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Research Article

Effects of carboxymethylated gum obtained from Entandophragma angolense tree on the compressional and release properties of ibuprofen tablets

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Abstract

The incorporation of modified polymers in drug formulations is primarily due to their low toxicity, affordability, availability, compatibility with biological membranes, economic feasibility and bio-degradability. This study investigated the compressional and release characteristics of ibuprofen tablet formulations containing natural and modified *Entandophragma angolense* gum. *Entandophragma angolense* gum (ENTA) was extracted and modified by carboxymethylation to yield CENTA. Ibuprofen tablets containing varying binder concentrations (2.5-10% w/w) of ENTA and CENTA (compared with gelatin BP) were formulated by wet granulation. Crushing strength (CS) and friability (FR) were used in assessing the mechanical properties of the tablets, while disintegration and dissolution times accounted for drug release parameters. Density measurements, Kawakita equations and Heckel plots were used to assess the compressional properties of the formulations. The results were analysed using ANOVA at α0.05. Generally, there was a direct relationship between the concentration of the polymers and the CS of the tablets, while an inverse relationship was observed for FR. The CS ranked ENTA > CENTA > gelatin BP. Carboxymethylation of ENTA enhanced drug release ($t_{30\%}$ and $t_{80\%}$). Formulations containing CENTA had a slower and faster onset of plastic deformation; mean yield pressure (P_y), ranked ENTA > CENTA > gelatin BP. A measure of the rearrangement phase at the early stages of compression (D_B) was highest for CENTA at all concentrations. CENTA compared favourably with gelatin BP and showed better mechanical and release characteristics than ENTA. Also, CENTA shows good potential as a binder in fast disintegrating ibuprofen tablets, especially when incorporated at low concentrations.

Keywords: *Entandophragma angolense* gum; carboxymethylated gum; compressional characteristics; release characteristics; ibuprofen tablets

Introduction

Utilization of modified natural gums as excipients in pharmaceutical drug delivery is increasing among formulation scientists due to enhancement of the extraction method and modification of the natural gum, consequently leading to improved incorporation of these polymers in drug formulations [1]. Frequent use of natural gums has been linked to their salient properties such as reduced toxicity, compatibility with bio-membranes, economic feasibility and availability [2], especially when they are incorporated as stabilizers, sweeteners, flow enhancers, adhesives or binders in the formulation of different dosage forms [3]. However, specific problems exemplified by pH stability changes, differential solubility and swelling, viscosity changes in storage and possibly microbial contamination are some setbacks that the use of natural gums is associated with [4].

Chemical modification, a method of modifying natural gums, is aimed at impacting different desired properties of the new modified polymer. Such properties range from enhanced flexibility and rigidity to stability at high temperatures and increased biological compatibility and rate of degradation [5]. To achieve this, natural gums are treated with approved chemical entities, adding functional groups to the molecular structure of the polymers [6]. Binding agents are essentially incorporated as inactive components of tablets during granulation, where they improve the agglomeration of the active pharmaceutical ingredient (API), thereby enhancing their compressibility. In the agglomeration process,

the API particles are coated, and the release rate of API from the tablet can then be modulated and determined [7]. The incorporation of a high concentration of binder produces hard tablets that disintegrate slowly, while low binder concentrations in solid dosage formulations lead to soft tablets that cap easily due to poor adhesion [8]. The structural strength required by tablets during dynamic handling activities during manufacturing processes and transportation is conferred by binders [9].

Naturally occurring *Entandophragma angolense* gum (Family: *Meliaceae*) is obtained by incising the tree trunk. The hydrophilic gum is widely available throughout the year in tropical Africa [10] and has been demonstrated to be non-toxic with good suspending and mucoadhesive potentials, forming a viscous gel when left standing for 30 minutes in water [11]. *Entandophragma angolense* gum was chemically modified by carboxymethylation, and it was demonstrated that carboxymethylation improved the physiochemical properties of the native gum as a result of increased particle size and densities with enhanced solubility and flow properties. Moreover, the modified gum showed good stability over 30 days when kept in a sealed container, while granules formed from the carboxymethylated gum also showed good compressibility potentials [12]. In this study, the effects of modifying native ENTA by carboxymethylation to yield CENTA and incorporating the modified polymer as a binder in ibuprofen tablet formulations (in comparison with gelatin BP) have been investigated. Ibuprofen, a non-steroidal anti-inflammatory drug freely soluble in ether but insoluble in water, has been used for this study [13]. Ibuprofen cannot be compressed independently, and a binder is required along with other excipients to form good tablets.

Materials and Methods

Materials

The materials used were Ibuprofen powder BP (BDH Chemicals Ltd., Poole UK). Magnesium stearate BP (Kansal polychem Industries, India), gelatin BP (100 bloom/E441, Jinhua Chemicals, China), 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. Exudates of the hydrophilic *Entandophragma angolense* gum (Family: *Meliaceae*) were obtained from early morning incisions made on the trunk of the *Entandophragma angolense* tree located in the Botanical Gardens of the University of Ibadan, Ibadan, Oyo State, Nigeria. The plant was authenticated at the Forest Herbarium, Ibadan, Nigeria. Analytical grade reagents were used for the study.

Methods

Purification and carboxymethylation of Entandophragma angolense gum extract

The procedures utilised to purify *Entandophragma angolense* gum extract have been described earlier [12]. In order to carboxymethylate the purified ENTA, 2 grams of ENTA were thoroughly mixed with 100 ml of ultrapure water (UPW). Then 15 ml of a sodium hydroxide solution containing 30% water by weight were added to the mixture at the rate of 1 ml every 15 minutes while the mixture was stirred. After this, 10% v/v chloroacetic acid was added (at a rate of 1.5 ml/minute) for 30 minutes. The final mixture was heated to 45±1.2ºC while continuously stirring for 4 hours. The pH level was brought down to its neutral state using glacial acetic acid. In order to obtain the powder containing the chemically modified *Entandophragma angolense* gum (CENTA), the precipitate was first lyophilized after being rinsed with ultra-pure water. Because gum has a high capacity to hold water, lyophilization had to be done to produce a formulation blend that would have a moisture content close to that of the other ingredients [12]. This was performed in order to achieve the desired result. The carboxylation of the gum was analysed with a Magna-IR, 560 spectrophotometer (Perkin Elmer, USA) by intimately combining one milligram each of ENTA (or CENTA) and 100 mg of dry potassium bromide. The spectrophotometer was used to measure the absorption of light by the mixture. We obtained the Fourier

Transform Infrared spectroscopy (FTIR) spectra for the specific functional groups present in the samples.

Determination of degree of swelling and solubility

An established method was employed in determining the swelling index [12]. One gram each of ENTA (or CENTA) 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 minutes, with gentle stirring to prevent the formation of lumps till the temperature rose to 80±0.3ºC. The slurry was transferred into the tarred centrifuge tubes and weighed. 7.5 ml of UPW was added, and the resulting liquid was centrifuged at 2,200 revolutions per minute (rpm) for 20 minutes. 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±0.6ºC and 80±0.3ºC. Determinations were made in triplicates.

Compression of tablets

Granules from homogenously mixed formulations (Table 1) containing ibuprofen, spray dried lactose BP, Talc BP and the binders (2.5% w/w, 5.0% w/w, 7.5% w/w, and 10.0% w/w) were formed from each batch based on a previous design of experiment described in the literature [14]. W. Huang et al. [15] reported the formulation of wet granules using spray-dried lactose, which resulted in products with good flowability and compressibility. For each batch, the weighed quantity of ibuprofen and either ENTA or CENTA (or gelatin BP) powders were premixed thoroughly in a Kenwood plenary mixer (United Kingdom, KVL65.001WH), this was followed by the addition of the weighed quantity of talc and spray dried lactose BP until a homogenous mixture was achieved. The mass was mixed with UPW as the granulating fluid until a homogenous paste was obtained. The homogenous mixture was then passed through a 250 μm sieve, and the resulting wet granules were dried using a single-stage spray drier (SiccaDania, Denmark, SD900). Each batch of the dried granulated formulations containing ENTA (or CENTA) as binders (in comparison with gelatin BP) was compressed into tablets at predetermined compression pressures using a Carver hydraulic hand press (model C Carver Incorporated, Menomonee Falls, Wisconsin, U.S.A), equipped with a 10.5 mm flat faced punch and die set lubricated with 1% w/v dispersion of magnesium stearate in acetone prior to compression. After ejection, silica gel was used in storing the tablets over a 24-hour period for elastic recovery to occur; this will ensure that the tablets are hard enough and accurate yield values are obtained. All the tablet batches were properly stored in airtight containers.

Table 1. Quantity used to prepare the directly compressed tablets.

Ingredients	**Formulations (mg)**			
	I	**II**	**III**	IV
Ibuprofen	200.00	200.00	200.00	200.00
ENTA (or CENTA or Gelatin BP)	8.13	16.26	24.39	32.52
Talc	12.00	12.00	12.00	12.00
Spray dried lactose BP	104.87	96.74	88.61	80.48

Weight of each tablet = 325mg; ENTA: Native *Entandophragma angolense* gum; CENTA: Chemically modified *Entandophragma angolense* gum

Determination of crushing strength (CS) and percentage friability

A tablet hardness tester (MHT-100, Model P&M 01, Pharma Alliance Group, Indonesia) was used to determine the tablets' CS. Each tablet was randomly selected, and after proper positioning between the anvil and the spindle of the tester, a diametric force was applied to the tablet. The force (N) at which the tablet broke into two halves was recorded. The process was carried out thrice for twenty (20) tablets that were randomly selected. Based on the 2009 United States Pharmacopoeia that specified the use of the combined weight of tablets equivalent to 6.5 g for tablets individually weighing less than 650 mg, friability (FR) was determined twice using a friability test apparatus (DBK Instruments, Mumbai-6, Model 40FTA01, India). The combined weight of twenty randomly selected tablets was determined on an electronic balance and then transferred into the friabilator to rotate at 25 rpm for 4 minutes. After the rotation was completed, the tablets were re-weighed, and the percentage friability was calculated.

Disintegration time test

Assessment of the disintegration time of the tablets was determined from each the compression pressure in 900 ml of distilled water at a 37±0.5ºC using a BP Manesty disintegration testing apparatus (Manesty Machines, Poole, UK). Six tablets from each formulation were placed on the wire mesh just above the surface of the distilled water. The time it took each tablet to pass through the mesh screen after breaking up was recorded. The procedure was repeated thrice for the tablet batches, and the mean disintegration time was calculated for each batch.

Dissolution test

The dissolution rate of the tablet was determined using a DBK dissolution test apparatus (Type 40DRT01, India) that contains 900 ml of 0.1 N HCL as the medium at a temperature of 37±0.5°C. The sample basket containing each tablet was lowered into dissolution before the rotation set at 100 rpm. At 5 minutes, aliquots of 5 ml were withdrawn from the dissolution medium into a volumetric flask. The aliquots withdrawn were replaced with equal volumes of 0.1 N HCL, also maintained at 37±0.5°C. The absorbance was recorded for each sample at a wavelength of 221 nm and assayed accordingly using standard calibration curves to extrapolate.

Heckel analysis

Densification at different pressures was obtained from data of Heckel plots generated by plotting values of In (1/1- D) against applied pressure (P) for the different formulations. The values of K were obtained from the slope, while values of A were derived from the intercept. The reciprocal of the slope gave the mean yield pressure (P_y), while D_A (relative density) was obtained from equation 1. The difference between D_A and D_0 (equation 2) is equivalent to the values of D_B (relative density at low pressures).

$$In[1/(1-DA)] = KP + A \quad (1)$$

$$D_B = D_A - D_0 \quad (2)$$

Kawakita analysis

The volume of the formulations before compression, V_0, and at different compression pressures, Vp, were determined using equation 3. Equation 4 was used to calculate the extent to which the volume of the bed was reduced (C). Data obtained from the plots of P/C against applied pressure, P (Kawakita plots) were plotted for each formulation. The slope and intercept of the plots gave the values of 'a' and 'ab', respectively.

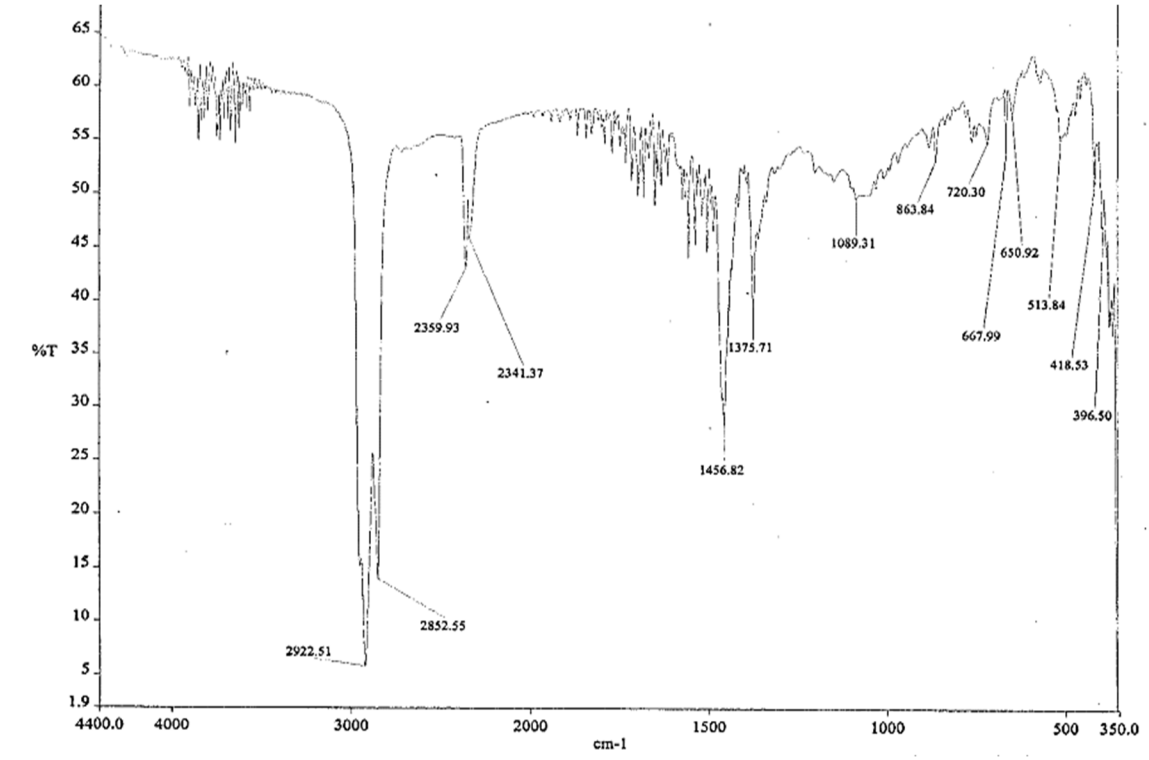
$$V_0 = \pi r2h \quad (3)$$

$$C = [V_0 - V] / V_0 = abP/ (1 - bP) \quad (4)$$

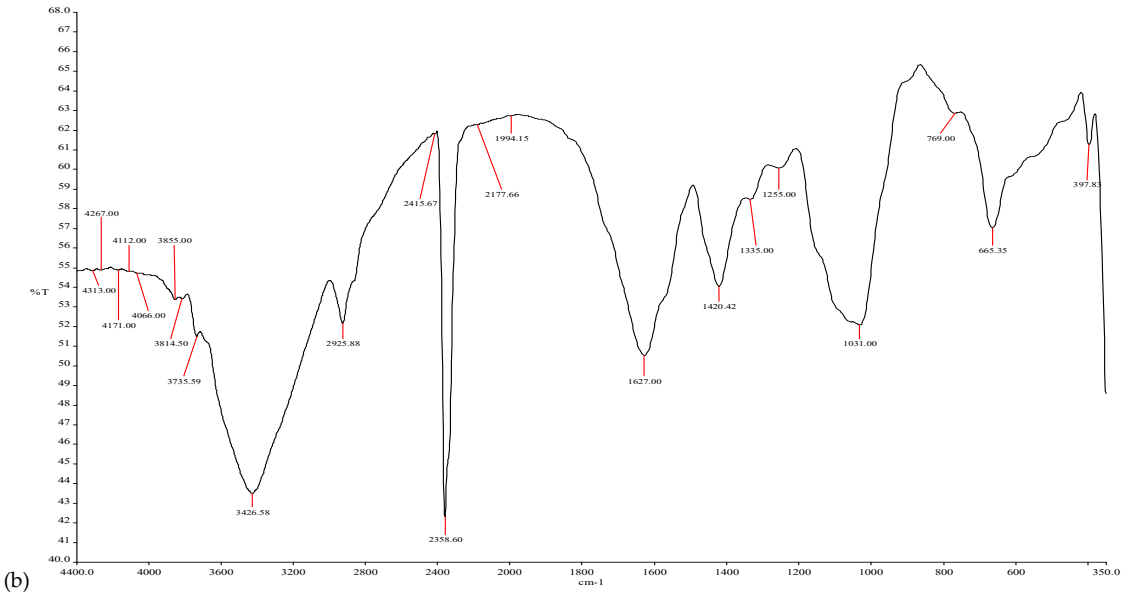
Results and Discussion

The results of the FTIR spectra for the unmodified ENTA and the carboxymethylated CENTA are presented in Figure 1. The functional group region of the FTIR spectra of ENTA showed distinct sharp peaks at 2926.85 cm^{-1} and 2853.19 cm^{-1}, characteristic of methyl C-H stretching due to aromatic rings and carboxylic acids, while the sharp peaks at 2359.93 cm^{-1} and 2341.37 cm^{-1} are indications of asymmetric C-O stretch. However, compared with the unmodified spectra, carboxymethylation 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 2358.47 $cm^{-1}$and 2358.56 cm^{-1} in the FTIR spectra of CENTA.

The swelling capacity of polymers indicates the 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 [12]. The ranking for swelling capacity for the polymers at 27±0.6 ºC and 80±0.3 ºC was CENTA < ENTA, thus indicating that carboxymethylation led to an enhancement of the water holding capacity of the gum.



(a)



(b)

Figure 1. (a) FTIR spectra of *Entandophragma angolense* gum. (b) FTIR spectra of carboxymethylated Entandophragma angolense gum.

All the tablets formed were within the official specifications for weight uniformity of uncoated tablets. The mechanical strength of a tablet is indicated by the crushing strength value, while the ability of the tablet to withstand abrasion during storage, handling or transportation is determined by the tablet's friability. The values of the crushing strength, friability, disintegration and dissolution times are shown in Table 2. Generally, the crushing strength values and the percentage friability had an inverse relationship. Tablets containing ENTA as binder had the highest crushing strength values but were also the most friable of the formulations. A formulation scientist needs to understand the forces that contribute to bond formation and breakage within a tablet matrix [16]. Attractive forces occurring between the components of the formulations (such as binders, APIs and other excipients) are all critical

factors that affect not only the mechanical properties of the tablets but also the rate and extent to which the API is released from the tablet matrix [17]. The parameters obtained from the Heckel and Kawakita plots are presented in Table 2, while Figure 2 and 3 show representative Heckel plots for polymers incorporated at 5.0% w/w and Kawakita plots for the carboxymethylated *Entandophragma angolense* gum (CENTA) respectively.

Table 2. Values of Crushing strength (CS), Friability (FR), Crushing Strength-Friability ratio (CS-FR), Disintegration time (D) and Dissolution time ($t_{30\%}$ and $t_{80\%}$).

Binder	Binder Conc. (%w/w)	CS (N) *	FR (%) *	D (min) *	$t_{30\%}$ (min)*	$t_{80\%}$ (min)*
ENTA	2.5	22.7±0.11	0.97±0.06	4.20±0.06	18.02	26.11
	5.0	23.0±0.27	1.00±0.01	4.41±0.04	19.22	31.21
	7.5	26.5±0.13	0.95±0.12	4.51±0.01	21.37	33.05
	10.0	26.8±0.08	0.93±0.03	4.64±0.08	22.26	37.14
CENTA	2.5	22.1±0.02	0.87±0.01	3.17±0.01	11.12	22.28
	5.0	22.5±0.13	0.87±0.11	3.29±0.05	19.13	26.18
	7.5	23.3±0.06	0.86±0.04	3.33±0.03	22.02	30.13
	10.0	24.9±0.06	0.83±0.03	3.40±0.07	26.16	37.27
Gelatin BP	2.5	20.2±0.12	0.86±0.02	4.51±0.05	21.04	32.11
	5.0	20.7±0.13	0.84±0.08	4.57±0.03	25.13	37.08
	7.5	21.5±0.04	0.81±0.03	4.61±0.07	32.14	41.22
	10.0	27.3±0.13	0.80±0.01	4.65±0.01	34.08	42.13

*Average of three determinations; N: Newton

The compaction of powders involves a volume reduction process on the application of an external pressure [17]. Generally, the ranking of the P_y, calculated from the regions of the Heckel plots showing the highest correlation coefficient for the plots is ENTA > CENTA > gelatin BP. This suggests that for formulations containing the modified gum (CENTA), the onset of plastic deformation is slower than formulations containing gelatin BP and faster than formulations containing the unmodified gum. A measure of the rearrangement phase at the early stages of compression (D_B), was shown to be highest for CENTA at all binder concentrations. The implication is that chemical modification enhanced particle de-segmentation; thus, the bed of powder in formulations containing the modified gum resisted forces that could have led to segregation at the onset of the compaction process, which are important parameters to consider in processes such as die filling. Generally, there was an inverse relationship between the binder's concentration and D_B's values. Relatively linear and near parallel relationships at all applied pressures were observed for most of the plots. The required pressures needed to reduce the powder bed by 50% are represented by values of P_k (inverse measure of the amount of plastic deformation occurring during the compression process) and D_I (initial relative density of the formulations) [18]. Materials that are soft and readily deform plastically under pressure give low values of P_k. The ranking of the P_k values was CENTA < gelatin BP < ENTA., thus indicating that the chemically modified gum has a greater tendency to be deformed after applying pressure when compared with the unmodified gum and gelatin BP. It can be seen that the value of P_k for the formulations had an inverse relationship with binder concentration.

The strength and weakness of a tablet are indicated by values obtained from the crushing strength and friability, respectively. When plasto-elastic binding agents are present in high concentration in a formulation, there is usually an increase in plastic deformation of the formulation leading to the introduction of more solid bonds in the system and consequently enhancing the tablet strength; eventually, fracture and abrasion of tablets are reduced significantly [19]. Evaluation of the ability of tablets to resist abrasion during handling, packaging and transportation is carried out using friability tests. The acceptance criteria for compressed tablets are for the percentage loss in weight to be less than or equal to 1% [20]. Generally, all the tablets fell within the acceptance criteria. However, carboxymethylation led to more resistance of the tablets to abrasion. Reduced binder concentrations

that result in loose inter particulate bonding or compression at low pressures sometimes explain why tablets fail to meet the standards set for friability tests [21]. A tablet is expected to remain intact during production, packaging, storage, distribution/transportation, dispensing and administration. Therefore, the formulation must be well concerted to ensure that attrition is avoided as much as possible after the compact has been formed [21]. There was a direct relationship between the polymers' concentration and the tablets' crushing strength, while an inverse relationship was observed for the percentage friability.

Table 3. Parameters obtained from density measurements, Heckel and Kawakita Plots.

Binder	Binder Conc. (%w/w)	D_0	P_y (MN/m²)	D_A	D_B	P_k (MN/m²)	D_I
ENTA	2.5	0.413	82.11	0.661	0.248	3.855	0.588
	5.0	0.428	82.03	0.657	0.229	3.709	0.572
	7.5	0.437	81.12	0.648	0.211	3.659	0.543
	10.0	0.448	81.21	0.636	0.188	3.629	0.514
CENTA	2.5	0.397	80.14	0.648	0.251	3.695	0.575
	5.0	0.418	79.33	0.642	0.224	3.676	0.553
	7.5	0.421	75.11	0.633	0.212	3.586	0.538
	10.0	0.422	69.28	0.629	0.207	3.513	0.501
Gelatin BP	2.5	0.408	10.15	0.629	0.221	3.856	0.513
	5.0	0.399	11.27	0.617	0.218	3.775	0.493
	7.5	0.381	13.24	0.592	0.211	3.704	0.486
	10.0	0.397	12.75	0.413	0.016	3.675	0.471

ENTA: *Entandophragma angolense* gum, CENTA: Carboxymethylated *Entandophragma angolense* gum; D_0: Density at zero compression pressure within the die; P_y: Mean yield pressure; D_A: Density due to original compact volume; D_B: Density at the early stages of compression (low pressures); P_K: Inverse measure of the amount of plastic deformation occurring during the compression process; D_I: Initial relative density of the formulations.

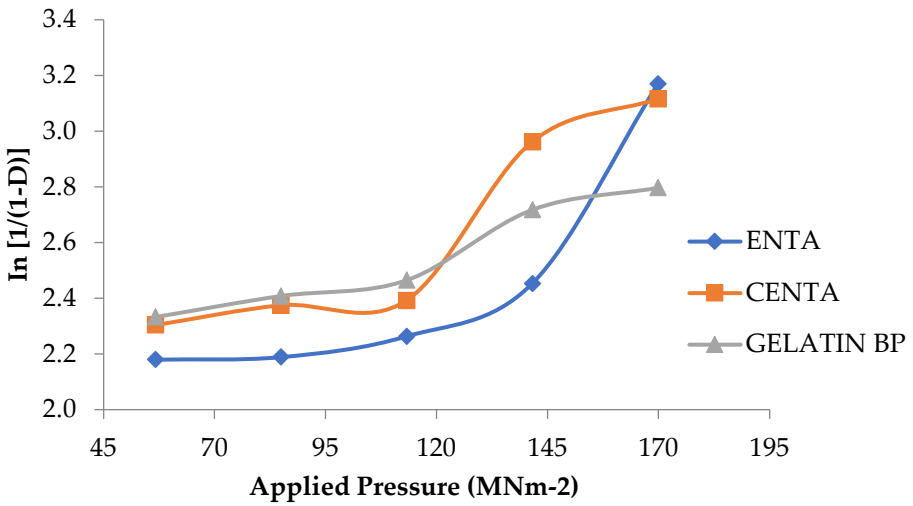


Figure 2. Representative Heckel plots for polymers incorporated at 5.0% w/w.

The release characteristics of the polymers were evaluated using parameters obtained from the disintegration and dissolution tests performed on the tablets (Table 2). The onset of the pharmacological effect of every solid dosage form depends on the product's bioavailability at the site of action [22]. Bioavailability is related to the break-down of the tablet (disintegration) and subsequent release (dissolution) of the API [23]. All the tablets disintegrated within the official specifications for uncoated tablets; however, tablets containing CENTA had the fastest disintegration time. From the dissolution profiles (Figure 4 and Table 2), it was observed that tablets containing CENTA had a better drug release pattern (30% and 80% of API released) when compared with tablets containing ENTA as binders, thus implying that carboxymethylation enhanced the rate of drug release from the tablets.

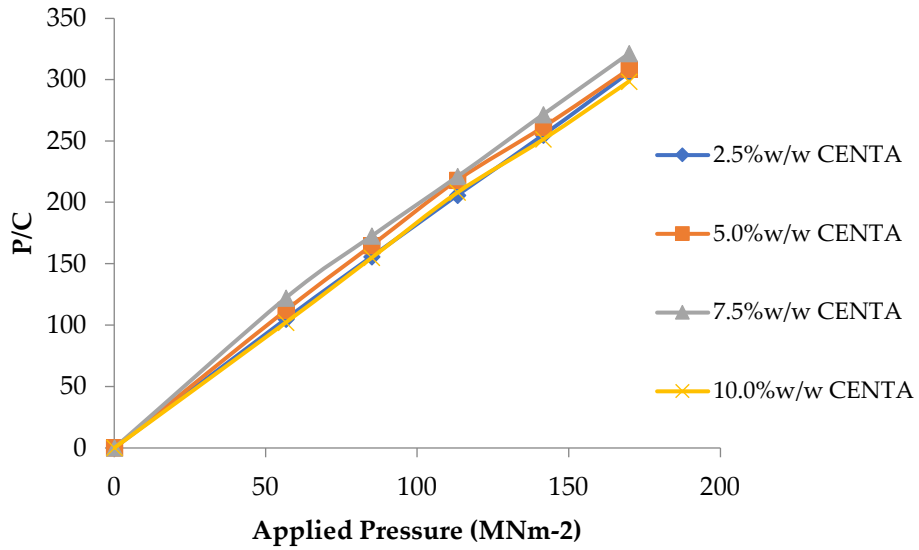


Figure 3. Kawakita plots for the carboxymethylated *Entandophragma angolense* gum.

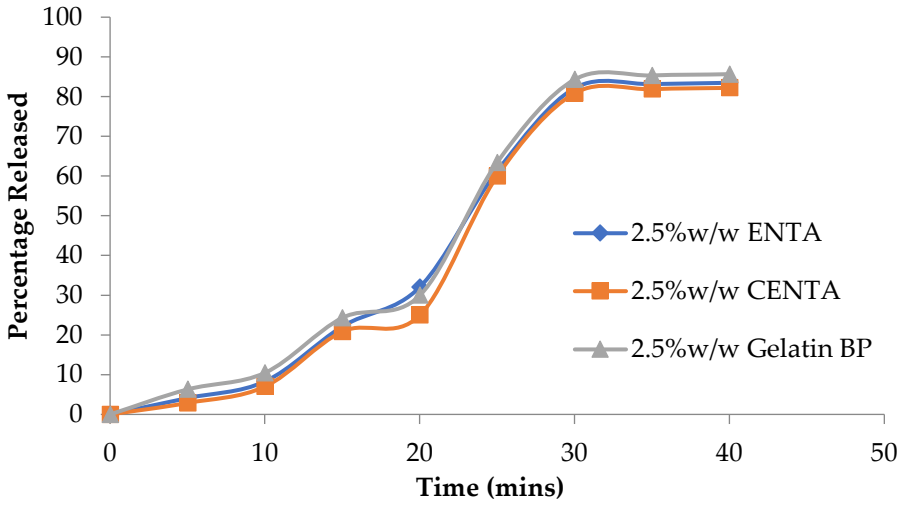


Figure 4. Representative dissolution plots for polymers incorporated at 2.5% w/w.

This is probably due to a rearrangement of the bonds within the lattice structure of the tablets due to the introduction of more functional groups [24]. This is also supported by the data obtained from the crushing strength determination, which generally ranked ENTA > CENTA > gelatin BP. For all the formulations, there was a significant increase in API release rate after 20 minutes.

Conclusion

The results suggest that the incorporation of carboxymethylated *Entandophragma angolense* gum as a binder in ibuprofen tablet formulations led to a faster onset of plastic deformation when compared with the native gum. The drug's release rate from the tablet was enhanced due to carboxymethylation of the gum, with a significant increase in release rate after twenty minutes. This release profile is evidenced by the crushing strength values of the tablets, where tablets containing the modified gum had lower values than tablets containing the native gum. Carboxylation also enhanced the swelling behaviour of the gum due to an enhancement of the water-holding capacity of the gum, consequently leading to a reduction in the disintegration time for the tablets containing the modified gum as a binder**.** In future, the authors intend to evaluate the mucoadhesive properties of carboxymethylated *Entandophragma angolense* gum using ex-vivo studies.

Key findings

- As evidenced by the FTIR spectra, the Carboxymethylation of *Entandophragma angolense* gum conferred significant functional groups to the native gum.
- There was an increase in the onset of plastic deformation for formulations containing the modified gum compared to the native gum.
- The ibuprofen was released faster from the tablets containing the carboxymethylated gum as a binder, with an as significant increase in release rate after twenty minutes.

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Authors contribution

All the authors have contributed equally.

Declaration of interest

The authors declare no conflict of interest.

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