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Synthesis and Characterization of Acid-Hydrolyzed Breadfruit Starch (*Artocarpus altilis*) Nanoparticles as a Potential Carrier for Doxorubicin

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ABSTRACT

Natural starch-based materials are promising for drug delivery due to their biodegradability, abundance, and biocompatibility. This study isolated starch from breadfruit (*Artocarpus altilis*) and converted into nanoparticles via acid hydrolysis using HCl 2.2 N under shaking incubation at 38°C for 24 hours. The process yielded nanoparticles with a recovery efficiency of 67% and an average particle size of 347.76 nm—within the optimal range for passive tumor targeting via the enhanced permeability and retention (EPR) effect. Compared to native starch, the nanoparticles exhibited enhanced solubility and reduced viscosity, indicating improved aqueous dispersion. FTIR spectroscopy confirmed the retention of major functional groups, while SEM analysis showed distinct changes in surface morphology indicative of granule disintegration. To evaluate pharmaceutical applicability, doxorubicin hydrochloride (DOX) was employed as a model drug. The breadfruit starch nanoparticles achieved a high drug loading efficiency of 78.3%. These results demonstrate the potential of breadfruit starch nanoparticles as a sustainable, low-cost drug delivery platform and highlight the value of underutilized tropical starches in nanomedicine.

Keyword: Acid Hydrolysis, Breadfruit Starch, Carrier, Doxorubicin, Nanoparticles.

ABSTRAK

Material berbasis pati alami menarik untuk sistem penghantaran obat karena sifatnya yang biodegradabel, biokompatibel, dan melimpah. Penelitian ini mengisolasi pati dari buah sukun (*Artocarpus altilis*) dan dikonversi menjadi nanopartikel melalui metode hidrolisis asam menggunakan HCl 2,2 N dengan shaker incubator pada suhu 38°C selama 24 jam. Proses ini menghasilkan nanopartikel dengan efisiensi pemulihan sebesar 67% dan ukuran rata-rata 347,76 nm, yang sesuai untuk penargetan pasif melalui efek permeabilitas dan retensi yang ditingkatkan (EPR). Dibandingkan dengan pati murni, nanopartikel menunjukkan peningkatan kelarutan serta penurunan viskositas, yang mengindikasikan peningkatan dispersi dalam medium akuatik. Analisis FTIR mengonfirmasi keberlangsungan gugus fungsi utama, sementara citra SEM menunjukkan perubahan morfologi permukaan yang mencerminkan degradasi struktur granula pati. Untuk mengevaluasi potensi aplikasinya di bidang farmasi, doxorubicin hidroklorida (DOX) digunakan sebagai model obat. Nanopartikel pati sukun menunjukkan efisiensi penjerapan obat yang tinggi, sebesar 78,3%. Hasil ini menegaskan potensi nanopartikel pati sukun sebagai sistem penghantaran obat yang berkelanjutan dan ekonomis, serta menyoroti nilai strategis pati tropis yang belum banyak dimanfaatkan dalam nanomedisin modern.

Kata Kunci: Hidrolisis Asam, Doksorubisin, Nanopartikel, Pati Sukun, Penghantar.

1. Introduction

Cancer remains a major global health concern. In Indonesia alone, 408,661 new cases and over 242,099 cancer-related deaths were recorded in 2022. Alarmingly, the World Health Organization (WHO) estimates that by 2040, approximately 63% of global cancer cases will occur in low- and middle-income countries [1]. As part of cancer therapy, drug delivery systems (DDS) have gained substantial attention for their ability to enhance the therapeutic performance of chemotherapeutic agents while reducing systemic toxicity and off-target effects.

Doxorubicin hydrochloride (DOX) is a well-established anticancer agent frequently used in DDS research due to its efficacy against a wide range of solid tumors, including breast, ovarian, and lymphomas [2]. However, conventional DOX administration often suffers from poor bioavailability, nonspecific distribution, and cardiotoxicity. These limitations have prompted the development of nanocarrier-based systems designed to improve pharmacokinetics, enable controlled release, and protect active ingredients from degradation [3].

Particle size plays a crucial role in determining the ability of nanocarriers to penetrate biological barriers such as tumor tissues or blood vessels. While particles under 200 nm are typically optimized to exploit the enhanced permeability and retention (EPR) effect, [4] demonstrated that nanoparticles up to 500 nm can still be effectively internalized by cancer cells via endocytic pathways, particularly in monoculture systems where they also exhibit favorable biocompatibility. This is especially advantageous for cancer therapy involving doxorubicin (DOX) as such particles can encapsulate larger amounts of the drug, thereby enhancing delivery efficiency and therapeutic outcomes at the target site [5].

Among biopolymers used for nanoparticle matrices, starch offers multiple advantages, such as its biodegradable, abundant, cost-effective, and modifiable. Composed of amylose and amylopectin, starch provides flexibility for structural tuning and functional optimization in pharmaceutical formulations [6]. Recent studies have explored the potential of local starches as drug carriers, yet data on breadfruit-based systems remain limited.

Breadfruit (*Artocarpus altilis*) is a tropical plant abundant in Indonesia and other equatorial regions. Its starch content is high, but its native form suffers from drawbacks such as high viscosity, thermal instability, and retrogradation tendency, which hinder its pharmaceutical utility [7]. Acid hydrolysis is an effective method to reduce starch granule size, improve solubility, and increase functionality. Prior work using 2.2 N HCl successfully produced breadfruit starch nanoparticles, demonstrating the method's scalability and effectiveness [8].

Despite these advancements, little has been reported on the application of breadfruit starch nanoparticles as drug carriers—particularly for DOX. This study aims to synthesize nanoparticles from breadfruit starch via acid hydrolysis and evaluate their potential as nanocarriers for doxorubicin hydrochloride. Key parameters such as particle size, solubility, viscosity, and drug loading efficiency are investigated to determine their suitability for use in nanomedicine.

2. Material and Method

2.1 Equipments

Laboratory equipment used in this study included beaker glasses, Erlenmeyer flasks, a shaker incubator, centrifuge, thermometer, oven, mortar and pestle, and a 200-mesh sieve. Viscosity measurements were conducted using an Ostwald viscometer. Advanced characterization was performed using a Particle Size Analyzer (PSA, ANALYSETTE 22 NanoTec Plus, FRITSCH), FTIR-ATR spectrometer (Shimadzu), and a Scanning Electron Microscope (SEM).

2.2 Material

The fresh breadfruit (*Artocarpus altilis*) was sourced locally from Tandam Hilir II District, Deli Serdang Regency, North Sumatra Province, Indonesia. All chemicals used, including ethanol, distilled water, double-distilled water, sodium hydroxide (NaOH), hydrochloric acid (HCl), and phosphate-buffered saline (PBS, pH 7.4), were analytical grade and obtained from Merck. Doxorubicin hydrochloride (DOX) was obtained from a commercial pharmaceutical preparation produced by Kalbe Farma, Indonesia, and used without further modification.

2.3 Isolation of Breadfruit Starch (BS)

A total of 6 kg of fresh breadfruit was peeled, washed, and chopped, then blended with distilled water at a 1:2 (w/v) ratio. The slurry was filtered through gauze and left undisturbed at room temperature for 24 hours to allow sedimentation. The resulting breadfruit starch precipitate was washed repeatedly with clean water until the supernatant was clear. After that, it was dried an oven at 45°C for 24 hours, ground, and passed through a 200-mesh sieve. The native starch was stored in a sealed container. Furthermore, FTIR analysis was used to confirm the presence of functional groups [9].

2.4 Synthesis of Breadfruit Starch Nanoparticles (BSN)

Approximately 29.4 g of native starch was dispersed in 150 mL of HCl 2.2 N and incubated at 38 °C for 24 hours in a shaker incubator. After hydrolysis process, the suspension was neutralized to reach pH 7.0 using 1 N NaOH. The sample was filtered, rinsed with distilled water and ethanol, dried at 40 °C, ground, and sieved. The particle size distribution was analyzed using PSA [8].

2.5 Drug Loading Studies

To evaluate drug loading, 90 mg of breadfruit starch nanoparticles was mixed with 3 mL of DOX solution (2 mg/mL) in PBS buffer (pH 7.4). The mixture was incubated at 37°C for 1 hour, then centrifuged at 7000 rpm for 10 minutes to separate the precipitate and supernatant. The supernatant was collected, and the concentration of unbound DOX was determined using UV-Vis spectrophotometry at 481 nm (λ max) [10]. Drug loading content (DLC) and loading efficiency (LE) were calculated using equations (1) and (2):

$$\text{DLC \%} = \frac{\text{Weight of DOX bound to starch}}{\text{Weight of BSN sample}}\ 100\% \quad (1)$$

$$\text{LE\%} = \frac{\text{Initial DOX} - \text{Unbound DOX}}{\text{Initial DOX}}\ 100\% \quad (2)$$

2.6 Characterization of BS and BSN

2.6.1 Swelling Power and Solubility

Swelling power and solubility assessments are conducted following established methodologies [11]. Approximately 0.1 g of sample was dispersed in 10 mL of distilled water and heated to 85°C for 30 minutes in a water bath. After cooling, the sample was centrifuged at 5000 rpm for 15 minutes. The supernatant was oven-dried at 110°C to determine solubility, while the sediment was weighed to calculate swelling power using Equations (3) and (4):

$$\text{Swelling Power} = \frac{\text{Mass of hydrated starch sediment}}{\text{Mass of initial dry starch sample}} \quad (3)$$

$$\text{Solubility (\%)} = \frac{\text{Mass of dried supernatant}}{\text{Mass of initial dry starch sample}} \text{ x } 100 \quad (4)$$

2.6.2 Viscosity Measurement

Viscosity was measured using the Ostwald viscometer. 0.5 g sample was dissolved in 25 mL distilled water, and 10 mL of the solution was transferred into the viscometer. The flow time was recorded, and viscosity was calculated accordingly [12].

2.6.3 Particle Size and Distribution Analysis

Particle size and distribution of BSN were determined using PSA in a wet dispersion unit. Next, nanoparticles were dispersed in distilled water and stirred until a stable signal (green indicator at 10–12 scale range) was achieved on the control unit [13].

2.6.4 Forier Transform Infrared (FT-IR) Spectroscopy

Spectral data were acquired at room temperature using an ATR accessory. The scans were conducted in the 4000–600 cm^{-1} range with 32 scans per sample and a resolution of 4 cm^{-1}. Finally, peaks were analyzed to identify characteristic functional groups [14].

2.6.5 Scanning Electron Microscope (SEM)

Samples were mounted on stubs with double-sided tape and coated with gold for 140 seconds using an autofine coater under vacuum. SEM imaging was performed at an accelerating voltage of 15 kV in secondary electron mode. Magnification was set to 3000x and 5000×. Images were used to examine the surface morphology and granule structure of BS and BSN. The SEM was running with the aperture maintained, as reported by [15].

3. Result and Discussion

3.1 Isolation of Breadfruit Starch (BS)

The starch was isolated from breadfruit (*Artocarpus altilis*) sourced from Tandam Hilir II District, Deli Serdang Regency, North Sumatra Province, Indonesia. Isolation was performed via a water-based sedimentation method involving sequential steps of washing, grating, filtration, sedimentation, and drying. Water, due to its high polarity, acts as an effective, environmentally friendly solvent that enhances extraction efficiency from plant matrices [16]. From 6 kg of fresh breadfruit, approximately 500 g of BS was obtained, corresponding to a yield of 8.33%. This yield is considered efficient for non-conventional starch sources and highlights the feasibility of *A. altilis* as a sustainable starch source in tropical regions.

3.2 Synthesis of Breadfruit Starch Nanoparticles (BSN)

Nanoparticles were synthesized via acid hydrolysis using a 19.6% (w/v) breadfruit starch suspension treated with 2.2 N HCl at 38°C for 24 hours in a shaker incubator. Acid hydrolysis selectively targets the amorphous regions of the starch granules, breaking them into smaller oligomeric chains while largely preserving the crystalline domains [17]. The resulting nanoparticle powder was fine and whitish in appearance, with a final yield of 69%. This relatively high recovery demonstrates good processing efficiency and scalability for nanoparticle production using local starch sources.

3.3 Characterization of Breadfruit Starch and Breadfruit Starch Nanoparticle

3.2.1. Physicochemical Properties

The physicochemical characteristics of breadfruit starch (BS) and breadfruit starch nanoparticles (BSN) are summarized in Table 1. Values presented in Table 1 were selected from the most consistent outcomes across multiple trials and aligned with trends reported in previous studies.

Table 1. Swelling power, solubility, viscosity of SN and BSN

Sample	Swelling power	Solubility (%)	Viscosity (cP)
BS	11.814	7.8	0.988
BSN	9.963	9.371	0.926

Acid hydrolysis induced a reduction in swelling power from 11.814 g/g in BS to 9.963 g/g in BSN. Swelling capacity reflects the ability of starch granules to absorb and retain water when heated. The observed reduction is attributed to the partial depolymerization of amylopectin and collapse of semi-crystalline regions, thereby limiting water uptake [8]. In contrast, solubility increased significantly from 7.8% in BS to 9.37% in BSN. This improvement can be linked to the hydrolysis of glycosidic bonds, which results in smaller starch fragments with higher surface area and hydrophilicity. Similar findings were reported by [18] where acid-treated starches exhibited enhanced solubility due to increased molecular fragmentation.

Viscosity analysis revealed a slight decrease from 0.988 cP (BS) to 0.926 cP (BSN). The lower viscosity of BSN may be due to the disruption of long-chain entanglements, as smaller fragments exhibit lower resistance to flow in aqueous systems. This observation is consistent with [18], who noted that starch nanoparticles exhibit reduced viscosity as a result of shorter chain lengths and diminished molecular interaction in solution. In summary, the observed reductions in swelling power, viscosity, and increase in solubility confirm the structural transformation of breadfruit starch upon acid hydrolysis. These physicochemical changes suggest that BSN may be more suitable for non-gelling applications such as injectable or fast-dissolving drug delivery systems.

3.2.2. Particle Size Analysis (PSA) Analysis

The particle size distribution of BSN was analyzed using PSA, as shown in Figure 1. This size falls within an advantageous range for nanoparticle-based drug delivery, particularly for chemotherapeutic agents like

doxorubicin. Although nanocarriers under 200 nm are typically engineered to exploit the enhanced permeability and retention (EPR) effect, [4] demonstrated that PLGA nanoparticles up to 500 nm could still be efficiently internalized by laryngeal cancer cells (UM-SCC-17A) in monoculture, with an uptake index of approximately 1.5. Despite reduced uptake in co-culture systems due to macrophage phagocytosis, the 500 nm particles remained bioavailable, suggesting that moderately sized nanoparticles can overcome some limitations of passive targeting. In this context, particles sized around 341.7 nm may offer an optimal balance between sufficient tumor penetration and high drug-loading capacity. Furthermore, their intermediate size may minimize rapid clearance by the mononuclear phagocyte system (MPS), extending circulation time and increasing accumulation at the tumor site. These findings support the suitability of breadfruit starch nanoparticles of this size as promising carriers for targeted doxorubicin delivery.

The relatively narrow distribution profile indicates uniformity in hydrolysis, a crucial factor for reproducibility in biological applications. Comparative studies by [10] reported smaller starch nanoparticles (<300 nm) synthesized from broken rice starch, likely due to differences in amylose-to-amylopectin ratio and acid accessibility. Breadfruit starch, with its higher branching density, may offer greater resistance to acid diffusion, thereby yielding slightly larger particles [8].

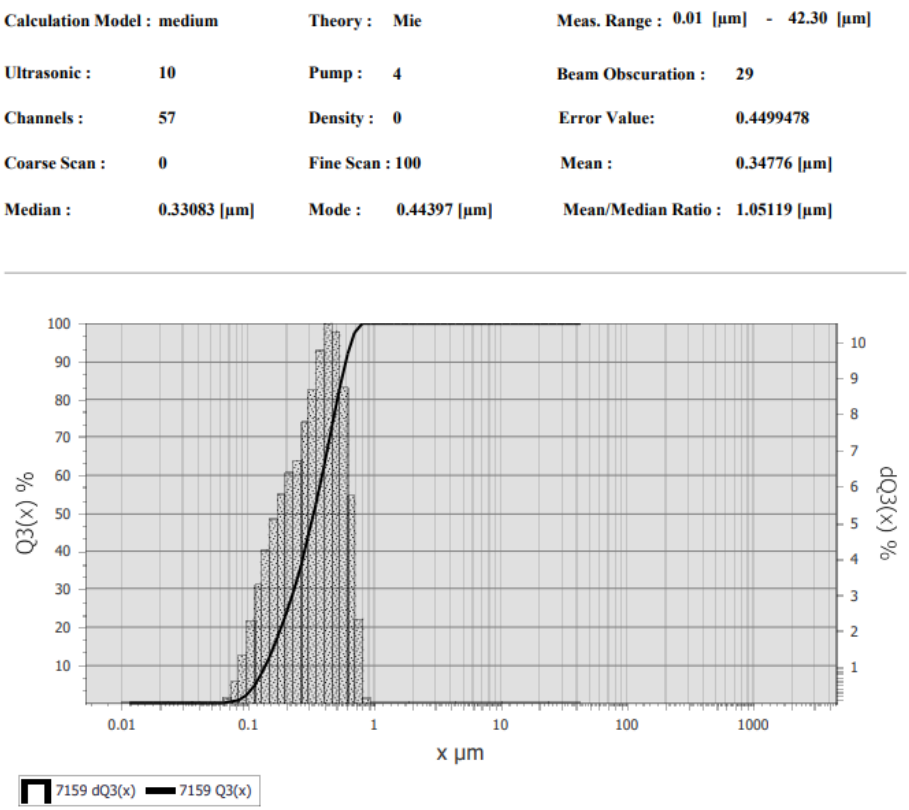

Figure 1. Particle size of breadfruit starch nanoparticle

3.2.3. Fourier Transform Infra Red (FT-IR) Analysis

FT-IR spectra of native breadfruit starch (BS) and breadfruit starch nanoparticles (BSN) are presented in Figure 2. Spectra were recorded using ATR mode with a resolution of 4 cm^{-1} and 32 scans per sample across the 4000–600 cm^{-1} range. Both spectra displayed similar overall profiles, indicating the preservation of core functional groups after acid treatment. Notably, a slight shift was observed in the O–H stretching vibration band from 3251 cm^{-1} (BS) to 3264 cm^{-1} (BSN), which suggests modifications in the hydrogen bonding environment due to molecular rearrangement. The peaks at 2928 cm^{-1} correspond to C–H alkane (–CH_3) vibrations [19]. A road absorption band at 1640 cm^{-1} is associated with O–H bending of absorbed water molecules. A slight shift band at 1146 cm^{-1} (BS) to 1145 $^{-1}$ (BSN) is indicative of C–O stretching in esters, while peaks at 1071 and 996 cm^{-1} represent C–O–C glycosidic linkages within the starch backbone [20].

These results suggest that although hydrolysis induced some molecular reorganization, the glycosidic structure of starch remained chemically intact—supporting the conclusion that structural degradation occurred physically rather than chemically.

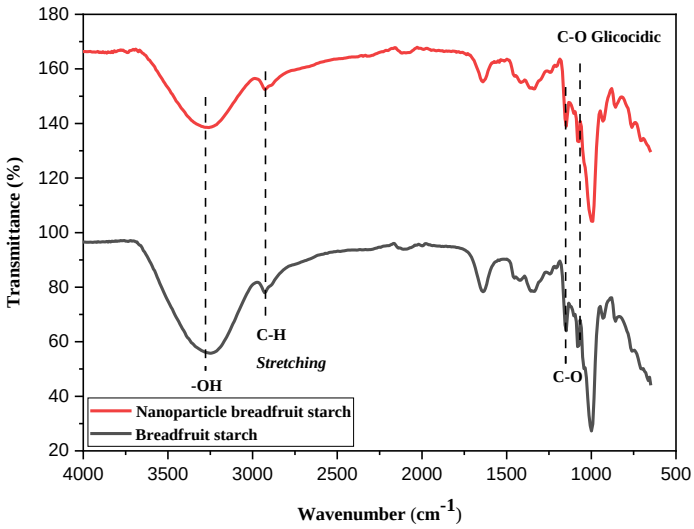

Figure 2. FT-IR spectra of BS and BSN

3.2.4. Scanning Electron Microscope (SEM) Analysis

The surface morphology of BS and BSN were examined using SEM at an accelerating voltage of 15 kV in secondary electron mode. Figure 3 presents representative micrographs captured at two magnifications (3000× and 5000×) for each sample.

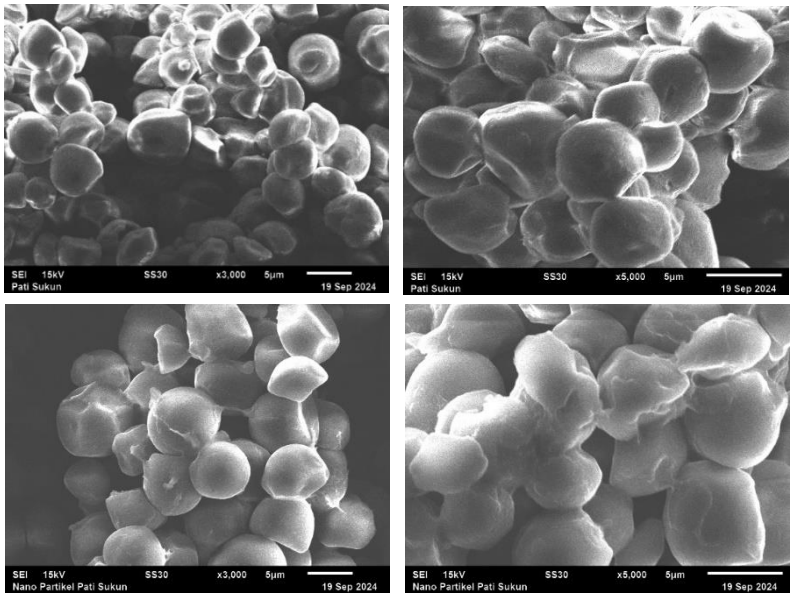

Figure 3. Morphological BS (above) and BSN (bottom) at 3000× and 5000× magnifications

At 3000× magnification, BS exhibited smooth, oval granules with uniform size distribution and well-defined edges, characteristic of unprocessed starch morphology. In contrast, BSN at the same magnification displayed irregular, fragmented granules with noticeable agglomeration, indicating disruption of granule structure following acid hydrolysis.

At 5000× magnification, the morphological differences became more pronounced. The native starch surface appeared compact and intact, while BSN exhibited coarse textures with visible surface erosion and porosity. These textural alterations confirm that acid hydrolysis effectively broke down the amorphous regions of the granules, increasing the surface area. The increased surface irregulari5ty and porosity of BSN are likely to improve aqueous dispersibility and enhance drug loading potential, as rougher surfaces offer more active binding sites for drug molecules [5] These findings align with previous reports on the effect of acid hydrolysis on starch morphology and support the potential of BSN as a functional carrier for hydrophilic drugs.

3.4 Drug Loading Performance

The BSN synthesized in this study exhibited a drug loading efficiency (LE) of 78.3% for doxorubicin (DOX), without chemical surface modifications. This finding underscores the ability of BSN to act as an effective drug carrier, eliminating the need for synthetic modifications that may introduce toxicity or increase production complexity.

The high LE achieved in this study is largely attributed to the physicochemical characteristics of BSN, including its particle size (~347.76 nm), increased surface area, and the presence of hydroxyl functional groups capable of hydrogen bonding with DOX. Furthermore, partial hydrolysis likely generated a porous matrix conducive to passive drug entrapment.

To further contextualize the performance of BSN, a comparison with previously reported starch-based and synthetic carriers is presented in Table 2. Acetylated rice starch nanoparticles exhibited a slightly higher LE (85.9%) but required chemical modification steps [10]. Similarly, hydrazine-functionalized starch-coated Fe_3O_4 nanoparticles (MNP@SPHP) exhibited an LE of 72.6%, offering magnetic targeting advantages but necessitating multistep synthesis involving magnetic core fabrication [21]. A corn starch conjugated Fe_3O_4-g-[poly(*N*-isopropylacrylamide-*co*-maleic anhydride)] yielded smaller particle sizes (~100 nm), yet its LE was limited to 74% [22], underscoring that smaller size alone does not guarantee enhanced encapsulation if carrier–drug interaction is suboptimal.

Carrier Source	Modification Type	Particle Size (nm)	LE (%)	References
Rice starch	Acetylated	<300	85.9	[10]
Starch-coated Fe_3O_4	Hydrazine-modified starch	93	72.6	[21]
Corn starch	Fe_3O_4-conjugated	100	74	[22]
Breadfruit starch	None	347.76	78.3	This study

The comparative data reinforce that BSN represents a biogenic, low-cost, and scalable nanocarrier capable of achieving competitive drug loading through a one-step, acid hydrolysis process. Its high LE, structural simplicity, and lack of chemical additives render it highly suitable for development in pharmaceutical applications—particularly in settings with limited access to advanced processing technologies. These findings support further exploration of underutilized tropical starches such as breadfruit for sustainable nanomedicine innovation.

4. Conclusion

This study successfully demonstrated the synthesis of starch nanoparticles from breadfruit (*Artocarpus altilis*) through a simple acid hydrolysis method. The resulting nanoparticles exhibited favorable physicochemical characteristics, including nanoparticle size (~347.76 nm), enhanced solubility, and reduced viscosity, with structural integrity confirmed by FTIR and significant morphological changes observed via SEM. The breadfruit starch nanoparticles (BSN) achieved a high drug loading efficiency (LE) of 78.3% for doxorubicin hydrochloride (DOX), a value that is comparable to or surpasses those reported for chemically modified starch systems such as acetylated rice starch (85.9%) and corn starch conjugated Fe_3O_4-g-[poly(*N*-isopropylacrylamide-*co*-maleic anhydride)] (74%). These findings confirm the suitability of BSN as a nanocarrier based on its particle size, structural stability, and drug loading performance without chemical modification, highlighting its potential as a cost-effective, sustainable, and scalable drug delivery platform. Overall, this work reinforces the promise of underutilized tropical starches such as breadfruit as viable candidates for nature-derived nanocarriers and supports their further development in pharmaceutical and nanomedicine applications.

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6. Conflict of Interest

Authors declare no conflicts of interest.

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