_3^+$, and at pH values up to 7.4 (pH of blood plasma), the carboxyl groups exist predominantly as carboxylate ions, while the amino groups are predominantly in the protonated form.[18] Due to the polar nature of both lysine and aspartic acid, their presence in the pH values lower than pH of blood plasma could be responsible for the alteration of the functional properties of the silicified

DDS at these pH values (4 and 7), and could suggest the reason why the shapes of granules made from silicified DDS at pH 10 have irregular shapes. In 2008, Lockwood *et al*[8] demonstrated that incorporation of charged amino acids (such as lysine and aspartic acid) altered the functional properties of starch, while acidic cross-linking of starch at various pH values shows enthalpy-entropy compensation.[19]

Fourier Transform Infrared (FTIR) spectroscopy is used in monitoring various stages of matter based on harmonic oscillations associated with the bending and stretching of bonds. FTIR spectroscopy has been applied to analyze the secondary and tertiary structures of compounds.[20] The presence of prominent peaks in FTIR plots depicts the presence of specific functional groups that are characteristic of the material undergoing analysis. In Fig. 2A, prominent peaks were observed to occur at wavelengths (cm^{-1}) of 901.60, 1145.60, 1704.80, 2368.80, 3044.00, 3448.80 and 3884.80. The stretching frequencies of Fig. 2B are shown in the region from 3884.80 – 1704.80 cm^{-1}, while those of Fig. 2A are shown in the region 3908.80 – 1687.20 cm^{-1}. A significant peak occurring at 1145.60 cm^{-1} is common to all the FTIR plots shown in Fig. 3.and it is associated with strong C-H stretching due to C-N group.[21] The peak is associated with starch moieties that are present in *Dioscorea dumetorum* (Fig. 2G), thus indicating that the basic integrity of the starch is not compromised, though there were additional functional groups incorporated in the starch depending on the amino acid used for the modification process.[22]

The rheological properties of starches are important since they are first converted into paste before being used as binding agents in tablet formulations.[23] The parameters determined from the rapid curve of a Rapid Visco Analyser (peak viscosity, setback, trough, breakdown and final viscosities, pasting temperature and time to reach peak viscosity) are important factors in the functionality and end product quality of starch products. Pasting involves heating and cooling of starch–water mixture under constant mechanical shearing forces at a temperature range of 50-95^{o}C.[23] It also gives an indication of the gelatinization time during processing[24], which involves swelling of starch granules, exudation of molecular amylose components and disruption of the granules, making them susceptible to thermal or mechanical breakdown.[25] The viscograms of the samples are presented in Fig. 3, while the parameters obtained from the curves are shown in Table 2. Peak viscosity, which is often correlated with final product quality, gives a purview of the water binding capacity of a material and the ease with which starch granules are disintegrated and often correlated with final product quality.[26] It was observed that the peak viscosity ranked D>E>B>F>C>G>A. This implies that silicified *Disocorea dumetorum* starch that was co-blended with aspartic acid in an acidic medium (sample D) had the highest water binding capacity, and may be targeted towards use as an excipient for drug delivery systems that require immediate constitution with water prior to use. Moreover, intrinsic swelling power and water binding capacity have been recognized as qualitative assessments of potential disintegrant effects of starches.[22] This is also correlated in the values obtained from the breakdown viscosity where the same sample D had the highest value. The breakdown viscosity is related to the rigidity of swollen granules, and the higher the breakdown viscosity, the more rigid the crystalline structure of the material.[27] Therefore, sample D with the highest values of both peak and breakdown viscosities demonstrated the fastest rate of swelling with the highest water retaining capacity. Setback viscosity indicates the tendency of the amylose content of starch to undergo retrogradation on cooling and measures the re-association of starch.[28] A high setback value is associated with cohesive paste, while low setback values are useful for products which require low viscosity and paste stability at low temperature Setback viscosity tells the resistance to retrogradation.[29] From the study, samples E and A had the highest and lowest set back viscosities respectively. Generally, it was observed from the final viscosity that silicified *Disocorea dumetorum* starch samples blended with aspartic acid were more viscous than silicified *Disocorea dumetorum* starch samples blended with lysine, while the unmodified *Disocorea dumetorum* starch had the least final viscosity value among all the samples. The two-step modification of *Dioscorea dumetorum* starch led to enhanced functional properties of the starch. Silicification caused an increase in the flow rates, while silicified granules that were blended with aspartic acid at pH 10 had better flow properties than other granules. Blending of silicified *Dioscorea dumetorum* starch with amino acids led to significant changes in the pasting properties of the starch granules, with silicified *Dioscorea dumetorum* starch samples blended with aspartic acid at pH 7 having the highest final viscosity. Further studies involving modification of the starch using uncharged non-polar amino acids is on-going.

ABBREVIATIONS

DDS = *Dioscorea dumetorum* starch,
sDDS = Silicified *Dioscorea dumetorum* starch
A=sDDS/lysine/pH4;
B= sDDS/lysine/pH7;
C= sDDS/lysine/pH10;
D= sDDS/aspartic-acid/pH4;
E= sDDS/aspartic-acid/pH7,
F= sDDS/aspartic-acid/pH10;
G=DDS

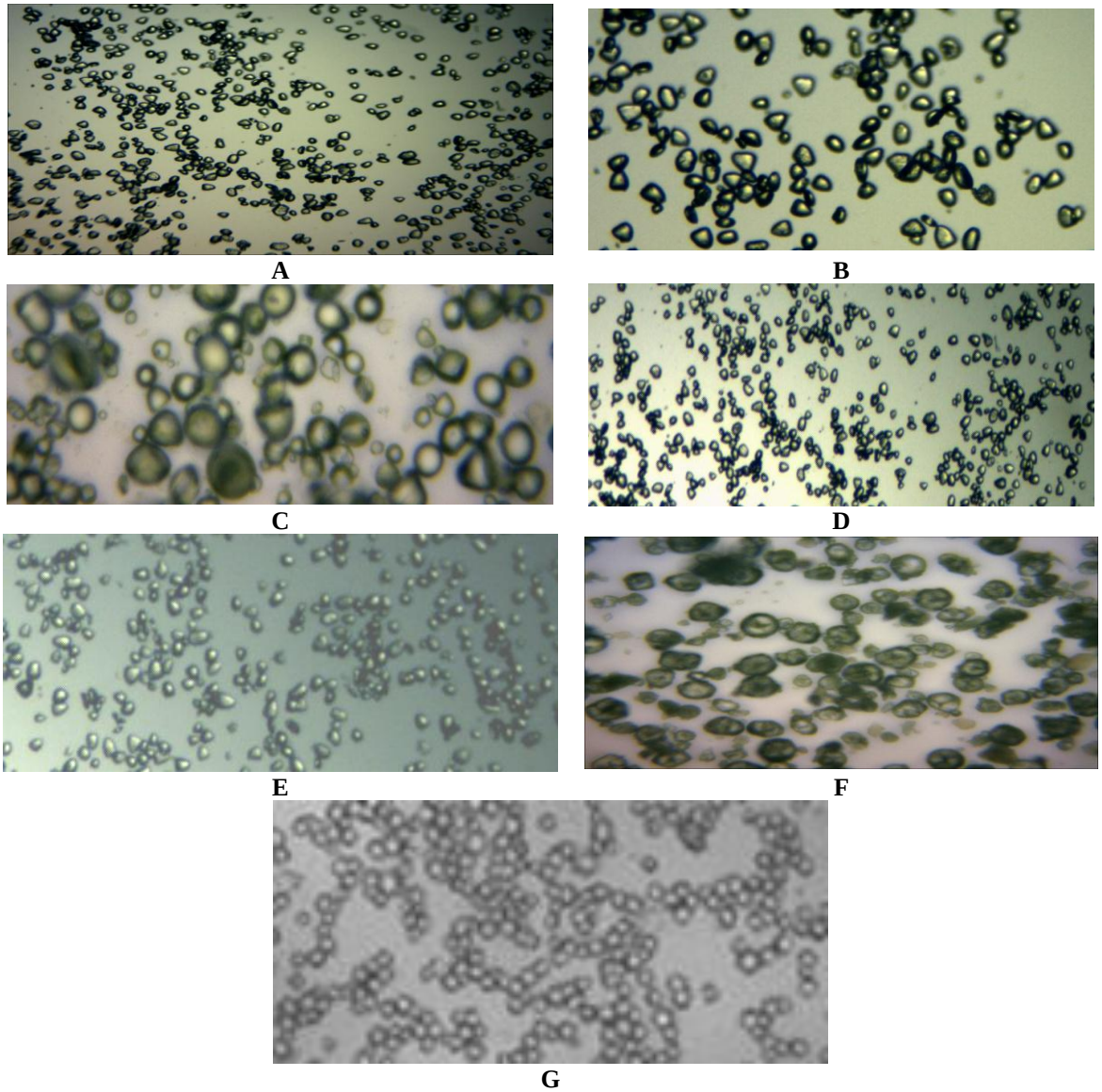
Table 1: Density and Flow Properties of Granules.

Granule Properties	A	B	C	D	E	F	G
Bulk Density (g/mL)	0.71	0.73	0.75	0.91	0.83	0.79	0.62
Tapped Density (g/mL)	1.01	1.07	0.92	0.89	0.86	0.72	1.12
Hausner's' Ratio	1.42	1.47	1.23	1.02	1.04	1.01	1.81
Carr's Index (%)	29.70	31.78	18.48	2.25	3.49	1.27	44.64
Angle of repose (^{0})	43.11	41.02	44.12	26.89	26.85	25.61	46.46

Table 2: Pasting Properties of Granules (n=3±SD).

Test sample	Peak Viscosity (cP)	Trough Viscosity (cP)	Breakdown Viscosity (cP)	Final viscosity (cP)	Setback Viscosity (cP)	Peak time (min)	Pasting temperature (^{0}C)
A	648.01±0.11	609.02±0.02	39.12±0.01	710.02±0.11	62.01±0.16	7.00±0.11	88.75±0.23
B	1392.11±0.02	1247.01±0.12	145.02±1.01	1143.13±1.13	248.02±0.11	5.67±0.25	86.45±0.18
C	759.01±0.13	680.00±0.21	79.14±1.12	964.02±1.04	205.02±0.12	7.00±0.47	89.55±0.06
D	2298.00±0.07	1417.03±0.01	881.03±1.14	1994±0.07	304.01±0.01	5.07±0.04	86.41±1.01
E	1972.10±0.12	1934.07±0.16	38.06±1.02	2575.02±1.04	602.04±1.15	6.47±0.13	86.35±1.02
F	992.24±0.15	954.03±0.11	38.12±0.03	1462.13±0.17	469.21±0.08	6.20±0.14	86.47±0.06
G	707.00±0.11	680.00±0.01	39.13±0.03	936.03±0.13	229.04±0.17	7.12±0.05	81.02±0.16

FIGURES



A **B** **C** **D** **E** **F** **G**

Fig. 1: Photomicrographs of modified starch granules.

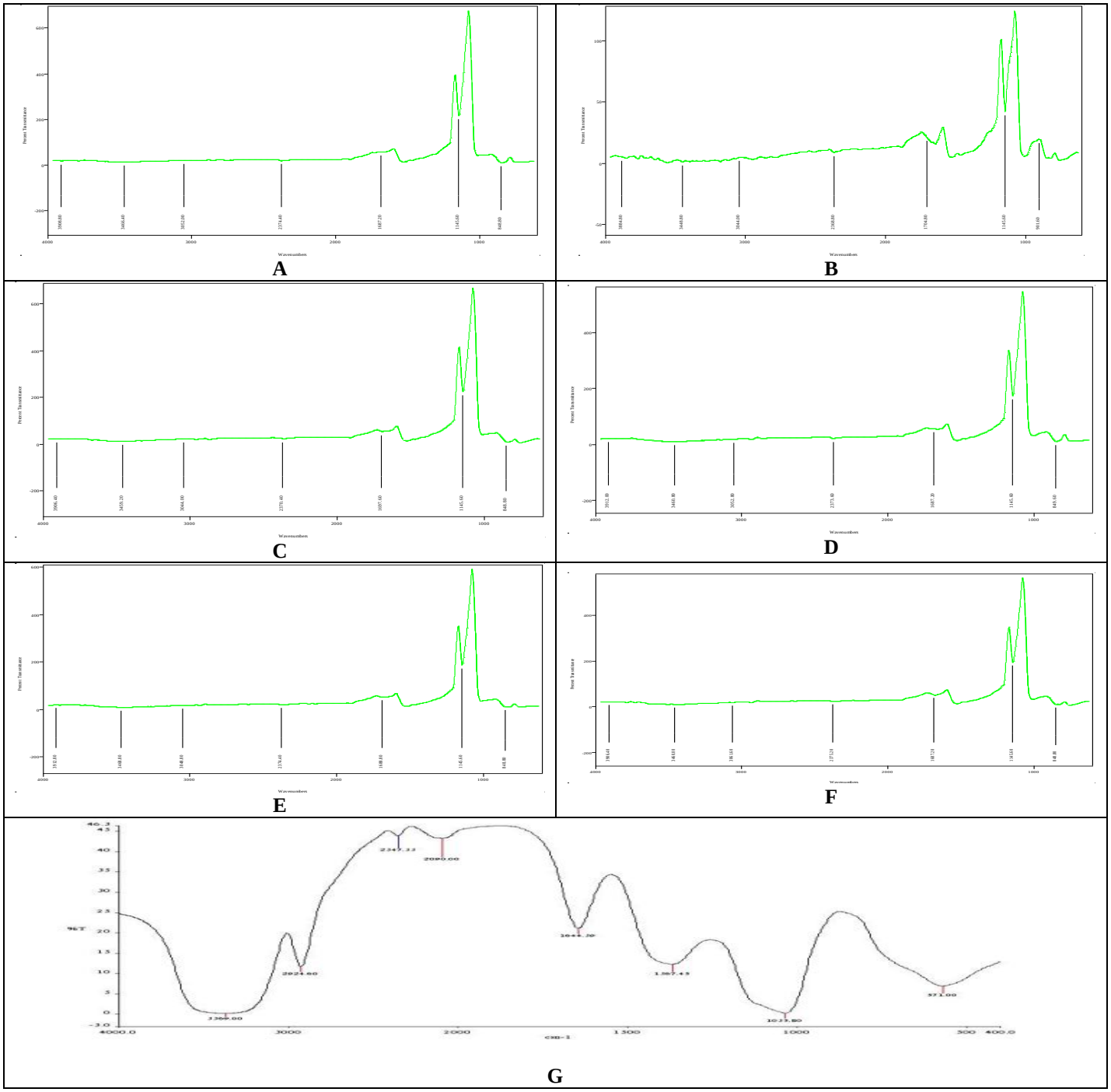
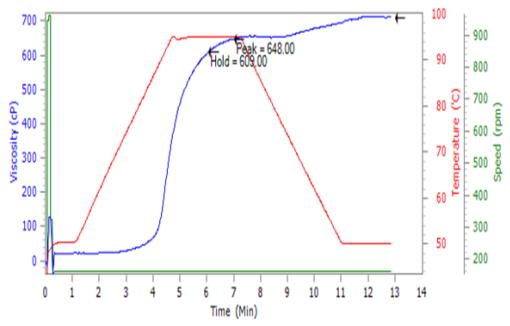
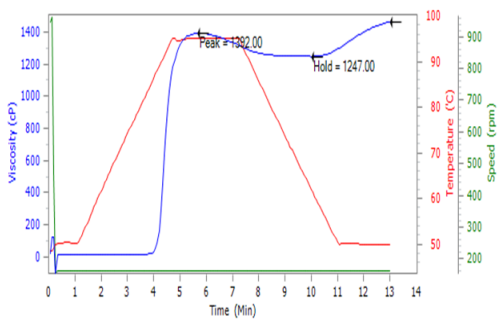


Fig. 2: FTIR Plots of the modified starch granules.



A



B

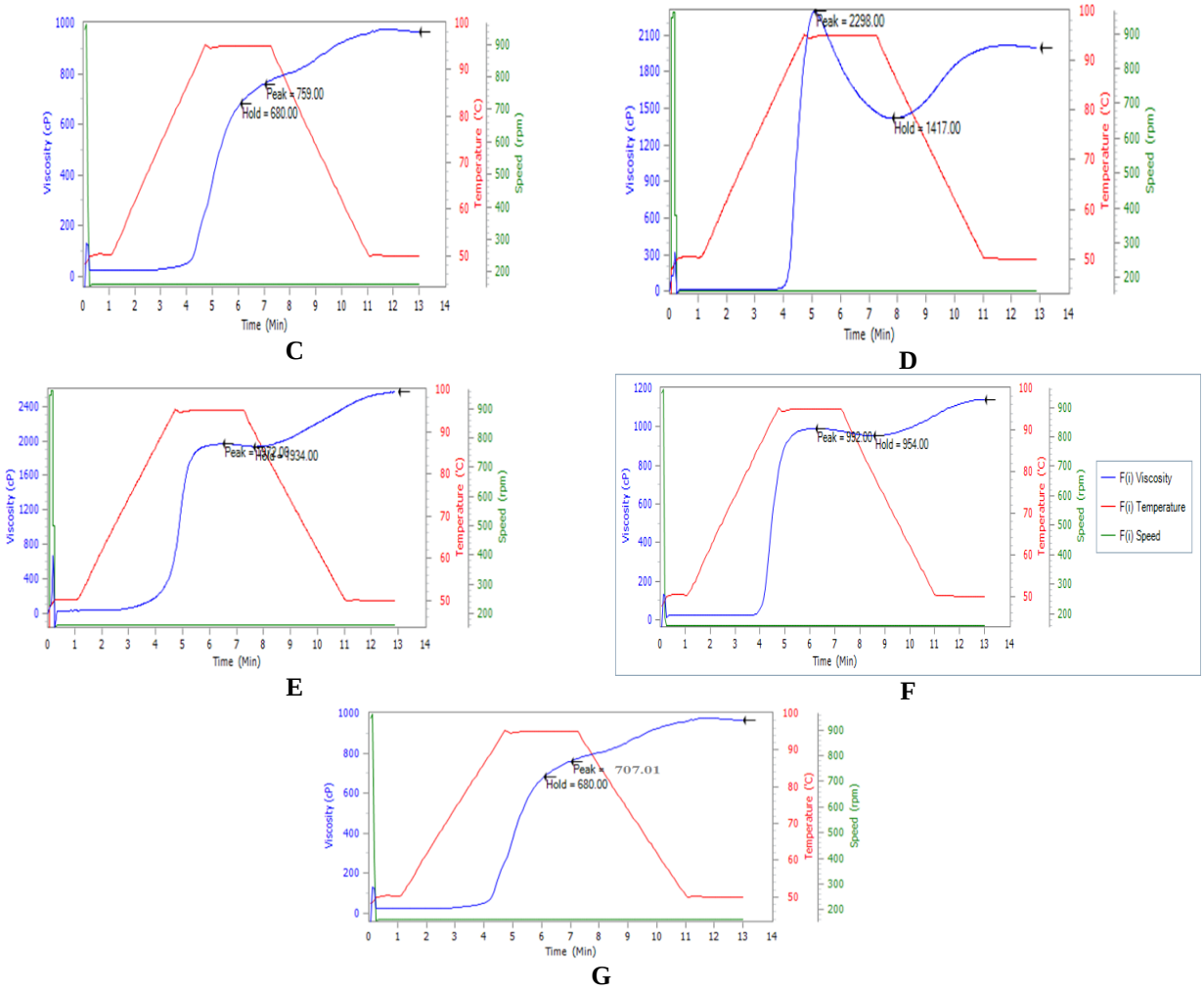


Fig.3: Viscograms showing pasting properties of modified starch granules.

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