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Fabrication and Release Properties of Naproxen-loaded *Dioscorea dumetorum* (Bitter yam) Starch Biodegradable Nanoparticles

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ABSTRACT: The growing demand for polymers to improve drug delivery profiles (particularly for poorly aqueous soluble drugs) has prompted a global search for new polymers. The drug loading, dissolution, and release characteristics of trifoliate yam (*Dioscorea dumetorum*) starch, a biodegradable polymer, were evaluated using naproxen as the model drug. Trifoliate starch nanoparticles (TSNP) were created by acid hydrolysis of trifoliate native starch (TNS) with H_2SO_4. In contrast, carboxymethylated trifoliate starch nanoparticles (CTSNP) were created by reacting the TSNP with sodium hydroxide and monochloroacetic acid. Scanning electron microscopy analysis revealed that TSNP were formed by acid hydrolysis. Modification of the TSNP resulted in a significant particle size reduction (86.5 ± 5.60 nm) and changes in the morphology of these starch forms compared to the native trifoliate starch (1616.0 ± 0.54 nm). The addition of a carboxylate functional group to the TSNP molecule as a means of modification was confirmed by significant peaks in the Fourier transform Infrared spectroscopy's 1600-1300 cm^{-1} absorption band region. All of the starch forms, TNS, TNSP and CTNSP demonstrated significant drug loading capacity and efficiency (86.7%, 86.4%, and 84.9%), respectively. The TNS demonstrated delayed naproxen release, whereas the TSNP and CTSNP demonstrated a biphasic release profile (immediate and sustained release). Naproxen release kinetics from most formulations followed the Korsmeyer-Peppas model of non-Fickian diffusion through the polymeric matrix. A loading time of one hour was found to optimize loading efficiency. The starch nanocarriers developed in this study can be used as vehicles to enhance, control, and prolong the release of poorly soluble drugs.

KEYWORDS: **Starch nanoparticles; Carboxymethylated starch nanoparticles; Dioscorea dumetorum; Naproxen; Drug release studies.**

1. INTRODUCTION

Nanotechnology in novel drug delivery systems (NDDSs) can improve the solubility of poorly soluble drugs for optimal delivery; control or extend the drug's dissolution rate, improving systemic bioavailability; ensure targeted drug delivery to anatomic sites in the body; and improve drug permeability into or across epithelial and endothelial cells [1-3]. Polymer-based nanoparticle (NP) formulations promote drug load efficiency, dose reduction, side effects and toxicity reduction, and predetermined drug release profiles [1,3-6].

Plants contain biodegradable starch. It is cheap, non-toxic, and used in food, pharmaceuticals, and other industries. Starch has unique properties that make it a useful pharmaceutical excipient. It targets drugs and delivers complex molecules to their target sites in the body [3,7,8]. Native starch, extracted from plants, must be modified physically, enzymatically, or chemically to meet pharmaceutical, food, textile, and cosmetic industry standards [9-12]. Native starch structure can be altered using multiple modifications [8].

Nanocarriers require polymers like starches as structural backbones due to their excellent properties. After being made, starch NPs still have the renewability, biodegradability, biocompatibility, eco-friendliness, and nontoxicity of their original starch [4,13-15]. Nanoparticles or starch nanoparticles (SNP) have better mechanical properties, water absorption capacity and solubility, diffusion drawbacks, surface features, and biological membrane penetration rates than native starch. Additionally, SNPs are typically smaller and have one

dimension in the nano-range [2,14-17]. SNP can be made by acid hydrolysis and enzyme debranching, nanoprecipitation, thermosensation, sonication, and milling. These methods alone or together can reduce processing time, particle size, SNP production yield, encapsulation efficiency, and drug loading capacity [14,17-19]. Already prepared SNP can be modified to increase their use or functionality. Enzymatic, chemical, grafting, and physical modifications can be applied to a synthesised SNP. SNP's initial hydrophilic/hydrophobic nature can be modified as appropriate to improve their functionality, transforming them into amphiphilic NPs. This modification the interfacial adsorption, mechanical strengths, dispersibility, and thermal stability of nanoparticle-based systems [14,20-23]. In contrast to other NPs, such as poly(lactic-co-glycolic acid) (PLGA) NPs, which are typically synthesized using organic solvents that may not be environmentally friendly with significant temperature, which can damage sensitive, thermolabile active agents and cause the degradation of the PLGA chains themselves, the green synthesis of starch NPs using enzymatic and mechanical methods with low or no temperature results in the production of drug nanocarriers that are more biocompatible, biodegradable, non-toxic, affordable, and environmentally friendly. The high biocompatibility of these starch NPs instils confidence in their potential for medical applications [3,24,25].

Trifoliate starch, extracted from *Dioscorea dumetorum* Pax (bitter yam) tubers, is a staple food in tropical Africa and is used in pharmaceuticals [26,27]. Adetunji et al. [28] found that trifoliate starch can produce oral solid-dosage forms with robust mechanical properties and extend the disintegration and dissolution period. This study used trifoliate yams because they are underutilized in industrial starch production and commercially under processed. Bitter yam is a little-studied tuber crop due to occasional reports of poisoning and post-harvest hardening, which reduces its pasting properties and starch productivity. Therefore, further research on this trifoliate yam is needed to improve its local and industrial applications. Creating this excipient will reduce African countries' dependence on expensive and scarce imported starches, which can be exported as pharmaceutical excipients in their native or modified forms [26,27,29,30].

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain and inflammation [31,32]. Although this drug has appealing pharmacological properties, such as good analgesic and anti-inflammatory properties with some gastrointestinal problems, [33] its poor water-solubility is a significant issue in developing formulations or dosage forms. Its low solubility and high permeability make it a Biopharmaceutics Classification System (BCS) class II drug. Their rate-limiting step is solubility, which causes low bioavailability in systemic circulation due to low dissolution in gastric or intestinal fluids before absorption [34]. Thus, this study creates and chemically modifies starch NPs from trifoliate yam starch (*Dioscorea dumetorum*) to determine their physicochemical properties and naproxen release profiles.

2. MATERIALS AND METHODS

2.1. Materials

SwissPharma, Nigeria Ltd generously donated Naproxen base BP. Trifoliate starch was prepared in the laboratory from *Dioscorea dumetorum* yam tubers obtained from the local market. Analytical-grade chemicals such as H_2SO_4, 2-propanol, monochloroacetic acid, glacial acetic acid, and 80% ethanol were used to synthesise and modify starch NPs.

2.2. Methods

2.2.1. Extraction of Dioscorea dumetorum starch

Freshly harvested *Dioscorea dumetorum* yam tubers were milled wet using a laboratory blender (Panasonic Mixer and Grinder MX-AC400) after being washed with distilled water, peeled, and processed. The chaff was removed from the slurry using a calico cloth, and the filtrate was allowed to settle before decanted. The starch sediment was washed continuously until the supernatant was colourless. The wet bulk was dried in a hot air oven (Gallenkamp BS Oven 250) for 48 hours at 50 °C. The dried yam starch was ground into a fine powder in a lab mill and screened through a 120-mesh sieve. After that, the powder was measured and stored in airtight containers until needed [2].

2.2.2. Synthesis of starch nanoparticles

The trifoliate yam starch NPs were formed using the procedure outlined by Huang et al. [35] and modified by Odeniyi et al. [5]. In a flat-bottomed flask, 3.16M H_2SO_4 was combined with trifoliate yam starch powder at a concentration of 20 g/100 mL (20.0% w/v). Employing a temperature-controlled shaker (New Brunswick Scientific, Incubator shaker), the suspension was constantly mixed at 100 rpm at 40 °C. The suspension was continuously washed in distilled water until a pH of 5 was reached after 5 days of hydrolysis. The attained starch NP suspension was vacuum freeze-dried (CHRIST/ALPHA 1-2 LD plus dryer) and stored in an airtight vessel.

2.2.3. Modification of starch nanoparticles

The carboxymethylation of trifoliate starch NPs followed the procedure outlined by Kittipongpatana et al. [36] for starch modification and was further modified with the method by Odeniyi et al. [6]. To achieve different degrees of substitution (DS) of the modified starch NPs (Table 1), 2-propanol was used to produce 1.4 and 2.9 M monochloroacetic acid, and then 5 g of the manufactured starch NP was distributed into 15 mL of the two different concentrations of the monochloroacetic acid with constant mixing. 2.5 mL of Aq. NaOH (0.5 and 1.5 M) solution was added to each mixture and heated to 50 °C for 30 minutes employing a magnetic stirrer. The chemical reaction was stopped by neutralizing it with glacial acetic acid. The powder product was washed in 80% ethanol after decanting the liquid supernatant. The resulting modified starch was oven-dried at 50 °C for 6 hours. The dried powder was broken into smaller pieces before being placed in an airtight vessel.

Table 1. Production parameters of carboxymethylated trifoliate starch NPs (CTSNP) from trifoliate starch NPs (TSNP).

Starch sample	Code	Sample quantity (g)	Conc. of MCA (M)	Volume of MCA (mL)	Conc. Of NaOH (M)	Volume of NaOH (mL)	Temp. (°C)
Trifoliate starch NPs	TSNP1	5	1.4	15	0.5	2.5	50
Trifoliate starch NPs	TSNP2	5	2.9	15	1.5	2.5	50

MCA: Monochloroacetic acid, NaOH: Sodium hydroxide; Conc.: concentration; Temp.: Temperature.

2.2.4. Determination of degree of substitution

To determine the degree to which the carboxymethyl group on the starch molecule was substituted. About 0.5 g of the modified trifoliate starch NPs with 20 ml of 0.2 M NaOH were mixed in a 100 ml volumetric flask, a further 50 ml of distilled water was added to make it up to 100 ml. Standard and 0.05 M HCL were used with phenolphthalein as an indicator to back titrate the excess NaOH. The titration was performed three times, and the average volume of HCl used in the reactions was used to calculate the degree of substitution using the formula below [37]. A blank titration was also carried out.

$$DS = \frac{162 \times nCOOH}{(MDS-58) \times nCOOH} \quad (1)$$

$$nCOOH = (Vb-V) \times C_{HCL} \times 4 \quad (2)$$

Where the molar mass of an anhydroglucose unit (AGU) is 162 g/mol, MDS is the mass of the dried sample (0.5 g), The value of nCOOH (in moles) is determined by calculating the amount of COOH based on the obtained equivalent volume, the net increase in the mass of an AGU (CH_2 COOH) for each carboxymethyl group substituted is 58 g/mol, Vb is the volume of HCl used for titration of the blank in back titration, and V is the volume used for titration of the sample.

2.2.5. Characterization of functional groups using Fourier transform infrared spectroscopy (FTIR)

This analysis was done with the Spectrum BX Fourier transform infrared spectrometer (Perkin Elmer Ltd., USA). A small amount of each sample was finely milled and mixed 1:100 with dry potassium bromide (KBr), which serves as the window material for the sample cell. The rectangular cuvette of the FTIR machine held the sample and blank. Peak plots of percentage transmittance (%T) versus wave number (cm^{-1}) were displayed on the computer. The plots were saved and processed in Microsoft Excel to identify sample functional groups or molecular structures [6].

2.2.6. Characterization of surface morphology and particle size

A JEOL JSM-6060LV Scanning Electron Microscope (Tokyo, JAPAN) was used to measure the size and surface structure of trifoliate native starch (TNS), trifoliate starch nanoparticles (TSNP), and carboxymethylated trifoliate starch nanoparticles (CTSNP). The samples were mounted on aluminium stubs with double-sided carbon tape, coated with gold in a sputter coater under vacuum, and examined at various magnifications [5]. The particle size of the starch forms was also determined using SEM. The particle size and distribution were additionally assessed using a digital microscope (VJ-2005 DN MODEL BIO-MICROSCOPE, CHINA) on 300 particles to confirm that the SEM's particle size measurement of the modified starches fell within the nano range. The digital microscope was utilized to ascertain the specific dimensions of the agglomerations. Morphometrical evaluations (globule diameter) were conducted utilizing TS View CX Image Software File version 6.2.4.3 and Motic Image 2000 (China).

2.2.7. Determination of swelling power of starch samples

A slurry was made by combining 0.5 g of starch powder with 10 mL of distilled water. It was stored at room temperature for 20 hours [6]. The swelling volume was measured and documented. The swelling power (SP) was calculated in the following manner:

$$SP = \text{weight of swollen starch} / \text{initial weight of dry starch} \quad (3)$$

This was also done for TNS, TSNP, and CTSNP.

2.2.8. Determination of pH of starch samples

An electronic balance was used to precisely weigh 2 g of starch powder, which was then dissolved in 100 mL of distilled water using a glass rod for 5 min and left to stand for 10 min. The pH was measured using a bench-top pH meter (pH-016, China) [6].

2.2.9. Drug loading into the starch forms

150 mg of each starch form was dispersed in 10mL of naproxen solution in distilled water (1.0 mg/mL) and incubated for 1hr, 3hr, and 6hr for drug loading. The precipitate was washed with distilled water after centrifuging the suspensions. The supernatant's naproxen content was measured using a UV-vis Spectrophotometer and absorbance to concentration standard curves [38]. The following formulae were used to calculate the drug loading capacity (DLC) and loading efficiency (LE):

$$DLC\% = \frac{\text{Weight of drug in starch sample}}{\text{Weight of starch sample}} \times 100 \quad (4)$$

$$LE\% = \frac{\text{Weight of drug in starch sample}}{\text{Initial Weight of the drug in the loading solution}} \times 100 \quad (5)$$

2.2.10. Dosage form design

Naproxen-loaded starch samples were air-dried overnight in an open space before being manually placed in an empty capsule shell and tightly sealed. Known amount of the naproxen-loaded trifoliate native starch (TNS),

trifoliate starch nanoparticles (TSNP), and carboxymethylated trifoliate starch nanoparticles (CTSNP) dried powder were weighed into these gelatine hard capsules.

2.2.11. *In-vitro drug release studies*

Drug-loaded capsules were suspended in 100mL pH 6.5 phosphate buffer solution (PBS) as the drug release medium. A dissolution apparatus model (COPLEY DIS 6000, UK) held the medium at 37 °C with gentle agitation (50 rpm) through a rotating basket. Sample (5 mL) was withdrawn at different time intervals and the release medium was replaced with 5 mL of PBS. The mass of naproxen released at the wavelength of 273 nm at each time interval was determined using a UV-vis Spectrophotometer (COPLEY Aquarius, Cecil 7400Series, UK) [6]. The rate at which the starch samples released naproxen (R) was calculated using the following relationship:

$$R=M_1/M_0 \qquad (6)$$

M_1 is the starch sample's total naproxen-loaded mass, and M_0 is its cumulative mass released over time. DDSolver, a Microsoft Excel add-in, was used to analyse starch release kinetics *in vitro*. Release kinetics were ranked using the Akaike Index Criterion (AIC) [39].

2.2.12. *Statistical analysis*

Statistics were done with GraphPad Prism 8. Specific data were shown as mean ± standard deviation ($\bar{X}$ ± SD). Statistical significance was determined using Student's t-test, with differences between evaluated parameters at $p \leq 0.05$.

3. RESULTS

3.1. Physicochemical properties of starch particles

Table 2 shows the physicochemical properties of native (trifoliate native starch (TNS)) and modified starches (trifoliate starch nanoparticles (TSNP) and carboxymethylated trifoliate starch nanoparticles (CTSNP)), including degree of substitution, particle size, swelling power, and pH.

Table 2. Physicochemical properties of native and modified starch (mean ± SD, n=3).

Code	DS	Particle size, (nm)	SP	pH
TNS	-	1616.0 ± 0.54	3.27 ± 0.31	5.14 ± 0.03
T SNP	-	86.5 ± 5.60	2.47 ± 0.12	5.70 ± 0.06
CTSNP	0.37	272.0 ± 92.5	2.73 ± 0.10	3.60 ± 0.21

TNS: trifoliate native starch; TSNP: trifoliate starch NPs; CTSNP: carboxymethylated trifoliate starch NPs; DS: degree of substitution; SP: swelling power.

3.2. The morphology of native starch and its modified forms

Figure 1 presents the scanning electron images of all starches. The SEM image of TSNP reveals irregularly shaped particles, some of which are elongated and exhibit smooth surfaces. In contrast, those of modified CTSNP show irregular polyhedral granules with distorted/wrinkled surfaces and perforations but almost no rupture. Rough, porous surfaces show crystalline structure loss and modification.

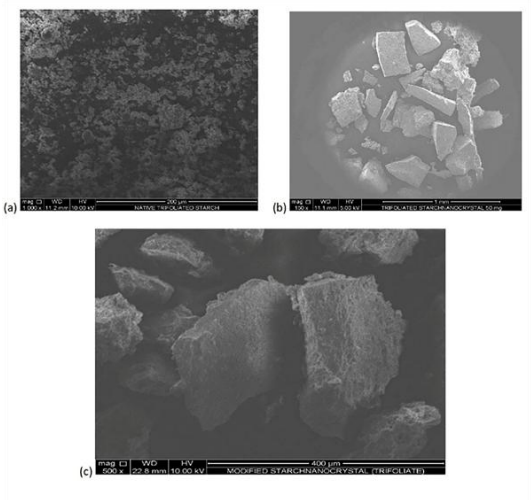

Figure 1. SEM micrographs of (a) native trifoliate starch (TNS), (b) trifoliate starch nanoparticles (TSNP), and (c) carboxymethylated trifoliate starch nanoparticles (CTSNP).

3.3. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the three starch forms are shown in Figure 2. All three spectra showed broad O-H and C-H stretching vibrations in the 2900-3600 cm^{-1} absorption band, but peak intensities differed [40-42] Spectra showed a unique pattern in the absorption band 970-1200 cm^{-1}, representing native starches' whole anhydroglucose ring stretching vibrations. Starch NPs' whole anhydroglucose ring stretching vibrations were altered. However, carboxymethylated starch NPs' stretching vibration intensities, shapes, and wavenumbers changed significantly [40,41,43].

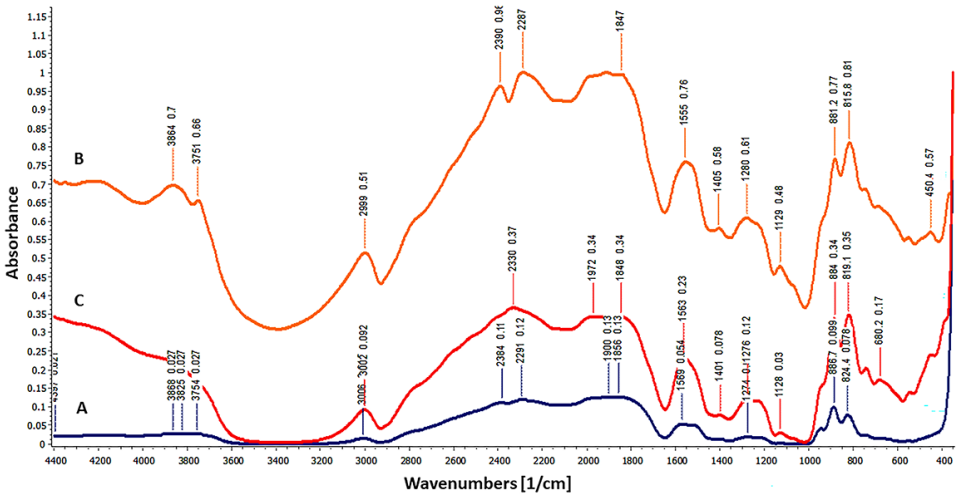

Figure 2. FTIR spectra of (a) TNS- trifoliate native starch, (b) TSNP- trifoliate starch NPs, and (c) CTSNP- carboxymethylated trifoliate starch NPs.

3.4. Drug loading capacity

A UV-vis Spectrophotometer and the standard naproxen absorbance to concentration in distilled water curve, y=0.0022x + 0.0995 (R^2 0.9915), determined the loading capacity of TNS, TSNP, and CTSNP starch samples (Table 3). The loading capacity and efficiency of naproxen in all starch forms are G > D > I > H > A > C > E > F > B. The ranking shows that G (native starch), D (starch NPs), and I (native starch) have the highest drug loading capacity of 5.8%, 5.8%, 5.7% and loading efficiency of 86.7%, 86.4%, and 84.9%.

Table 3. Drug loading capacity (DLC) and loading efficiency (LE) of naproxen in trifoliate native starch-TNS, trifoliate starch nanoparticles-TSNP, and carboxymethylated trifoliate starch nanoparticles-CTSNP with corresponding loading hour(s).

Sample	Code	Loading time (h)	Drug weight in loading solution (mg)	Amount of drug in NP, mean±SD (mg)	DLC (%), mean±SD	LE (%), mean±SD
CTSNP	A	1	10	8.39 ± 0.52	5.6 ± 0.35	83.9 ± 5.16
	B	3	10	7.46 ± 2.65	4.9 ± 1.77	74.6 ± 26.5
	C	6	10	8.27 ± 0.35	5.5 ± 0.28	82.7 ± 3.46
TSNP	D	1	10	8.64 ± 0.43	5.8 ± 0.28	86.4 ± 4.31
	E	3	10	8.09 ± 1.97	5.4 ± 1.27	80.9 ± 19.7
	F	6	10	8.04 ± 0.64	5.4 ± 0.42	80.4 ± 6.36
TNS	G	1	10	8.67 ± 0.63	5.8 ± 0.42	86.7 ± 6.29
	H	3	10	8.42 ± 0.23	5.6 ± 0.14	84.2 ± 2.33
	I	6	10	8.49 ± 0.42	5.7 ± 0.28	84.9 ± 4.24

Table 4 shows the correlation coefficient (r^2), diffusional release exponents (n), and kinetic constants (K) of all starch forms from zero-order, first-order, Korsemeyer-Peppas, Hixson-Crowell, and Higuchi release models. Except for starch NPs E (loading time: 3 h, DLC: 5.4%, LE: 80.9%) and modified starch NPs C (loading time: 6hrs, DLC: 5.5%, LE: 82.7%), all starches had high Korsemeyer-Peppas model correlation values. Additionally, the Korsemeyer-Peppas model had the highest correlation (0.9997) [44].

Table 4. *In vitro* release kinetics (zero order, first order, Higuchi, Hixson-Crowell, and Korsemeyer-Peppas) for naproxen-loaded TNS- trifoliate native starch, (b) TSNP- trifoliate starch NPs, and (c) CTSNP- carboxymethylated trifoliate starch NPs in Phosphate buffer solution (PBS) (pH-6.5) with the corresponding correlation coefficients (r^2) obtained.

Release kinetics	Zero order		First order		Higuchi		Hixson-Crowell		Korsemeyer-peppas			AIC				
	r^2	k_o	r^2	K_1	r^2	k_H	r^2	k_{HC}	N	r^2	K	Zero	First	Hig.	Hix-C	Kors.
A	0.9697	0.273	0.980	0.005	0.986	4.719	0.982	0.001	0.595	**0.994**	2.866	71.26	65.81	62.70	64.84	**53.89**
B	0.8524	0.164	0.896	0.003	0.949	3.529	0.883	0.001	0.331	**0.997**	8.515	79.61	75.37	65.93	76.86	**36.44**
C	0.9165	0.340	0.981	0.009	0.974	5.904	0.979	0.002	0.590	0.968	3.548	89.34	71.62	83.38	72.72	**79.71**
D	0.9939	0.222	0.992	0.003	0.963	3.828	0.995	0.001	0.832	**0.997**	0.586	46.77	50.03	75.56	43.27	**39.12**
E	0.9313	0.228	0.976	0.004	**0.994**	3.881	0.965	0.001	1.082	0.918	0.134	77.29	**64.53**	78.55	69.09	81.36
F	0.9848	0.232	0.995	0.004	0.989	3.815	0.995	0.001	0.724	**0.998**	1.103	58.92	44.84	79.08	45.33	**37.42**
G	0.9546	0.238	0.983	0.004	0.996	3.975	0.977	0.001	0.483	**0.996**	4.363	72.95	60.86	79.27	64.58	**45.85**
H	0.9779	0.137	0.960	0.002	0.989	2.765	0.967	0.001	1.052	**0.999**	0.117	50.78	57.80	78.78	55.63	**11.79**
I	0.9306	0.095	0.911	0.001	0.984	2.464	0.917	0.000	1.101	**0.999**	0.082	56.43	59.49	74.20	58.53	**-6.59**

r^2: Correlation coefficient; n: Diffusional release exponents; K: kinetic constants; AIC: Akaike information criterion.

3.5. Drug release from naproxen-loaded TNS, TSNP, and CTSNP

Figure 3 shows the percentage drug release of naproxen from naproxen-loaded TNS, TSNP, and CTSNP at physiological pH-6.5 phosphate buffer. CTSNP-C had the highest cumulative release (96% after 300 minutes) with a loading time of 6 hours, a drug loading capacity of 5.5%, and a loading efficiency of 82.7%, while TNS-I had the lowest (30% after 300 minutes).

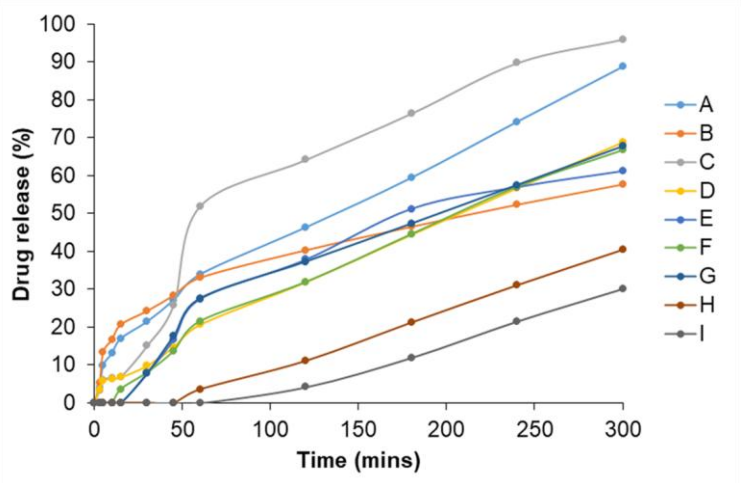

Figure 3. Release profiles of naproxen from naproxen-loaded CTSNP- carboxymethylated trifoliate starch NPs (A-1 hr, B-3 hr, C-6 hr), TSNP- trifoliate starch NPs (D-1hr, E-3 hr, F- 6 hr), and TNS- trifoliate native starch (G-1 hr, H-3 hr, I-6 hr).

4. DISCUSSION

Starch nanoparticles (SNP) are starch nanocrystals (SNC) with amorphous matrices [18]. Most SNP is formed through a top-down process that involves modifying large starch granules' morphology and particle size into smaller portions and a more crystalline form as amylose content is reduced [2,15,16]. SNP has a lower crystallinity than SNC because native starch (NS) amorphous regions are not converted to crystalline, or some amylose is retained. Instead of total disruption of amorphous areas from semi-crystalline NS granules during acidic hydrolysis, gelatinized starch forms SNP [6]. Acid hydrolysis of NS to SNP adds a functional group to starch structural molecules, improving their physical, chemical, and biological properties [2,17]. Angellier et al. [40] found that sulfuric acid hydrolysis of NS reduces production time and increases SNP yield compared to hydrochloric acid hydrolysis. Further research found that sulfate-ester linkages on sulfuric acid hydrolysed SNP molecules prevent aggregation in hydrochloric acid, making SNP more stable [45].

The SNP can be chemically modified to improve their properties and utility [14,23]. Carboxymethylation replaces SNP's polar hydroxyl groups with an anionic moiety (bulky hydrophilic group). The presence of negatively charged function groups (CH_2COO-) in the molecular structure of SNP results in the following: higher water solubility, reduced flocculation of nanosuspension, lower crystallinity of SNP, increased thermal and enzymatic stability of materials, alteration of rheological properties, lower gelatinization temperature, lower recrystallization, increase bio-adhesiveness, and pH-sensitivity of the NP-base system that controls the delivery or release of hydrophilic and hydrophobic drugs in the gastrointestinal tract (GIT) at a predetermined time, place and rate [14,46,47,48].

Because carboxylate functional groups are more hydrophilic or polar than hydroxyl groups, SNP derivatives are more soluble. After the synthesis, the SNP's size, shape, crystallinity, hydrophilicity/hydrophobicity, and zeta potential can be modified to customize its functionality for various applications [14].

The degree of substitution (DS) is the average number of functional groups (CH_2COO-) inserted into the polymer, which affects product properties [8,43]. DS typically ranges from 0 to 3.40 (Table 2). CTSNP (DS-0.37)

matches commercial carboxymethylated starches' DS values [8,47]. Theoretically, DS value can be predicted by varying reaction processes parameters like temperature, processing duration, polymer concentration ratio to monochloroacetic acid, sodium hydroxide concentration ratio to polymer, and manufacturing technique [8,43,46,48,49]. Acidic hydrolysis of native starch reveals the nano-blocklet amylopectin lamellae structure in the amorphous starch granules [2,50]. TNS's lack of granular aggregate in TSNP molecules supports Angellier et al. [45] finding that sulfuric acid hydrolysis limits flocculation and stabilizes nano-suspensions. The modified CTSNP show irregular polyhedral granules with distorted/wrinkled surfaces and perforations but almost no rupture. Rough, porous surfaces show crystalline structure loss and modification. The following reasons made carboxymethylated starches less crystalline than their native or precursors: Heat treatment with water ruptures the starch granule by pregelatinizing starch molecules, strong alkaline conditions (NaOH) during modification breaks intermolecular hydrogen bonding, and solvents like propanol and ethanol reduce derivative product crystallinity [36,47-49,51]. This study found that the TSNP derivative (CTSNP) had granule agglomeration on its surface instead of significant damage, confirming its modification and the fusion of the carboxymethyl group with the NP-based system (precursor) and crystallinity loss due to gelatinization rather than rupture [36,43,51].

SEM shows that the TNS particle size is 1616.0 nm (Table 2), and sulfuric acid hydrolysis yields a TSNP of 86.5 nm after five days. The intense acidic conditions and heat application at 40 °C led to significant disruption and rupture of the starch's granular structure through hydrolysis with sulfuric acid. The prolonged duration of acid hydrolysis is likely linked to the increased size reduction, as starch fragments are gradually released from the granule's surface, leading to a smaller particle size [48]. The CTSNP particle size was 272 nm. Carboxymethylated starch NP-based systems exhibit larger particle sizes than their precursors due to the introduction of carboxymethyl groups into their molecular structure. This modification enhances their hydrophilicity, facilitating water retention and increasing particle diameter [6,8].

Native and modified starches' swelling power, solubility, and water absorption are interconnected polymer functions [2]. The swelling index of trifoliate starch was found to be 3.27 in this study, while TSNP and CTSNP were 2.47 and 2.73, respectively. The native starch had a higher swelling index than their modified forms ($p<0.05$) (Table 2). Compared to native starch, CTSNP had poor swelling power and an insignificant higher swelling index (0.26) than starch NPs (TSNP). Kittipongpatana et al. found that 2-propanol-prepared carboxymethylated starch was more soluble than swelling [36]. The DS of CTSNP carboxymethyl groups (0.37) was like the literature's carboxymethylated starch prepared with 2-propanal (0.3443), which showed free solubility in unheated water. In contrast, the partially soluble carboxymethylated starch swelled somewhat [36].

Carboxymethyl starches form viscous solutions in room-temperature water [50]. Carboxymethyl starch samples will not significantly swell because of their high cold-water solubility [51]. Furthermore, compared to its precursor, the structural changes in carboxymethylated samples improved its amorphous molecules, increasing water uptake or absorption to form a solution with insignificant swelling [8,45]. The carboxymethylated polymer's water solubility suggests that the amylose portions, less water-soluble than amylopectin, were involved in the substitution reaction that made them soluble. Amylose's straight-chain structure gives reacting chemicals better access to glucose-OH groups. However, the branched chain and larger amylopectin structure limit access [47].

The pH of trifoliate starch is within pharmaceutical standards [7]. Generally, drugs tend to be either weakly acidic or weakly basic and adding starch excipients to their formulation is unlikely to create notable pH stability issues [6,8]. Table 2 shows the pH values of starch NPs and modified carboxymethylated starch. Trifoliate starch NPs had a pH of 5.7, while modified carboxymethylated starch had a much lower pH (3.6). The lower pH of the modified starch NPs may be due to the acidic carbonyl ($-CH_2COO-$) groups on starch molecules, which dissolve quickly in the aqueous medium to lower the pH of the starch slurry [6]. The pH of carboxymethylated starch affects its stimuli response in physiological media. This pH value can also impact protonation or ionisation in simulated gastric or intestinal fluid, directly controlling drug diffusion from their polymeric matrix to the surrounding medium. Stable, weakly acidic CTSNPs may delay drug release from their matrix in stimulated gastric juice. In contrast, stimulated intestinal fluid ionises the NP-based system, releasing its contents due to repulsive forces [46,52].

The broadness and intensity of the O-H stretching vibration in the CTSNP spectrum decreased compared to TSNP, and the peak was shifted from 3336 cm^{-1} to 3358 cm^{-1}. The NP derivative had a lower C-H stretching peak at 2928 cm^{-1} than the precursor [43]. Changes in the two absorption bands were caused by decreased hydroxyl group intermolecular forces and carboxymethyl group replacement [53]. CTSNP had carbonyl, CH2 scissoring, and OH bending absorption bands at 1652, 1444, and 1352 cm^{-1}. TSNP only showed an absorption band at 1644 cm^{-1} in the 1600-1300 cm^{-1} region but at a higher intensity and lower wavenumber than CTSNP. Only carboxymethylated NP-based systems had these three vibration bands, confirming carboxymethylation [41,43].

Compared to modified starches, trifoliate native starch generally demonstrated higher loading capacity and efficiency. There was stronger intermolecular ionic interaction or hydrogen bonding between naproxen molecules and trifoliate native starch side chains than between the two modified starches. Compared to starch NPs and carboxymethylated starch NPs, native starch has a larger particle size, a smaller surface area for drug loss, and a larger core for drug incorporation, improving drug loading and entrapment [54] Native starch G, with a loading time of 1 hour, was ranked first among the native starches G > I > H. Therefore, it takes 1 hour for naproxen to reach saturation or complete binding to the polymer. The drug slightly leached into the aqueous drug-loading environment for 3–6 hours.

Ranking starch NP forms showed D > E > F. Trifoliate starch NP D ranked first with a 1hr loading time, 5.8% loading capacity, and 86.4% loading efficiency. F ranked last with a 6hr loading time, 5.4% loading capacity, and 80.4% loading efficiency. Trifoliate native starch NPs showed the same trend of increasing drug loading time and leaching into an aqueous medium.

The modified starch NPs are ranked as follows: A > C > B. Modified trifoliate starch NPs A have the highest loading capacity (5.6%) and loading efficiency (83.9%) among all modified forms, while modified trifoliate starch NPs B have the lowest loading capacity (4.9%) and loading efficiency (74.6%). The study found that a loading time of 1 hour was best for loading capacity and efficiency within the same starch form and across the groups of starch forms studied, while 3 and 6 hours reduced loading capacity and efficiency.

The three CTSNP formulations released slight bursts of naproxen (A-4.15%, B-5.34%, and C-3.25%) into the physiological medium at 3 minutes, followed by steady or sustained release from all three polymeric matrices. Thus, these formulations released drugs biphasically. Unbound drug particles may cause the burst release on NP surfaces not incorporated into polymers and the large surface-to-volume ratio of the NPs [6,54]. After 300 minutes of testing, CTSNP-C released 96% of the drug inside its matrix, followed by A (86.77%) and B (57.63%). Thus, CTSNP-B is ideal for naproxen's immediate and extended release.

The TSNP formulations (E and F) released naproxen similarly to the CTSNP formulations (A, B, and C), except for TSNP-D, which burst after 15 minutes. The three TSNP formulations consistently released naproxen from NP matrices. After 300 minutes, formulations D, E, and F released 68.86%, 61.17%, and 66.86% naproxen into the stimulated intestinal fluid, respectively.

Interestingly, all three TNS formulations delayed naproxen release. Drug release was delayed by 30 minutes for TNS-G, 60 minutes for H, and 120 minutes for I. A strong ionic interaction between naproxen and trifoliate starch may have delayed drug release. At the end of the dissolution study, formulations G, H, and I released 67.17%, 40.53%, and 30% of naproxen.

The improved release of naproxen from CTSNP, likely linked to hydrophilic interactions between the drug and CTSNP molecules, has practical implications for drug formulation. In contrast, the slower release pattern of naproxen from TNS and TSNP, which have higher loading capacities and efficiencies, can be attributed to the stronger hydrophobic interactions between the drug and these excipients. The more pronounced hydrophobic interaction of Drug-TNS polymer is a key insight with potential practical applications. This interaction may be associated with improved partitioning of hydrophobic drug molecules into the hydrophobic core-shell structure of TNS and their subsequent retention. Consequently, in addition to the hydrophobic characteristics of the TNS polymer, the release profile is also influenced by the solubility and partition coefficient of the molecule that has been incorporated [55]. The accelerated drug release from the CTSNP can be attributed to the quicker hydration of starch particles upon contact with water, enhancing the naproxen

particles' wettability. This results in improved drug solubility and increased drug concentration at the diffusion layer around the naproxen particles. The dissolution medium plays a crucial role in this process, facilitating the release of the drug [8]. Consequently, CTSNP is a nanocarrier that improves the dissolution or solubility of poorly water-soluble naproxen, thereby potentially enhancing its intestinal absorption and bioavailability *in vivo* [56].

The anionic biopolymer in carboxymethylated starch is protonated and compacted in gastric fluid, preventing buffer diffusion into the carrier structure and drug release, according to Pooresmaeil and Namazi [46]. These carboxyl groups are ionized in intestinal fluid, promoting buffer penetration into the carrier structure and drug release. A highly polar carboxymethyl group on the precursor TSNP increases the solubility of the derivative CTSNP (Water-soluble starch derivative) on the poorly soluble naproxen, increasing its dissolution rate in water [57]. The CTSNP developed in this study exhibited limited swelling power alongside free solubility and a low pH, attributed to the hydrophilic (-CH_2COO-) group. This characteristic notably facilitated the substantial release of naproxen into the physiological medium at elevated pH levels, as the stimulated intestinal fluid ironizes the carboxymethylated NP-based system, releasing its contents driven by repulsive forces [6,46,52].

The choice of dissolution medium pH 6.5 instead of 7.5 or 1.2 in this study stimulates the site-specific delivery of naproxen to the intestine (pH 6.5) and not the colon (pH 7.5) or stomach (pH 1.2) [58]. The limited-release study timeframe was 300 minutes or 5 hours to mimic the small intestine transit time [59]. The gastrointestinal absorption of orally taken medications is influenced by the gastrointestinal mucosa's permeability and the transit rate within the gastrointestinal tract. The gastric emptying rate significantly influences the plasma concentration profile of orally administered drugs. In contrast, the intestinal transit rate plays a crucial role in drug absorption by determining the drug's residence time at the absorption site. Residency time is a key element for drug absorption due to the variability in absorbability at different sites for some medicines [60].

Release exponent (n) values for modified trifoliate starch NPs (A & C), starch NPs (D), and native starch (G) were < 0.89 but > 0.45, indicating non-fickian transport drug release. The release exponent (n) of modified trifoliate starch NPs (B) was < 0.45, indicating a quasi-fickian diffusion mechanism. Trifoliate starch NPs (E) and native starch (H & I) had exponent (n) values greater than 0.89, indicating Super Case II transport and multiple release mechanisms, including diffusion and erosion-controlled drug release [44].

Korsmeyer-Peppas, or power law, is a diffusion-based semi-empirical method kinetics model of release research designated for drug formulation like polymeric NPs dosage form. It is illustrated when more than one release mechanism is employed, including diffusion, erosion, and swelling, or when the release mechanism is unknown in a formulation dosage form. Drug release is influenced by drug classes (BCS), particle size, nanocarrier, and co-materials. The erosion process governs the release rate of poorly water-soluble drugs, such as naproxen. The Korsmeyer-Peppas model, a comprehensive tool, applies to all classes of drugs [61]. This mathematical framework was developed to elucidate and simulate the pharmacokinetic properties of drug formulations *in vitro*, aiming to quantify and characterize drug behaviour in vivo, instilling confidence in its use [62].

The Akaike information criterion (AIC) measures a model's fit to data. Each statistical model in a data set is compared to others by AIC. AIC helps choose models; the best-fit model explains the most variations with the fewest independent variables. The best model has the lowest AIC [39]. The Korsemeyer-Peppas model fits best in most formulations with the highest r^2 value. They had the lowest AICs except for starch samples C and E.

5. CONCLUSIONS

Trifoliate starch NPs and their modified derivatives demonstrated potential as carriers for poorly soluble naproxen, with improved dissolution and release kinetics. NPs were prepared by acid hydrolysis from native trifoliate starch. Modified (carboxymethylated) starch NPs were further prepared from the NPs by reaction with monochloroacetic acid, propanol, and sodium hydroxide (NaOH). The native and modified starch forms were characterized by their morphological and physicochemical properties. All the starch forms demonstrated drug load capacity and efficiency above 80%. The loading content of starch nanocrystals and their modified forms

was above 50%, and the loading efficiency was above 80%. The native starch demonstrated delayed naproxen release, while the trifoliate starch NPs demonstrated a biphasic release profile (immediate and sustained release), and release kinetics were mainly achieved by diffusion through the polymeric matrix. A loading time of one hour was found to optimize loading efficiency. The starch nanocarriers developed in this study can be used as vehicles to enhance, control, and prolong the release of poorly soluble drugs. However, further studies are needed to compare these systems with free naproxen or a standard formulation to validate their efficacy.

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