

Carboxymethylated and Cross-Linked Tapioca Starch as a Multifunctional Excipient for Hydrochlorothiazide Tablet Formulation

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ABSTRACT:

Tapioca starch is an abundant, low-cost natural polymer with limited direct application in tablet formulations due to poor flowability and compressibility. This study aimed to improve its functionality through carboxymethylation and cross-linking, and to evaluate its performance as a multifunctional excipient in hydrochlorothiazide tablet formulation. Tapioca starch was carboxymethylated using sodium monochloroacetate at different NaOH concentrations (1.0–5.0 M) and subsequently cross-linked with sodium trimetaphosphate. Degree of substitution and reaction efficiency were determined. Powder flow, compressibility, FTIR, and XRD analyses were performed. Tablet properties were evaluated using hardness, friability, and dissolution testing. The degree of substitution peaked at 1.5 M NaOH (0.44 ± 0.22) with the highest reaction efficiency. Carboxymethylation improved flow properties (Carr's index reduced from 30.7% to 13–22%), while cross-linking further enhanced compressibility (Carr's index 11–14%). Tablets formulated with cross-linked carboxymethylated tapioca starch (cCMTS) demonstrated superior mechanical strength (hardness 9.5–14.3 kgf) and low friability (<1%). FTIR confirmed successful modification without drug–excipient interaction, and XRD showed retention of A-type crystallinity. Dissolution testing revealed rapid drug release (80–85% in 45 min) for low DS batches and slower release for highly modified batches, indicating tunable functionality. Carboxymethylation and cross-linking transformed tapioca starch into a multifunctional excipient with excellent flow, compressibility, and adjustable release characteristics. This work provides a novel, cost-effective excipient platform for both immediate and controlled release formulations, with significant implications for local pharmaceutical manufacturing in resource-limited settings.

Keywords: Compressible starch; Highly functional starch; Directly compressible starch.

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1. Introduction

Pharmaceutical excipients play a critical role in determining the manufacturability, stability, and performance of solid dosage forms. Beyond their traditionally “inert” role, excipients influence powder flow, compressibility, tablet mechanical strength, and drug release behavior. The increasing complexity of drug molecules and formulations has placed greater demands on excipient functionality, driving the search for multifunctional excipients capable of serving multiple roles simultaneously—such as filler, binder, and disintegrant—within a single formulation [1, 2]. Multifunctional excipients can reduce formulation

complexity, improve processing robustness, and lower manufacturing costs.[3]

Starch is one of the most widely used natural excipients in pharmaceutical technology. It is biodegradable, biocompatible, abundant, and inexpensive, making it an attractive alternative to synthetic polymers [4]. However, native starches typically exhibit poor flowability, low compressibility, and variable performance during tableting, which limits their use in direct compression—a widely preferred method in modern tablet manufacturing due to its simplicity, cost-effectiveness, and reduced processing steps [5]. To overcome these limitations, chemical and physical modifications of starch have been extensively explored to enhance its functionality as a pharmaceutical excipient [6-8].

Among chemical modification strategies, carboxymethylation has received considerable attention because it introduces carboxymethyl groups into the starch backbone, increasing hydrophilicity, water uptake, and swelling power [9, 10,11]. Carboxymethyl starch derivatives have been used as disintegrants, fillers, and stabilizers in various oral dosage forms, and have been shown to perform competitively with conventional excipients such as sodium starch glycolate and microcrystalline cellulose [12-14].

Another powerful strategy for functional enhancement is cross-linking, which involves the introduction of covalent or ionic linkages between starch chains. Cross-linking enhances matrix rigidity, mechanical strength, and resistance to enzymatic or thermal degradation [15]. By combining carboxymethylation with cross-linking, it is possible to simultaneously increase hydrophilicity and structural stability, yielding materials with unique performance characteristics [16]. While individual modification approaches have been well documented, their combined application to tapioca starch and systematic evaluation of the resulting multifunctionality has received limited attention.

Tapioca starch, derived from *Manihot esculenta* (cassava), is widely cultivated in many tropical regions. It is inexpensive, renewable, and has a high starch yield with good purity [17]. Compared with maize and potato starches, tapioca starch granules are relatively uniform, with low lipid and protein content—features that make them highly suitable for chemical modification [18]. Despite these advantages, tapioca starch remains underutilized in pharmaceutical applications, especially in low- and middle-income countries where it is locally available. Its poor native flow properties, low bulk density, and weak mechanical behavior under compression have limited its use primarily to pregelatinized or blended forms [19]. Consequently, developing cost-effective modification approaches to unlock the pharmaceutical potential of tapioca starch represents a significant and underexplored opportunity. Hydrochlorothiazide, a thiazide diuretic commonly used in the management of hypertension, is a poorly compressible drug typically formulated using direct compression with robust filler–binders [20]. This model drug provides an excellent platform to evaluate excipient functionality, particularly powder flow, compressibility, tablet strength, and dissolution behavior. A critical factor determining the performance of carboxymethyl starch is the degree of substitution (DS). Studies have shown that moderate DS values (0.2–0.6) often produce optimal excipient properties by increasing hydration and compressibility without compromising structural stability [21]. Excessive substitution, however, may lead to excessive swelling, loss of compactability, or uncontrolled gelation [22]. Likewise, the extent of cross-

linking modulates matrix density and hydration kinetics. At low levels, cross-linking can improve tablet strength while maintaining disintegration, whereas high levels can produce sustained-release matrices [23, 24]. Several studies have evaluated modified starches from different botanical sources for pharmaceutical use, including maize, yam, potato, rice, and cassava [25-28].

This study therefore addresses a critical gap by developing and characterizing carboxymethylated and cross-linked tapioca starch as a multifunctional excipient. The overall goal is to establish a cost-effective, locally sourced, and tunable excipient platform that can support both immediate- and controlled-release applications, offering a viable alternative to more expensive imported excipients.

2. Materials & Methods

2.1. Materials

Fresh root tubers of tapioca (*Manihot esculenta*) were obtained from Ipata Market, Kwara State, Nigeria (8.4993° N, 4.5616° E). Lactose (Milkaut SA, Argentina), ethanol (96%) and acetone (LobaChemie, India), sulfuric acid (BDH Analar, England), glacial acetic acid (Guangdong Guanghua, China), ammonia solution (Oxford, India), acetic anhydride (Sigma-Aldrich, Germany), 2-naphthol (BDH Analar, England), deionized water (Peace Standard, Nigeria), nutrient broth (Acumedia, USA), and sodium monochloroacetate (Sigma-Aldrich, Germany) were used. Commercial hydrochlorothiazide (HCT) 25 mg tablets were obtained from Tuyil Pharmaceutical Industries (Nigeria). All chemicals and reagents were of analytical grade and used without further purification.

2.2. Extraction of Native Tapioca Starch

Tapioca starch was extracted using a modified wet milling method based on previous studies [29,30]. Briefly, 50 g of peeled and sliced tubers were soaked in 10 L of distilled water at room temperature, milled, and filtered through double-fold cheesecloth. The filtrate was allowed to stand to sediment the starch, after which the supernatant was decanted. The starch slurry was centrifuged at 4000 rpm for 5 minutes (Thermo Electron IEC FL40R, France). The wet starch cake was oven-dried at 45 °C (Nurve FN055, Germany), ground (Super Master Co. Ltd. SMB-3377), sieved through a 100-mesh sieve, and stored in an airtight container at room temperature until use.

2.3. Preparation of Carboxymethyl Tapioca Starch (CMTS)

Carboxymethylation of tapioca starch was carried out using the organic slurry method as described by Lawal et al. [31]. Native starch (20 g) was suspended in 400

mL of 2-propanol, and 40 mL of aqueous NaOH (1.0, 1.5, 2.0 or 5.0 M) was added. The suspension was stirred at 40 °C for 10 minutes, followed by addition of 160 mL sodium monochloroacetate (2.0 M). The reaction was allowed to proceed for 2, 4, 6 or 8 hours under continuous stirring. The pH was then adjusted to 5.0 using 50% glacial acetic acid. The product was filtered, washed with 80% aqueous ethanol until neutral pH, dried at 50 °C for 6 hours, passed through a 100-mesh sieve, and stored.

2.4. Determination of Degree of Substitution

The degree of substitution (DS) of CMTS was determined based on sodium content using flame atomic absorption spectrometry (AAS) as previously described [32,33]. Fifty milligrams of the sample were digested with 4 mL of concentrated nitric acid on a hot plate, and the digest was made up to 100 mL with deionized water. Sodium content was determined at 589 nm using an air–acetylene flame. DS was calculated using the following equation:

$$DS = (162 \times \%Na) / (2300 - 80 \times \%Na)$$

where 162 represents the molecular weight of the anhydroglucose unit.

2.5. Determination of Reaction Efficiency

Reaction efficiency was determined according to Lawal et al. [34] as follows:

$$RE (\%) = (DS / D_{st}) \times 100$$

where D_{st} is the theoretical degree of substitution determined based on the limiting reagent (NaOH or sodium monochloroacetate).

2.6. Preparation of Cross-linked Carboxymethyl Tapioca Starch (cCMTS)

Cross-linking of CMTS was performed according to previously reported methods [35]. CMTS prepared at each NaOH concentration (1.0, 1.5, 2.0 and 5.0 M) was dispersed in distilled water at 40% w/w and adjusted to pH 10.2 with 1 M NaOH. Sodium trimetaphosphate (1.5% w/w dry starch basis) was added and the suspension maintained at 45 °C for 2 hours with oscillation. The pH was then adjusted to 6.5 using 0.5 M HCl. The product was washed four times with distilled water, filtered, oven-dried at 45 °C for 12 hours, sieved through a 100-mesh sieve, and stored as cCMTS.

2.7. Tablet Formulation

2.7.1. Placebo tablets

CMTS and cCMTS were compressed directly into 150 mg tablets on a rotary tableting machine at 1-ton compression force. Each batch contained 50 tablets. The formulations are shown in Tables 1a and 1b.

Table 1a. Composition of placebo CMTS tablets.

Ingredient	Batch 1 (1 M)	Batch 2 (1.5 M)	Batch 3 (2 M)	Batch 4 (5 M)
CMTS (mg)	150	150	150	150

Table 1b. Composition of placebo cCMTS tablets.

Ingredient	Batch 1 (1 M)	Batch 2 (1.5 M)	Batch 3 (5 M)
cCMTS (mg)	150	150	150

2.7.2. Hydrochlorothiazide (HCT) tablets

HCT (25 mg) was incorporated with CMTS or cCMTS (125 mg) and mixed thoroughly prior to compression. Each batch contained 50 tablets (Tables 2 and 3).

Table 2. Composition of CMTS + HCT tablets.

Ingredient	Batch 1 (1 M)	Batch 2 (1.5 M)	Batch 3 (2 M)	Batch 4 (5 M)
CMTS (mg)	125	125	125	125
HCT (mg)	25	25	25	25

Table 3. Composition of cCMTS + HCT tablets.

Ingredient	Batch 1 (1 M)	Batch 2 (1.5 M)	Batch 3 (5 M)
cCMTS (mg)	125	125	125
HCT (mg)	25	25	25

2.8. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of NTS, CMTS, cCMTS and HCT were recorded using a Bruker Invenio FTIR spectrophotometer (Karlsruhe, Germany). Five milligrams of sample were blended with potassium bromide, pressed into pellets, and scanned between 4000 and 500 cm^{-1} at 4 cm^{-1} resolution [36].

2.9. X-Ray Diffraction (XRD)

Crystallinity patterns of NTS, CMTS and cCMTS were analyzed using a Bruker D8 Advance X-ray diffractometer (Karlsruhe, Germany) operated at 40 kV and 40 mA with Cu K α radiation over a 2θ range of 5–45° [37].

2.10. Powder Flow Properties

Angle of repose was measured using the fixed funnel method [38]. Bulk and tapped densities were determined in a 10 mL graduated cylinder. Carr's index and Hausner's ratio were calculated using standard equations:

Carr's index (%) = $(D_t - D_b) / D_t \times 100$
 Hausner's ratio = D_t / D_b
 where D_b is bulk density and D_t is tapped density.

2.11. Tablet Evaluation

Weight variation was determined using 20 tablets in accordance with USP specifications [39]. Tablet hardness was measured using an Erweka hardness tester, and thickness was measured using a digital Vernier caliper. Friability was determined in an Erweka friabilator at 25 rpm for 4 minutes:

$$\text{Friability (\%)} = (W_1 - W_2) / W_1 \times 100$$

Disintegration time was assessed using an Erweka ZT disintegration tester in 900 mL distilled water at 37 ± 0.5 °C. Swelling capacity was determined by weighing tablets before and after immersion in water:

$$\text{Swelling capacity (\%)} = (W_2 - W_1) / W_1 \times 100$$

where W_1 and W_2 are tablet weights before and after swelling, respectively [40].

2.12. Drug Content and Dissolution Testing

Drug content uniformity was determined spectrophotometrically. Ten tablets were crushed, and powder equivalent to 1 mg of HCT was dispersed in 0.1 N HCl, shaken for 15 minutes, diluted to 100 mL, and filtered (Whatman No. 1). Absorbance was measured at 270 nm against a standard calibration curve [41].

Dissolution testing was carried out using USP Apparatus II (paddle method) at 37 ± 0.5 °C and 50 rpm in 900 mL of 0.1 N HCl [42]. Five-milliliter aliquots were withdrawn at predetermined intervals and replaced with fresh medium. Samples were filtered through 0.45 µm membrane filters and analyzed at 270 nm using a UV-Vis spectrophotometer. Drug release (%) was calculated using:

$$\% \text{ Content} = (AT / AS) \times 100$$

where AT and AS are the absorbances of the test and standard solutions, respectively.

2.13. Statistical Analysis

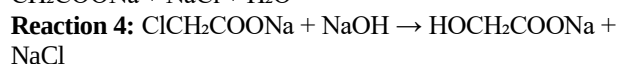
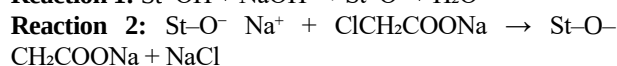
All measurements were performed in triplicate, and results are expressed as mean $\pm$ standard deviation. Statistical comparisons were made using one-way

analysis of variance (ANOVA) with Infostat v2009 software (Córdoba, Argentina). Differences were considered statistically significant at $p < 0.05$ [43].

3. Results & Discussion

3.1. Carboxymethylation Reactions

The carboxymethylation of tapioca starch occurred via alkalization and subsequent carboxymethylation. During alkalization, sodium hydroxide reacted with tapioca starch to form sodium starchate (Reaction 1). The sodium starchate then reacted with sodium monochloroacetate to yield sodium carboxymethyl starch (Reaction 2). The overall reaction is shown in Reaction 3, while a side hydrolysis reaction (Reaction 4) led to the formation of sodium glycolate.



3.2. Powder Flow Properties

The powder flow properties of native tapioca starch (NTS) are shown in Table 4. The bulk density was 0.548 ± 0.01 g/mL and tapped density was 0.791 ± 0.01 g/mL. The angle of repose was $30.9 \pm 0.03^\circ$, Carr's index was 30.7 ± 0.01 , and Hausner's ratio was 1.443 ± 0.31 .

The flow properties of carboxymethylated tapioca starch (CMTS) prepared at different NaOH concentrations are summarized in Table 5. The angle of repose values ranged from 26.7° to 28.1° , Carr's index from 13.26% to 22.13%, and Hausner's ratio from 1.153 to 1.284.

3.3. Degree of Substitution and Reaction Efficiency

The degree of substitution and reaction efficiency of CMTS at varying NaOH concentrations are shown in Table 6. The highest degree of substitution (0.44 ± 0.22) and reaction efficiency (1.34 ± 0.78) were obtained at 1.5 M NaOH.

Table 4. Flow properties of native tapioca starch (n = 3).

Powder	Bulk density (g/mL)	Tapped density (g/mL)	Angle of repose (°)	Carr's index (%)	Hausner's ratio
NTS	0.548 ± 0.01	0.791 ± 0.01	30.9 ± 0.03	30.7 ± 0.01	1.443 ± 0.31

Table 5. Flow properties of CMTS at different NaOH concentrations (n = 3).

Batch (NaOH)	Bulk density (g/mL)	Tapped density (g/mL)	Angle of repose (°)	Carr's index (%)	Hausner's ratio
1 M	0.714 ± 0.03	0.833 ± 0.01	28.1 ± 0.1	14.29 ± 0.1	1.167 ± 0.21
1.5 M	0.667 ± 0.01	0.769 ± 0.03	27.1 ± 0.4	13.26 ± 0.3	1.153 ± 0.14
2 M	0.667 ± 0.01	0.769 ± 0.03	27.4 ± 0.7	13.26 ± 0.1	1.153 ± 0.38
5 M	0.556 ± 0.04	0.714 ± 0.07	26.7 ± 0.3	22.13 ± 0.7	1.284 ± 0.7

Table 6. Degree of substitution and reaction efficiency (n=3).

Batch (NaOH)	Degree of substitution	Reaction efficiency
1 M	0.15 ± 0.05	0.69 ± 0.25
1.5 M	0.44 ± 0.22	1.34 ± 0.78
2 M	0.13 ± 0.02	0.35 ± 0.08
5 M	0.12 ± 0.07	0.33 ± 0.06

3.4. Cross-Linked Carboxymethylated Tapioca Starch

The flow properties of cross-linked CMTS (cCMTS) are shown in Table 7. Bulk density ranged from 0.556 ± 0.07 g/mL to 0.714 ± 0.41 g/mL and tapped density from 0.625 ± 0.03 g/mL to 0.833 ± 0.11 g/mL. Angles of repose were between 24.9° and 27.9° .

Table 7. Flow properties of cross-linked CMTS (n=3).

Batch (NaOH)	Bulk density (g/mL)	Tapped density (g/mL)	Angle of repose (°)	Carr's index (%)	Hausner's ratio
1 M	0.556 ± 0.07	0.625 ± 0.03	24.9 ± 0.01	11.04 ± 0.06	1.124 ± 0.61
1.5 M	0.625 ± 0.10	0.714 ± 0.05	26.3 ± 0.90	12.47 ± 0.21	1.142 ± 0.57
2 M	0.625 ± 0.08	0.714 ± 0.14	26.3 ± 0.41	12.47 ± 0.11	1.142 ± 0.38
5 M	0.714 ± 0.41	0.833 ± 0.11	27.9 ± 0.08	14.29 ± 0.09	1.167 ± 0.03

3.5. Tablet Properties

Tablet characteristics for CMTS, CMTS-HCT, cCMTS, and cCMTS-HCT are presented in tables 8–9.

In tables 8 and 9, all batches of placebo CMTS and CMTS-HCT granules formed acceptable tablets and disintegrate within the official stipulate time of 30 minutes.

In table 10 and 11, the tablets evaluation of placebo cCMTS and cCMTS-HCT granules follow similar pattern as

Table 8. Tablet properties of CMTS (n = 3) placebo.

Batch	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kgf)	Friability (%)
1 M	149 ± 1.01	8.07 ± 0.21	3.90 ± 0.10	8.67 ± 0.56	0.3
1.5 M	147.3 ± 2.50	8.00 ± 0.10	3.93 ± 0.06	8.33 ± 1.15	0.2
2 M	149 ± 1.10	7.97 ± 0.06	3.90 ± 0.10	6.97 ± 1.00	0.2
5 M	148 ± 2.32	7.93 ± 0.12	3.93 ± 0.12	12.33 ± 0.58	0.3

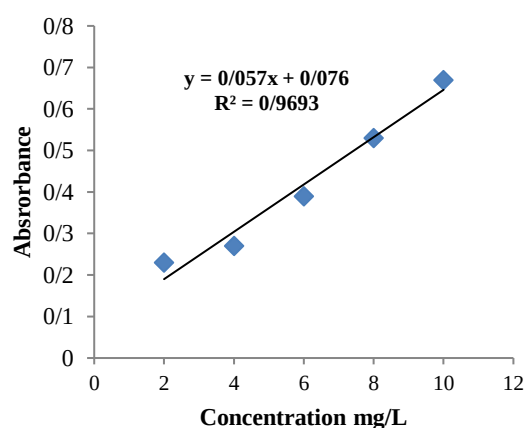
Table 9. Tablet properties of CMTS containing 25 mg hydrochlorothiazide (HCT) (n = 3).

Batch	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kgf)	Disintegration Time (min)	Friability (%)
1 M	148.3 ± 1.51	8.00 ± 0.20	3.90 ± 0.10	6.67 ± 0.78	8 ± 0.10	0.7
1.5 M	149.6 ± 0.63	8.03 ± 0.15	3.87 ± 0.06	6.33 ± 0.58	14 ± 0.10	0.3
2 M	149.3 ± 1.21	8.07 ± 0.12	3.93 ± 0.06	5.67 ± 0.11	16 ± 0.10	0.3
5 M	149.3 ± 1.21	8.03 ± 0.15	3.87 ± 0.03	10.67 ± 0.37	30 ± 0.10	0.5

observed for the CMTS and CMTS-HCT tablets (tables 8 and 9) but with much higher compactness measured as hardness and lower disintegration time

3.6. UV Spectrophotometric Analysis

The maximum absorbance of hydrochlorothiazide was observed at 270 nm with an absorbance of 0.42. The calibration curve showed a linear relationship with an $R^2 = 0.9693$ and a regression equation of ($y = 0.057x + 0.076$) (Fig. 1).

**Figure 1.** Standard calibration curve of hydrochlorothiazide at 270nm using UV spectrophotometer.

3.7. Dissolution Profile

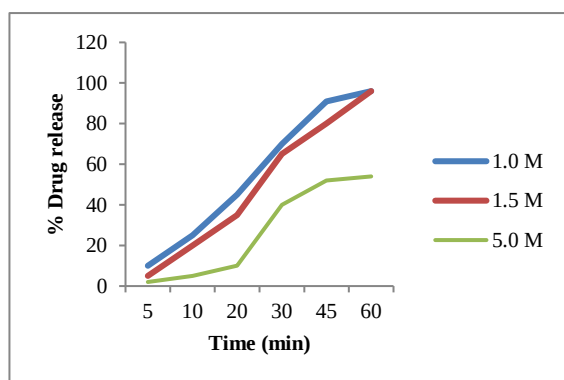
The dissolution profile of cCMTS tablets containing HCT is presented in and Figure 2. Batches prepared at 1 M, 1.5 M and 5 M NaOH concentrations showed mean percentage drug release after 45 min as 84 %, 80 % and 52 % respectively. While considering the drug release after 60 min. 91.43 %, 98 % and 58 % respectively.

Table 10. Tablet properties of cross-linked CMTS (n=3).

Batch	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kgf)	Friability (%)
1 M	149 ± 1.73	8.03 ± 0.17	3.90 ± 0.17	10.33 ± 0.58	0.1
1.5 M	147.3 ± 0.64	8.00 ± 0.10	3.80 ± 0.17	9.10 ± 1.00	0.3
2 M	148 ± 1.01	8.07 ± 0.15	3.87 ± 0.15	9.67 ± 0.58	0.1
5 M	148.3 ± 0.66	8.03 ± 0.21	3.93 ± 0.06	14.33 ± 0.67	0.2

Table 11. Tablet properties of cross-linked CMTS containing 25 mg HCT (n = 3).

Batch	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kgf)	Disintegration time (min)	Friability (%)
1 M	149.7 ± 0.61	7.97 ± 0.21	3.96 ± 0.05	9.50 ± 0.50	6 ± 0.01	0.5
1.5 M	149.3 ± 0.63	8.00 ± 0.17	3.93 ± 0.05	8.67 ± 0.29	7 ± 0.20	0.3
2 M	149.7 ± 0.61	7.97 ± 0.21	3.90 ± 0.10	7.83 ± 0.58	7 ± 0.01	0.3
5 M	149.3 ± 1.23	8.00 ± 0.17	3.93 ± 0.11	12.00 ± 0.50	20 ± 0.22	0.4

**Figure 2.** Dissolution profile graphs cCMTS tablets containing HCT.

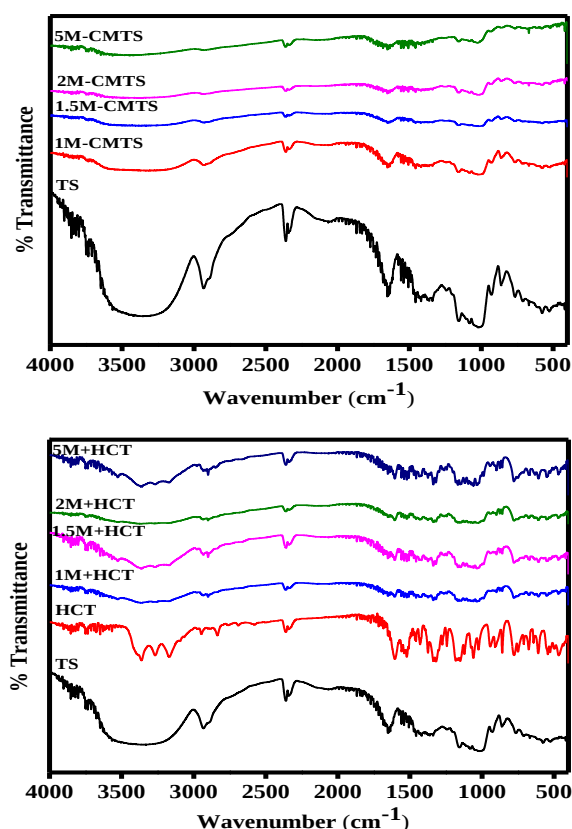
3.8. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of native tapioca starch and CMTS at different NaOH concentrations are presented in Figures 3a–b. Characteristic peaks were observed at 3366 cm^{-1} (–OH stretching), 2929 cm^{-1} (C–H stretching), and 1157, 1087, and 1011 cm^{-1} (C=O vibrations). Carboxylic stretching (3000–2800 cm^{-1}) was more pronounced in CMTS than in native starch. No new peaks were observed after drug incorporation.

For cCMTS at 1.5 M NaOH, increased stretching was observed at 3426 cm^{-1} , attributed to cross-linking between phosphate and hydroxyl groups. A stronger absorption at 1050–970 cm^{-1} confirmed P–O–C bond formation.

3.9. X-Ray Diffraction (XRD)

The XRD patterns of tapioca starch and cCMTS are shown in Figure 4. Sharp diffraction peaks were observed at 15°, 26°, 35°, and 38°, corresponding to an A-type crystalline structure. The modified starches retained the same crystalline pattern as the native starch, indicating that cross-linking did not alter the crystal type.

**Figure 3.** (a) FTIR spectra of TS, 1M-CMTS, 1.5M-CMTS, 2M-CMTS and 5M-CMTS and (b) FTIR spectra of TS, HCT, 1M-cCMTS+HCT, 1.5M-cCMTS+HCT, 2M-cCMTS+HCT and 5M-cCMTS+HCT.

3.10. Statistical Analysis

The result was considered to be statistically significant as the p value was <0.05. The mean $\pm$ SD of the Degree of substitutions (DS) was used.

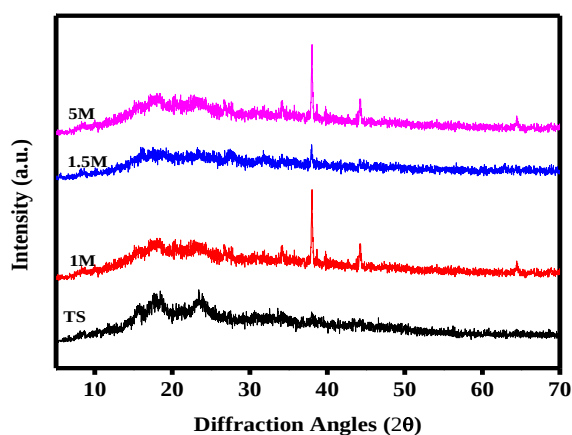


Figure 4. XRD pattern of tapioca starch (TS).

This study demonstrates that controlled chemical modification of tapioca starch through carboxymethylation and subsequent cross-linking leads to a multifunctional excipient platform with tunable physicochemical and functional properties suitable for oral solid dosage formulations. The findings provide new evidence that a single native starch source can be tailored to meet diverse formulation needs—ranging from immediate to controlled release—through systematic alteration of its substitution and cross-linking profile.

The reaction pathway of carboxymethylation observed in this work mirrors classical base-catalyzed substitution, where sodium hydroxide activates the hydroxyl groups of the starch backbone to form alkoxide intermediates that subsequently react with sodium monochloroacetate. Notably, the degree of substitution (DS) and reaction efficiency increased to a maximum at 1.5 M NaOH before declining at higher concentrations. This non-linear response reflects the dual role of alkali: facilitating activation and nucleophilic substitution at optimal concentrations, while promoting competing hydrolysis of monochloroacetate at excessive levels, leading to the formation of sodium glycolate. Similar substitution profiles have been reported for maize, rice, and potato starch systems [44–46].

The DS value of 0.44 obtained at 1.5 M NaOH is pharmaceutically relevant. Moderate substitution levels are known to induce functional modifications such as improved hydration, flow, and compressibility, without causing excessive structural disruption or gel formation [47,48]. This balance is crucial for ensuring both manufacturability and performance of the resulting excipient.

Native tapioca starch displayed poor flowability, as indicated by high Carr's index and Hausner's ratio values. After carboxymethylation, these values decreased significantly, and cross-linking further improved flow to levels comparable to those required for direct compression. These improvements likely stem from changes in surface

chemistry and granule morphology, which reduce interparticle cohesion and enhance packing efficiency. Previous work on modified cassava and maize starches similarly reported improved powder flow due to decreased particle roughness and increased apparent density [49–52]. Improved flow is not merely a technical convenience but a critical attribute for robust pharmaceutical manufacturing. Flowable excipients ensure uniform die filling, tablet weight consistency, and reduced manufacturing variability. Achieving such flow enhancement from a locally sourced, inexpensive material like tapioca starch underscores the practical significance of the modification strategy used in this study.

The improved mechanical strength of tablets formulated with modified starch reflects enhanced plastic deformation and bonding capacity. Cross-linked carboxymethylated tapioca starch (cCMTS) produced tablets with higher hardness and lower friability than native starch, indicating better inter- and intraparticle bonding during compression. This behavior is attributable to the presence of carboxymethyl and phosphate groups, which provide additional hydrogen bonding and ionic interactions, strengthening the tablet matrix. Similar trends have been reported with cross-linked maize and yam starches [53–55]. Friability values for all formulations remained below 1%, meeting pharmacopeial standards and reinforcing the suitability of the modified starch as a filler–binder for direct compression. This is particularly notable because many natural starches require co-processing with synthetic binders to achieve such mechanical performance. The ability of cCMTS to provide sufficient compactability without additional binders represents an important advancement for excipient design.

FTIR analysis revealed the retention of characteristic starch peaks after carboxymethylation and cross-linking, with no new peak's indicative of drug–excipient interaction. The intensified P–O–C vibration band confirmed successful cross-linking, while preservation of hydroxyl and carbonyl stretches indicated that the modification was localized primarily in the amorphous domains. XRD data corroborated this finding, demonstrating that the A-type crystalline structure of tapioca starch was retained.

This selective modification of amorphous regions while preserving the crystalline core is advantageous for excipient functionality because it enhances hydration, flow, and compressibility without compromising the structural predictability of the polymer [56–59]. Moreover, the absence of chemical interaction with hydrochlorothiazide confirms the chemical inertness of the modified excipient—a critical requirement for pharmaceutical compatibility.

One of the most novel findings of this study is the demonstration that the degree of carboxymethylation and extent of cross-linking can be used to modulate drug release kinetics from the same excipient platform. Batches modified at lower alkali concentrations (1.0–1.5 M) exhibited rapid

drug release exceeding 90% within 45 minutes, which aligns with the behavior expected of hydrophilic disintegrants and filler-binders in immediate release formulations. By contrast, tablets prepared with starch modified at 5 M NaOH showed markedly slower dissolution, consistent with the formation of a denser, more rigid matrix with reduced water penetration.

This tunable functionality allows the same excipient system to be applied for both immediate-release and controlled-release dosage forms, depending on the processing parameters. Such versatility is rarely achieved with a single natural excipient and represents a clear point of innovation. Comparable approaches with modified maize and rice starches typically target one functionality at a time—either disintegration or matrix formation [60–62]. The current findings therefore extend the application space for tapioca starch as a multifunctional excipient.

Multifunctional excipients simplify formulation design by reducing the number of excipients required, improving process efficiency, and enhancing cost-effectiveness. This is particularly relevant in settings where imported pharmaceutical excipients are expensive or subject to supply chain vulnerabilities. Tapioca starch is abundant in many tropical countries, and its chemical modification is relatively simple and scalable. By demonstrating excipient functionality on par with, and in some respect's superior to, established materials such as microcrystalline cellulose, this study provides a pathway for developing **cost-effective**, locally sourced excipients that can support domestic pharmaceutical manufacturing.

The structural stability observed after modification further underscores the formulation reliability of this excipient. Unlike some modified polysaccharides that undergo irreversible gelation or loss of crystallinity, cCMTS retains desirable physical characteristics while gaining functional advantages. This aligns with current trends in excipient science that emphasize sustainability, multifunctionality, and adaptability [63–65].

Previous studies on modified starches have demonstrated improvements in one or two performance attributes—most commonly flow enhancement or disintegration [66–67]. The present study advances the field by systematically demonstrating how the extent of chemical modification can be used as a design variable to tune multiple functional properties in a single material system. This dual-functional behavior (as both disintegrant and matrix former) sets cCMTS apart from most starch-based excipients reported to date.

These findings not only support the feasibility of using tapioca starch as a multifunctional excipient but also provide a conceptual framework for engineering excipient performance through chemical modification. Such frameworks are essential for advancing rational formulation design, especially in resource-limited settings where locally sourced excipients offer economic and strategic advantages.

4. Conclusion

In conclusion, this study successfully demonstrated that controlled carboxymethylation and cross-linking significantly improved the physicochemical and functional properties of tapioca starch, transforming it into a versatile, multifunctional excipient suitable for pharmaceutical tablet formulation. The modified starch exhibited enhanced powder flow, compressibility, mechanical strength, and tunable drug release behavior, with optimal performance achieved at moderate degrees of substitution. Structural analyses confirmed the chemical modification of the amorphous domains while preserving the crystalline framework, ensuring excipient stability and compatibility with hydrochlorothiazide. These findings highlight the potential of locally sourced tapioca starch as a cost-effective and sustainable alternative to conventional synthetic excipients for both immediate- and controlled-release formulations. This work provides a practical framework for excipient design from natural polymers, supporting innovation in resource-limited pharmaceutical manufacturing settings.

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Conflict of interest

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Ethics statement

Not applicable.

Author contribution

Abiodun Oyetunji Shittu: Conception and design of the study.

Abdulrasheed Sidiq Olatunde: acquisition of data.

Adeola Tawakalitu Kola-Mustapha: drafting of article

Njinga Ngaitad Stanilaus: data analysis.

Sa'ad Toyin Abdullahi: revising the article for intellectual content.

Using AI declaration

The authors declare that no artificial intelligence (AI) tools or technologies were used in the writing, editing, or preparation of this manuscript.

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