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PHYSICOCHEMICAL AND MORPHOLOGICAL PROPERTIES OF THERMALLY MODULATED CARBOXYMETHYLATED *ENTANDOPHRAGMA ANGOLENSE* GUM

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ABSTRACT

Modification and subsequent use of natural polymers as excipients in drug delivery is due majorly to their affordability, low toxicity, biocompatibity, physiological inertness and bio-degradability, and also to eliminate poor cohesive and dynamic properties that are characteristic of the natural polymers. In this study, *Entandophragma angolense* gum (ENTA) was modified by carboxymethylation at different reaction conditions and comparatively investigated for physicochemical and morphological properties. The ENTA was carboxymethylated at different reaction conditions (45^0C and 60^0C at 30 min and 60 min) to yield $CENTA_{45/30}$, $CENTA_{45/60}$, $CENTA_{60/30}$ and $CENTA_{60/60}$ granules, which were characterized using morphology, crystallinity, swelling index, rheology measurements, FTIR spectra, flow properties and density measurements. Results were analyzed using mean and standard deviation. $CENTA_{45/30}$ and $CENTA_{45/60}$ granules were spherically shaped discrete structures with smooth surfaces, while ENTA, $CENTA_{60/30}$ and $CENTA_{60/60}$ granules were round to oval shaped clumped structures. All granules exhibited some degree of crystallinity, while swelling indices at $27^0\pm0.6^0$C and $80^0\pm0.3^0$C ranked $CENTA_{45/60}$<$CENTA_{45/30}$<$CENTA_{60/60}$ < $CENTA_{60/30}$ <ENTA. The peak and breakdown viscosities ranked ENTA>$CENTA_{45/60}$>$CENTA_{45/30}$>$CENTA_{60/60}$ >$CENTA_{60/30}$, while for the trough and final viscosities, the order was the reverse. FTIR spectra for CENTA batches showed similar absorption peaks, with strong absorption bands at 2358.47cm^{-1} and 2358.56cm^{-1}. Modification enhanced flowability, while density measurements show that $CENTA_{45/60}$ was the most compressible. Carboxymethylation improved the physiochemical properties of ENTA due to introduction of functional groups to its crystalline structure. The carboxymethylation carried out at 45^0C for 60 mins produced granules with the highest pasting temperature and most compressibility profile.

KEYWORDS: Natural polymers, *Entandophragma angolense* gum, Carboxymethylation, Reaction conditions, Physicochemical properties.

INTRODUCTION

Gums are important families of natural polymers derived from the seeds or tubers of plants and seaweed, and are one of the most fast developed environmentally friendly polymers[1] Affordability, low toxicity, biocompatibity, physiological inertness, cost effectiveness, non-irritant nature, easy accessibility and bio-degradability are some of the reasons for the frequent use of native gums in pharmaceutical drug delivery processes.[2] Native gums have been extensively incorporated as binders, disintegrants, thickeners, stabilizers, emulsifiers, suspending agents, sweeteners and mucoadhesives[3] In recent times, there has been an increase in the utilization of modified natural gums as excipients in the formulation of solid dosage forms[4], due to problems such as pH dependency, incoherent solubility, uncontrollable swelling, viscosity changes on storage and microbial contamination,; all of which are characteristic of natural gums.[5] Modification of natural gums, which can be physical, chemical, enzymatic, biotechnological or genetic), is intended to impact thermal stability, enhance compatibility, degradability, flexibility and rigidity of natural gums, especially when incorporated in solid dosage forms.[6] Chemical modification describes the modification, addition or removal, through chemical reaction, of any of a variety of macromolecules, including proteins and nucleic acids. It involves the treatment of natural gums with small amounts of approved chemical reagents, resulting in the introduction of certain functional groups into the molecular structure of the natural gum.[7] The temperature and duration at which the chemical reaction proceeds also affects the product formed.[8]

Entandophragma angolense gum (Family: *Meliaceae*), derived from the incised trunk of the tree, is a natural hydrophilic polymer that is widely available throughout the whole year in tropical Africa.[9] The gum has been demonstrated to be non- toxic and to exhibit a good potential as a suspending agent,[10] with good mucoadhesive properties.[11] In this study, *Entandophragma angolense* gum has been chemically

modified by carboxymethylation at different reaction conditions (45^{0}C and 60^{0}C at 30 min and 60 min) and formulated as granules. The physicochemical and morphological properties of the resulting chemically modified granules were investigated in comparison with the native gum.

MATERIALS AND METHOD

Materials: The materials used were double strength chloroform water (Alfa Chemistry Ltd., USA), glacial acetic acid (Sigma Aldrich, USA:EC27221), ethanol (Moko Pharmaceuticals Ltd., Nigeria), sodium hydroxide (Sigma Aldrich, USA:S8045), chloroacetic acid (Sigma Aldrich, USA:C19627) and diethyl ether (Sigma Aldrich, USA:296082) were obtained as gifts from Bond Chemical Industries limited, Awe, Nigeria. Ultra-pure water (UPW) was obtained from the Research Laboratories of the Centre for Drug Discovery, Development and Production, University of Ibadan, Nigeria. *Entandophragma angolense* gum was obtained from the early morning exudates of the trunk of the tree (Family: *Meliaceae*) available as a tree crop in the Botanical Gardens of the University of Ibadan, Ibadan, Oyo State, Nigeria and authenticated at the Forest Herbarium, Ibadan, Nigeria. All the reagents used were of analytical grade.

Purification and carboxymethylation of gum extract: The brown coloured gum, collected as early morning exudates from previous incisions made on the tree trunk of *Entandophragma angolense* tree (Family: *Meliaceae*), which has been sprayed with ethephon according to the method of Nair,[12] was thoroughly washed in double strength chloroform water to remove associated earth particles. The washed exudates were spread on sterile drainers at 27±1.2^{0}C for a period of 3 h, and dried in hot air oven (Model UF 75) at a temperature of 40±0.6^{0}C for 48 h. The dried gum was pulverized, hydrated in double strength chloroform water for 120 h, while stirring intermittently and the resulting mucilage was strained through a clean calico cloth prior to precipitation with 95 %v/v ethanol. The precipitated gum was filtered, washed with diethylether and further dried in the hot air oven at a temperature of 40 ±0.6^{0}C for 24 h. The dried gum was pulverized and passed through a 250 µm sieve size.[11,13] The dried gum (0.005g) was dissolved in water, mounted on the microscope and observed for the presence of any foreign organic matter to determine the level of gum purity,[14]

The method used for the carboxymethylation of *Entandophragma angolense* gum employed was the Williamson ether synthesis procedure.[7] Exactly 2 g of purified *Entandophragma angolense* gum (ENTA) powder was dispersed in 100 mL ultra-pure water, in a 250 mL jacketed glass reactor connected to a thermostated bath equipped with magnetic stirrer and gas-purging system. After the gum was well dispersed, 15 mL sodium hydroxide solution (30 %w/w) was added at the rate of 1 mL/ 15 min, with continuous stirring at 27 ±2^{0}C. An aliquot of 15 mL chloroacetic acid (10 %v/v) was added to the reaction mixture, over a period of 10 min. The reaction mixture was heated at 45 ±0.7^{0}C with continuous stirring for 30 min and the pH was adjusted to 7 with glacial acetic acid. The precipitate was washed with ultra-pure water before it was lyophilized to achieve CENTA$_{45/30}$. The reaction temperature and times were further fixed at 45 ±0.7^{0}C for 60 min, 60 ±0.5^{0}C for 30 min and 60 ±0.5^{0}C for 60 min resulting in different batches: CENTA$_{45/60}$, CENTA$_{60/30}$ and CENTA$_{60/60}$ respectively. The batches were stored in air-tight containers.

Granulation of powdered samples: Each powdered sample of ENTA, CENTA$_{45/30,}$ CENTA$_{45/60}$, CENTA$_{60/60}$ and CENTA$_{60/30}$ was moistened with UPW and the homogeneous wet mass was screened through a 1.7 mm sieve. The wet granules were dried in the hot air oven at 60°C for 1 h. Thereafter, the dried granules were screened through a 1.0 mm sieve and stored in air-tight containers.

Characterization of granules

Morphology: The particle size and particle size distribution of ENTA, CENTA$_{45/30,}$ CENTA$_{45/60}$, CENTA$_{60/60}$ and CENTA$_{60/30}$ granules were each determined using an optical microscope (Olympus model 312545, Japan). Photomicrograph of each batch sample was taken to examine the shapes.

Density measurements

Bulk and Tapped Densities: Thirty (30) grams each of ENTA, CENTA$_{45/30,}$ CENTA$_{45/60}$, CENTA$_{60/60}$ and CENTA$_{60/30}$ granules was separately measured into a 100 mL measuring cylinder of known diameter at an angle of 45^0 through a funnel. The height at which the granules reached was measured. The bulk density was calculated as mass per volume of the powder (gcm^{-3}) in the cylinder. The cylinder was subjected to 38 taps/minute from a predetermined height of 2.50 cm for each tap made at approximately 2 seconds interval between each tap for a period of 3 minutes (Reus-Medina *et al.,* 2004). After the time lapsed, the tapped density was calculated for both samples as the mass per new volume of the powder (gcm^{-3}) in the cylinder. The percentage of porosity (P%) for the granules were calculated from the equation:

$$P_{\%} = (1-P_F) \times 100 \quad (1)$$

Where P_F (Packing fraction) is the ratio of the bulk density of each sample to its particle density. All the determinations were done in triplicates (Alebiowu and Itiola, 2002).

Particle Density: The particle density of ENTA, CENTA$_{45/30,}$ CENTA$_{45/60}$, CENTA$_{60/60}$ and CENTA$_{60/30}$ granules was separately determined using the pycnometer method with xylene as the displacement fluid. A 50 mL pcynometer bottle was weighed when empty (W), it was then filled with xylene to the brim till

it overflowed and the difference between the two weights was determined (W_2). A 2g quantity of each sample was weighed (W_3) and carefully transferred to the xylene-filled pcynometer bottle; the excess solvent was then wiped off and the bottle weighed again (W_4). The particle density (ρ_s), was calculated from the equation below (Itiola, 1991):

$$\rho s = \frac{W_2 - W_3}{50\,[((W_3 - W_4) + W_2 + W} \quad (2)$$

The particle density determinations were done in triplicates.

Hausner's ratio: The Hausner's ratio was determined as the ratio of the bulk volume to the tapped volume for ENTA, $CENTA_{45/30}$, $CENTA_{45/60}$, $CENTA_{60/60}$ and $CENTA_{60/30}$ granules (Herman *et al.* 1989).

Carr's compressibility indices: Carr's compressibility indices (percentage compressibility) were calculated from the results obtained from the bulk and tapped densities using the equation below:[15]

$$\text{Carr Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped Density}} \text{x } 100 \quad (3)$$

Flowability determination using angle of repose method: The flowability of ENTA, $CENTA_{45/30}$, $CENTA_{45/60}$, $CENTA_{60/60}$ and $CENTA_{60/30}$ granules was evaluated using the angle of repose method. Exactly 10 g each of sample was poured through a funnel clamped on a retort into an open ended glass tube placed on a flat surface. The tube was carefully removed after producing a cone. The height (h) of the resultant cone and the radius (r) was determined using a ruler and a pair of dividers. The angle of repose (Θ) was then calculated using the formula:

$\text{Tan } \Theta = h/r$, (4)

Determination of hydrogen ion concentration (pH): Two (2) grams each of ENTA, $CENTA_{45/30}$, $CENTA_{45/60}$, $CENTA_{60/60}$ and $CENTA_{60/30}$ granules was separately weighed on an electronic balance, dispersed in 100 mL of ultra-pure water (UPW) and gently stirred with glass rod stirrer for about 5 min. The solution was allowed to stand for 10 min. The pH was determined using a bench-top pH meter (pH-016, China). The determination was done in triplicates.[16]

Determination of degree of swelling and solubility: The swelling index was determined using an established method (AOAC, 1990). One (1) gram each of ENTA, $CENTA_{45/30}$, $CENTA_{45/60}$, $CENTA_{60/60}$ and $CENTA_{60/30}$ granules was transferred into a 10 mL cylinder, 15 mL of UPW was added and the slurry was heated in a water bath fitted with a thermostat for about 40 min, with gentle stirring to prevent formation of lumps till the temperature rose to 80±0.3 ^{0}C. The slurry was transferred into the tarred centrifuge tubes and weighed. 7.5mL of UPW was added, and the resulting liquid was centrifuged at 2,200 revolutions per minute (rpm) for 20 min. The supernatant was decanted immediately after centrifuging into the tarred can. The weight of the sediment was determined. The procedure was also carried out at 27±0.6 ^{0}C. Determinations were made in triplicates. The swelling and solubility index were determined using the formula:

$$\text{Swelling} = \frac{\text{Weight of sediment}}{\text{Initial weight of sample} - \text{Weight of soluble fraction}} \quad (5)$$

$$\text{Solubility Index (\%)} = \frac{\text{Weight of soluble fraction}}{\text{Initial weight of sample}} \text{ x } 100 \quad (6)$$

Determination of moisture content: Two (2) grams each of ENTA, $CENTA_{45/30}$, $CENTA_{45/60}$, $CENTA_{60/60}$ and $CENTA_{60/30}$ granules was transferred into a previously weighed crucible (W_0) to get a new weight (W_1), before transferring into an oven set at 100^{o}C for 24 hours. After 24 h, the crucible was transferred to the desiccator, cooled for 10 min and weighed (W_3). The percentage moisture content (PMC) was calculated as:

$$PMC = \frac{W_1 - W_3}{W_1 - W_0} \text{ x } 100 \quad (7)$$

Fourier Transform Infrared (FTIR) Spectroscopy: One (1) milligram each of ENTA, $CENTA_{45/30}$, $CENTA_{45/60}$, $CENTA_{60/60}$ and $CENTA_{60/30}$ granules was finely ground to about 2 µm in size and intimately mixed with approximately 100 mg of dry potassium bromide, which acted as the window material in the sample cell. The spectra for the characteristic functional groups present in the samples were obtained using a Magna-IR, 560 spectrophotometer (Perkin Elmer, USA).

Determination of Dynamic Rheological Properties: Dynamic rheological characteristics were determined with a Rapid Visco Analyzer (RVA), (model RVA 3D$^+$, Network Scientific, Australia). Exactly 0.625 g each of ENTA, $CENTA_{45/30}$, $CENTA_{45/60}$, $CENTA_{60/60}$ and $CENTA_{60/30}$ granules was separately weighed into a pre-dried empty canister; UPW was dispensed into the canister to form 2.5 %w/v slurry. The slurry was heated to 95^{o}C followed by cooling to 50^{o}C with 2 min. holding time. The rate of heating and cooling were at a constant rate of 11.25 ^{o}C/min. Peak viscosity, trough, breakdown, final viscosity, set back, peak time and pasting temperature were read with the aid of thermocline for windows software connected to a computer (Newport Scientific, 1998).

RESULTS AND DISCUSSION

The shape and size of excipients incorporated in drug formulations has an impact on the in process behavior of such formulations.[17] The photomicrographs of the granules (Fig.1) shows that carboxymethylation of ENTA at 60^{0}C for 30 min and 60 min led to the production of clumped granules that were round to oval

shaped ($CENTA_{60/60}$ and $CENTA_{60/30}$), while carboxymethylation carried out at a lower temperature (45^0C) led to spherically shaped granules with discrete structures and smooth surfaces. Granule size and shape have been indicted as major factors involved in the dynamic process of manufacturing, such as capsule shell filling and movement from the hopper to the die during tabletting.[17] Irregular shaped particles cause clumping and subsequent frictional drag due to enhanced forces of association within the particle beds, while spherically shaped particles have a better tendency to flow.[18] The results of the photomicrograph indicate that granules of products obtained from carboxymethylation at 45^0C have a tendency to flow better, while carboxymethylation of ENTA generally improved the shape of the granules formed.

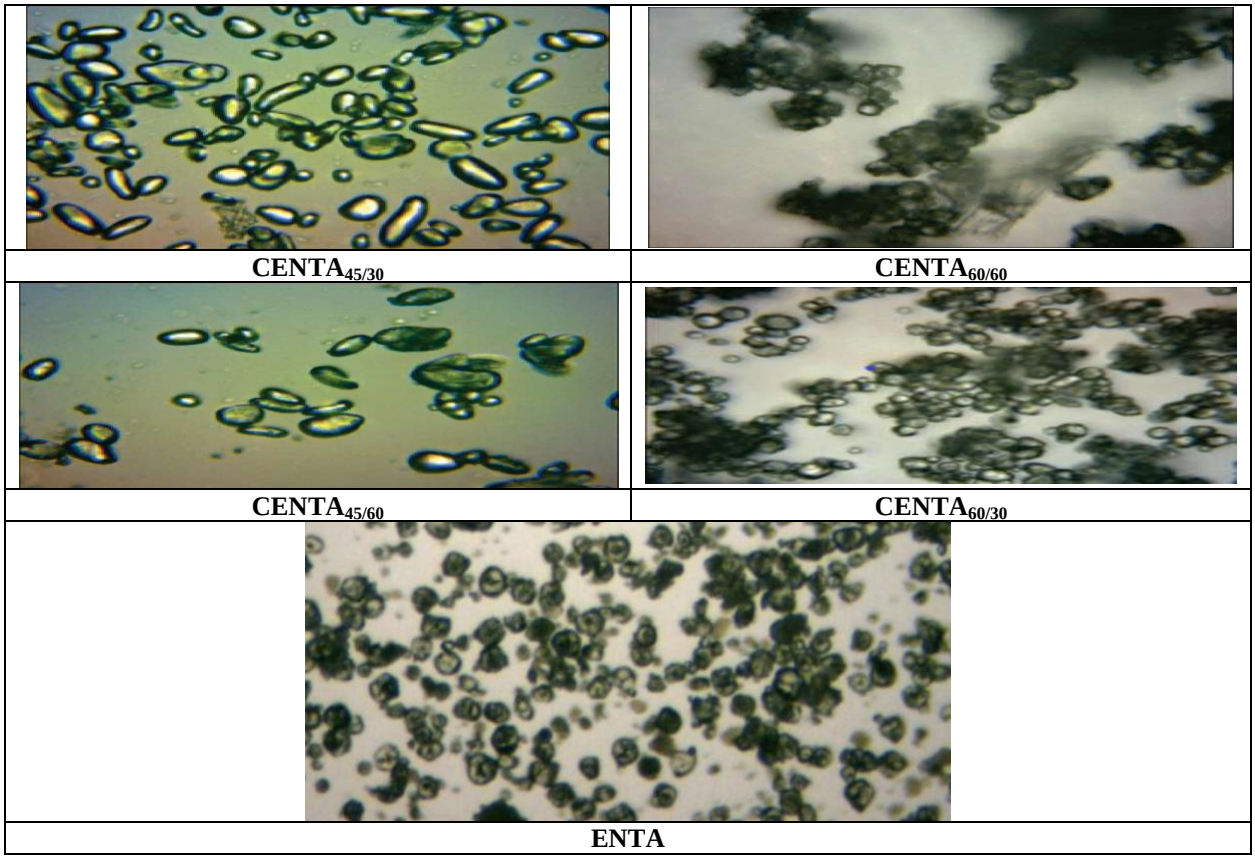


Fig. 1: Photomicrographs of the purified *Entandophragma angolense* gum (ENTA) granule and the carboxymethylated ENTA granules at different reaction conditions.

Granulation is not only aimed at increasing the particle size of powders, but also driven by factors that tend to increase the bulk density. The microstructure of granules is also a function of their density.[19] The ranking of particle and bulk densities was $CENTA_{45/30}$ > $CENTA_{45/60}$ > $CENTA_{60/30}$ > $CENTA_{60/60}$ > ENTA, while the ranking for the tapped densities was the reverse. The bulk and tapped densities of materials give insight into the packing behaviour during the various unit operations of tabletting such as fiiling, mixing, granulation and compression.[20] Tapped density represents the maximum packing density of a bed of granules or powder achieved under the influence of well defined, externally applied forces; the minimum packed volume thus achieved depends on a number of factors including particle size distribution, true density, particle shape and cohesiveness due to surface forces including moisture.[21] The chemically modified gum had lower tapped densities compared with the native gum and this may be due to the increase in particle size due to modification.

The value of the Carr's (compressibility) index is a measure of flowability and compressibility. Hausner's ratio provides an indication of the degree of densification that could result from vibration of the feed hopper during tableting.[22] The higher the Hausners ratio, the greater is the propensity to form a compact mass,[23] while the smaller the compressibility index, the better is the flow property. Hausner's ratios greater than 1.25 indicate poor flow; compressibility index of 5-10, 12-16, 18-21, and 23-28 represent excellent, good, fair and poor flow properties respectively;[16, 24] From the study (Table 1), only $CENTA_{45/30}$ and $CENTA_{45/60}$ indicated good flowability and compressibility.

The angle of repose is the qualitative measure of the cohesiveness or the tendency of the powdered or granulated materials to flow, for instance, from hoppers through the feed frame into the tabletting machine. Such uniformity of flow will minimize weight variations in tablets produced.[25] Values of angle of repose generally

below 30° indicate good flow properties and are considered appropriate for solid dosage formulations, while angle of 40 ^{0} and above indicates poor flow characteristics.[26] All the samples had angles of repose below 30 °, with $CENTA_{45/60}$ having the least value (19.2 ± 0.1^{0}).

The swelling capacity and solubility of polymers provide evidence of magnitude of interaction within the lattice structure of the polymer and between water molecules. It has also been suggested that the swelling characteristics of a pharmaceutical polymer could be used in the preliminary determinations of some excipient properties[16] The ranking for swelling capacity for the polymers at 27 ± 0.6^{0}C and 80 ± 0.3^{0}C was $CENTA_{45/60}$< $CENTA_{45/30}$< $CENTA_{60/60}$ < $CENTA_{60/30}$ < ENTA, while the reverse was obtained for the solubility index at both temperatures, thus indicating that carboxymethylation reduced the swelling ability of ENTA, but enhanced the solubility at low and high temperatures. All the pH values were within the 4.5- 7.0 specification of the United States Pharmacopoeia for dried gums; this implies that the near pH values of the granules may be an indication of elimination of gastrointestinal upsets when the modified gum is used as an excipient for GIT drug delivery.

Table 1: **Physicochemical composition of polymers (mean ± SD, n=3)**

Parameters	**ENTA**	**$CENTA_{45/30}$**	**$CENTA_{45/60}$**	**$CENTA_{60/30}$**	**$CENTA_{60/60}$**
Particle Density(g/cm^3)	1.58±0.07	1.72±0.03	1.63±0.05	1.61±0.02	1.60±0.09
Bulk Density(g/cm^3)	0.54±0.05	0.71±0.02	0.82±0.01	0.63±0.02	0.59±0.02
Tapped Density(g/cm^3)	1.08±0.03	0.82±0.01	0.75±0.02	0.85±0.01	1.01±0.04
Compressibility index(%)	49.53±0.05	13.41±0.03	9.33±0.01	25.88±0.05	41.58±0.06
Hausner's ratio	2.0±0.02	0.91±0.08	1.16±0.09	1.35±0.13	1.71±0.02
Angle of repose	21.7^{0}±0.2	24.3^{0}±0.1	19.2^{0}±0.1	27.1^{0}±0.3	29.6^{0}±0.1
Swelling capacity in water at $27^{0}\pm0.6^{0}$C	61.4±0.7	52.7±1.1	40.5±0.3	57.7±0.9	54.8±0.1
Swelling capacity in water at 80 $\pm0.3^{0}$C	75.7±0.2	67.9±0.9	54.8±0.7	74.6±0.1	72.1±0.2
Solubility index (%) at 27 ± 0.6^{0}C	38.4±0.6	43.1±0.3	57.1±1.8	41.3±0.1	42.1±0.5
Solubility index (%) at 80 $\pm0.3^{0}$C	53.2±0.1	59.6±0.5	76.2±0.3	57.3±0.4	58.2±0.3
pH at 27 ^{o}C	6.22±0.02	6.64±0.03	6.54±0.05	6.29±0.10	6.36±0.03
pH at 80 ^{o}C	5.24±0.05	5.82±0.01	5.46±0.02	5.27±0.01	5.05±0.02

The results of the FTIR spectra for the unmodified (ENTA) and carboxymethylated samples ($CENTA_{45/60}$, $CENTA_{45/30}$, $CENTA_{60/60}$ and $CENTA_{60/30}$) of *Entandophragma angolense* gum are presented in Fig. 2. The functional group region of the FTIR spectra of ENTA showed distinct sharp peaks at 2926.85 cm^{-1} and 2853.19 cm^{-1}. These sharp peaks are characteristic of methyl C-H stretching associated with aromatic rings and carboxylic acids. The sharp peaks at 2359.93 and 2341.37 cm-1 are indications of asymmetric C-O stretch. The peaks obtained at 1573.69 and 1558.36 showed similar functional groups consisting of strong N=O nitroso and weak C-O stretch. The FTIR spectra of the modified ENTA showed similar absorption peaks. The characteristic absorption bands appearing at 1645.71cm^{-1} and 1635 cm^{-1} are due to the presence of strong aromatic characters consisting of N-H bend. The fingerprint region consists of C-S stretch and aliphatic halogenated compounds, which are assigned to absorption band located at 665.93 cm^{-1}, 665.35 cm^{-1}, 670.70 cm^{-1} and 664.90 cm^{-1}[27] There are no significant changes in the FTIR spectra of the carboxymethylated ENTA at different reaction conditions. However, when compared with the unmodified spectra, modification conferred the presence of amine, methyl and hydroxyl groups. Moreover, there was a shift in the asymmetric C-O stretch, which now occurred as strong bands at 2358.47cm^{-1} and 2358.56cm^{-1} in the spectra of the modified ENTA.

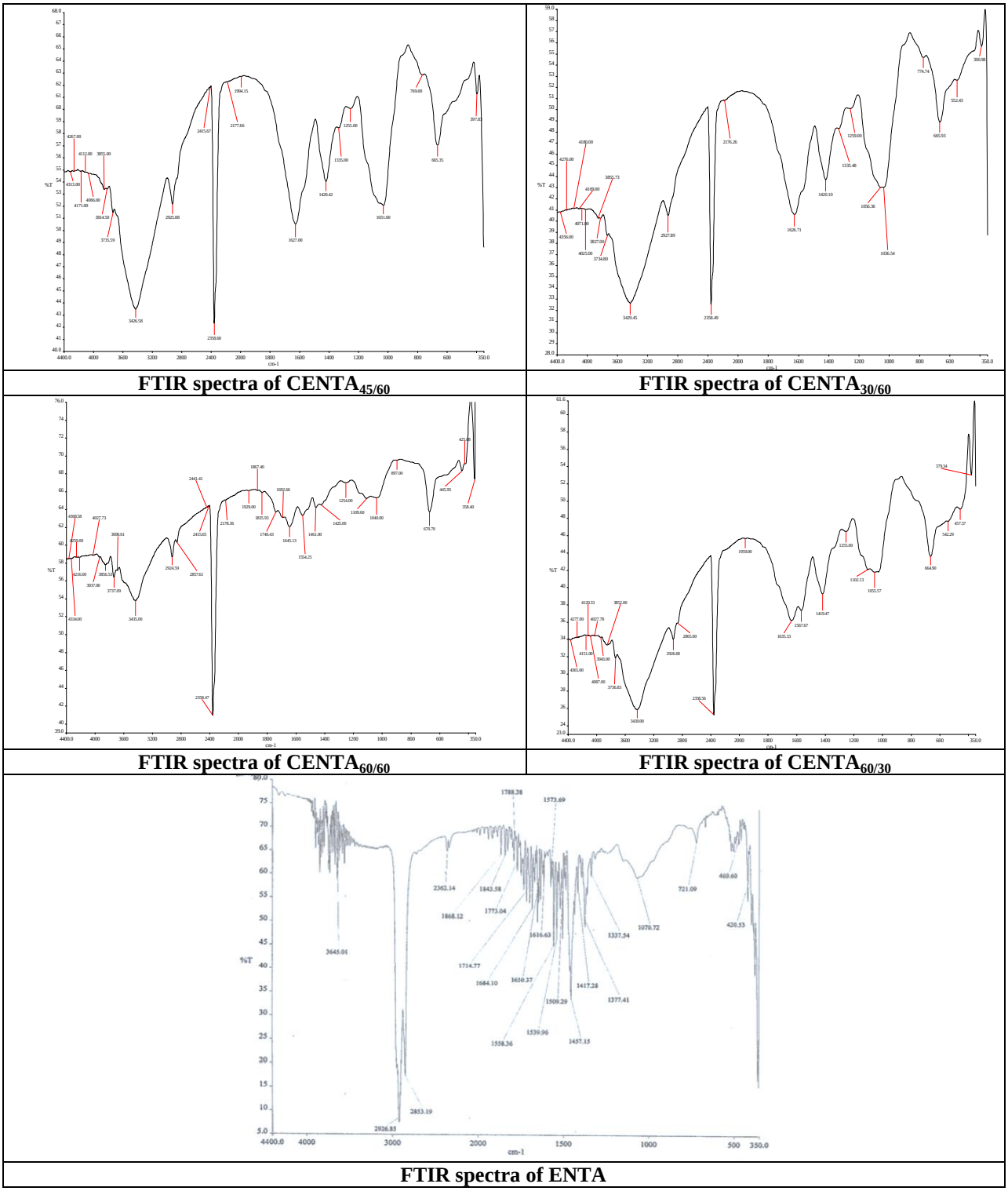
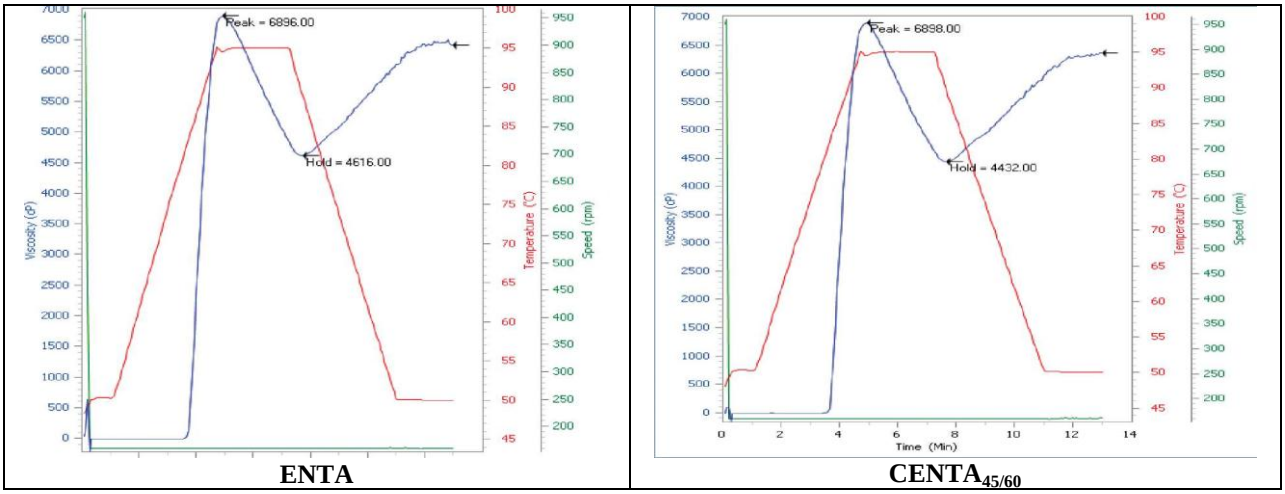


Fig. 2: Fourier Transform Infrared spectroscopy (FTIR) of polymers.

The parameters obtained from the dynamic rheological measurements of the polymers are shown in Table 2, while representative viscoamylographs are shown in Fig. 3. The rheological property of a material is an indication of the changes in elasticity of a material on the application of heat, which helps to predict the behavior of the materials when undergoing thermal processes such as lyophilization, coating or dipping; it could also be an indication for the type of equipment to use during manufacturing processes.[28] The order for the peak and breakdown viscosities is ENTA > $CENTA_{45/60}$ > $CENTA_{45/30}$ > $CENTA_{60/60}$ > $CENTA_{60/30}$, while for the trough and final viscosities, the order was the reverse. Carboxymethylation of ENTA led to an increase in the final viscosity of the polymer. The peak viscosity, which is an indication of the water holding ability of the polymer, was reduced as a result of carboxymethylation, with the reaction carried out at a temperature of 60^0C

producing modified granules with the least viscosities. This may be as a result of less susceptibility to heat changes during the heating and cooling cycle.[29] Buchholz *et al*[30] reported that pasting temperature and crystallinity have a direct relationship. The polymer granule with the highest pasting temperature was $CENTA_{45/60}$, which is also the polymer with the most compressibility profile.



ENTA **$CENTA_{45/60}$**

Fig. 3: Representative viscoamylograph plots.

Table 2: Parameters obtained from the viscoamylographs.

Parameters	ENTA	$CENTA_{45/30}$	$CENTA_{45/60}$	$CENTA_{60/30}$	$CENTA_{60/60}$
Peak viscosity (cP)	6898	6891	6896	6879	6886
Peak time (min)	4.9	4.8	4.9	4.8	4.7
Trough viscosity (cP)	4432	4627	4616	4703	4641
Breakdown viscosity (cP)	2466	2263	2280	2251	2259
Pasting temperature (°C)	81.65	81.67	81.70	81.41	81.53
Final Viscosity(cP)	6364	6423	6413	6512	6521
Set back from trough(cP)	1932	1846	1802	1826	1804

CONCLUSION

Carboxymethylation of *Entandophragma angolense* gum improved the physiochemical properties of the native gum as a result of increased particle size and densities, enhanced solubility and enhanced flow properties; these were also evident as a result of the introduction of functional groups to the crystalline structure of the native gum due to the chemical modification. The carboxymethylation carried out at 45^0C for 30 mins produced granules with the highest pasting temperature and most compressibility profile.

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