Research in Molecular Medicine

Encapsulation Strategies in Starch Nanoparticles: Role of Agent Hydrophilicity and Hydrophobicity in Fabrication for Biomedical Use

Pooya Javaherchian[1], Farid Mahinizadeh[2,3], Maryam Sadat Nabavinia[4*]

1. Department of Pharmacognosy, Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
2. Department of Clinical Biochemistry, Faculty of Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
3. Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
4. Department of Pharmacognosy, Traditional Pharmacy and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

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ABSTRACT

Background: Starch nanoparticles (SNPs) are biocompatible carriers for drug delivery in molecular medicine, leveraging their biodegradability and versatility for diseases, like cancer and infections. This narrative review evaluated fabrication methods and their suitability for encapsulating hydrophilic and hydrophobic compounds.

Materials and Methods: A systematic search of PubMed, Scopus, and Web of Science (2010–2025) identified 34 studies on SNP fabrication. Seven methods of nanoprecipitation, emulsion/microemulsion, emulsion cross-linking, dialysis, sacrificial template, ball milling, and ultrasound were categorized as bottom-up or top-down approaches. We extracted data on particle size, morphology, encapsulation efficiency (EE), and drug release kinetics, focusing on hydrophilic (e.g. ciprofloxacin) and hydrophobic (e.g. paclitaxel) compounds. We also reviewed medical uses of SNPs and summarized them to link applications to method selection.

Results: Bottom-up methods (e.g. nanoprecipitation) offer precise control, producing 30–870 nm particles with 20.5–97.56% EE, ideal for lab-scale applications. Top-down methods (e.g. ultrasound) enable scalability, yielding 40–600 nm particles. Hydrophilic compounds integrate well in aqueous-based methods, while hydrophobic compounds benefit from organic phases and chemical modifications (e.g. acetylation). Amphipathic compounds show variable outcomes, requiring optimized conditions. SNPs enhance drug delivery for cancer (e.g. paclitaxel) and infectious diseases (e.g. ciprofloxacin), improving solubility and reducing toxicity.

Conclusion: The polarity of encapsulated compounds governs SNP fabrication method selection, with chemical modifications enhancing stability and EE. This review provides a framework for optimizing SNP production for targeted drug delivery in molecular medicine, particularly for cancer and infectious diseases, highlighting the need for tailored fabrication strategies.

*** Corresponding Author:**
Maryam Sadat Nabavinia, Assistant Professor.
Address: *Department of Pharmacognosy, Traditional Pharmacy and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.*
Phone: *+98 (913) 2476460*
E-mail: *Maryamsadatnabavinia@gmail.com*

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Introduction

Starch, a prevalent biopolymer in plants, serves as an energy reservoir and is prized for its abundance, affordability, non-toxicity, biodegradability, and biocompatibility [1]. These properties position starch as a valuable material across diverse industrial sectors, including food, pharmaceuticals, and medical applications. The physicochemical attributes and morphology of starch vary depending on extracted sources, such as corn, cassava, wheat, and potato, as well as climatic and geographic factors, with corn accounting for approximately 75% of global starch production [2].

As biomaterials, these nanoparticles offer significant potential for improving product quality and enabling innovative applications, such as food packaging, encapsulation, nanocomposite films, emulsion stabilization, and pharmaceutical excipients (e.g. diluents, disintegrants, and binders) [3].

In food packaging, starch-based nanocomposite films and edible coatings can substantially improve tensile strength and water/oxygen-barrier performance, and they can be formulated as active agents with antimicrobial/antioxidant functionality [4]. Starch-based biomaterials are also used in wound dressings and tissue-engineering scaffolds, where hydrogels offer a moist healing environment, tunable degradation, and matrices that support cell adhesion and regeneration [5].

However, native starch faces limitations, including poor thermal and mechanical stability and high hydrophilicity, constraining its industrial utility [6]. Various methods have been proposed to address this issue, including chemical modifications to the constituent units of starch [7], which can be highly complex and may involve changes to the fundamental nature of the materials, and altering the size of starch particles [8], which are comparatively simpler and more feasible for industrial-scale applications. Another method to improve the properties of starch in the pharmaceutical and food industries is by reducing the particle size of starch. Reducing starch particle size to the nanoscale through various fabrication techniques enhances its functionality by increasing surface-to-volume and surface-to-weight ratios [9]. Starch nanoparticles (SNPs) are classified into starch nanocrystals (SNCs), formed by disrupting amorphous granule structures to isolate crystalline regions, and SNPs, produced via the gelatinization of amorphous regions [10].

The fabrication of SNPs employs diverse methodologies, each imparting distinct characteristics in terms of size, solubility, and stability, tailored to specific types of starch. These nanoparticles facilitate targeted or controlled drug release, mitigating risks associated with excessive drug concentrations and toxicity. Fabrication methods are broadly divided into top-down and bottom-up approaches. Top-down methods mechanically or chemically reduce starch into smaller particles using techniques such as ultrasonication, homogenization, or hydrolysis, while bottom-up methods synthesize nanoparticles through controlled molecular aggregation [11, 12].

Bottom-up approaches yield nanoparticles with precise control over size and morphology, high efficiency, and rapid production; however, they require specialized equipment. While suitable for laboratory-scale synthesis, top-down methods are preferred in industrial applications due to their simplicity and cost-effectiveness [13]. The choice of method depends on factors, such as molecular size, hydrophilic or hydrophobic properties, stability, and drug release kinetics.

Starch is gaining importance across medicine and the pharmaceutical industry, as well as in related fields such as food systems and advanced packaging. This paper systematically reviewed the applications of SNPs in medicine, along with seven key fabrication methods: nanoprecipitation, emulsion/microemulsion, emulsion cross-linking, dialysis, sacrificial template, ball milling, and ultrasound. These methods are categorized based on the hydrophilic or hydrophobic nature of the encapsulated compounds, emphasizing the critical role of these properties in method selection.

Application of SNPs in medicine

Beyond starch's role as a drug carrier, SNPs and related starch-based nanoforms are increasingly used in wound care. When incorporated into hydrogel dressings, they help maintain a moist healing microenvironment and can be endowed with antibacterial, pro-angiogenic, and hemostatic functions to accelerate repair in both acute and chronic wounds [14]. Recent prototypes include nitric-oxide–releasing thiolated SNPs embedded in gelatin sponges and starch-fabricated silver nitroprusside nanoparticles, both showing antimicrobial activity and faster closure in preclinical models [15, 16].

SNPs also contribute to medical barrier devices and biofabrication. As reinforcing fillers, SNCs/SNPs have been dispersed into natural-rubber latex to strengthen

thin films relevant to medical gloves [17]. In tissue engineering, starch is used as a printable bio-ink and in starch-hydroxyapatite composites to create cell-compatible scaffolds with controllable mechanics and degradation [18]. Additionally, in biosensing, starch's film-forming and functional chemistry are leveraged to build electrochemical sensors and biosensors for clinical analytes [19]. Taken together, these converging applications position SNPs as a versatile medical material. We therefore turn next to fabrication strategies, emphasizing how the polarity of agents shapes method selection and performance.

Materials and Methods

The review systematically analyzed 34 studies from PubMed, Scopus, and Web of Science (2010–2025), prioritizing transparency in data selection and reporting. All referenced studies were evaluated for ethical compliance, including proper acknowledgment of authorship and funding sources. The following sections detail the seven fabrication methods, organized into bottom-up and top-down approaches, with a focus on their suitability for encapsulating hydrophilic and hydrophobic compounds. Table 1 shows recent studies that we discuss further.

Bottom-up methods

Bottom-up processes for synthesizing SNPs involve the controlled assembly of molecular or macromolecular units into nanostructured particles, offering precise control over size, morphology, and functionality [2, 54]. Unlike top-down methods that mechanically or chemically reduce starch granules, bottom-up approaches rely on thermodynamic and molecular interactions, such as hydrogen bonding, Van der Waals forces, and hydrophobic effects, to drive particle formation [55]. The hydrophilic nature of native starch, attributed to its amylose and amylopectin components, and the hydrophobic properties introduced via chemical modifications (e.g. acetylation, octenyl succinylation), significantly influence nanoparticle structure and stability [56]. These properties determine how starch interacts with organic and aqueous phases, surfactants, and encapsulated compounds, tailoring SNPs for applications in drug delivery, food encapsulation, and emulsion stabilization [57]. This section reviews key bottom-up methods: nanoprecipitation, emulsion/microemulsion, emulsion cross-linking, dialysis, and sacrificial template, emphasizing how hydrophobic and hydrophilic interactions shape SNP structure, with insights drawn from recent studies.

Nanoprecipitation

Nanoprecipitation involves mixing an organic phase containing dissolved starch or modified starch with an aqueous phase to induce controlled precipitation [9, 54]. The process leverages the differing polarities of the phases, with hydrophobic and hydrophilic interactions driving the assembly of starch molecules into nanoparticles [58]. Native starch, rich in hydrophilic hydroxyl groups from amylose and amylopectin, is typically dissolved in the aqueous phase (e.g. water with NaOH or urea), while hydrophobic loading compounds enhance compatibility with organic phases, like acetone or ethanol [3]. The gradual addition of the organic phase to the aqueous phase causes starch to precipitate around encapsulated compounds, with particle size and morphology governed by the hydrophobicity or hydrophilicity of both the starch and the compound [12]. Figure 1 presents a diagrammatic illustration of the nanoprecipitation technique. The hydrophilicity or hydrophobicity of the encapsulated compound significantly shapes SNP structure and encapsulation efficiency (EE). Studies demonstrate nanoprecipitation's versatility. The studies below demonstrate nanoprecipitation's versatility across compound polarities, with outcomes influenced by solvent selection, starch modifications, and compound properties.

Hydrophilic compounds

Mahmoudi Najafi et al. encapsulated ciprofloxacin, a hydrophilic antibiotic, in acetylated corn starch SNPs using acetone as the organic phase, achieving particle sizes of 221–324 nm, a polydispersity index (PDI) below 0.5, and encapsulation efficiencies of 20.5–89.1% depending on phase ratios [20]. Because ciprofloxacin is hydrophilic, it preferentially partitions into the external aqueous phase during nanoprecipitation. This typically lowers EE [59] and depending on phase ratios and mixing, can shift formation toward growth-dominated regimes, yielding larger and/or more polydisperse particles [60, 61].

Hydrophobic compounds

Acevedo-Guevara et al. encapsulated curcumin, a hydrophobic polyphenol, in acetylated green banana SNPs, yielding 135–190 nm particles with 85–90% EE [22]. Fu et al. encapsulated lutein, a hydrophobic carotenoid, in corn and high amylose starch SNPs (250–350 nm), noting that ethanol as the organic phase improved dispersibility and oxidative stability [23].

Table 1. Overview of studies on starch nanoparticle fabrication

Variables	Ref.	Agent	Physical Chemistry	Starch Type	Aqueous Solvent	Organic Solvent	Particle Size (nm)	EE (%)	LE (%)	Property	Proposed General Application (Specific Application)
Nano precipitation	[20]	Ciprofloxacin	Hydrophilic	Acetylated corn starch	Water	Acetic anhydride and acetic acid	221–324 nm	20.5–89.1%	N/A	Sustained release for prolonged and controlled drug delivery.	Drug delivery (antibiotic delivery)
	[21]	Paclitaxel	Hydrophobic	Porous corn starch	Water	Acetone	N/A	73.92±0.54%	14.13±0.27%	Porous morphology, IC_{50} value: 85.68±7.38 µM	Drug delivery (anticancer chemotherapy delivery)
	[22]	Curcumin	Hydrophobic	Acetylated green banana starch	Water	Acetone	135–190 nm	85–90%	N/A	V-shaped crystalline structure for enhanced stability and functionality in nanoparticle applications.	Dietary bioactive delivery (anti-inflammatory/antioxidant effects)
	[23]	Lutein	Hydrophobic	Corn and high amylose starch	Water	Ethanol	250–350 nm	N/A	N/A	Improved dispersibility, enhanced oxidative stability	Dietary bioactive delivery (ocular health)
	[24]	Propolis	Hydrophobic	Potato and cassava starch	Water	Ethanol	8–340 nm	N/A	65–73%	Broad size range, adaptable formation	Dietary bioactive delivery (antimicrobial/anti-inflammatory)
	[25]	(No agent loaded)	(No agent loaded)	Seven starch types (e.g. waxy corn, potato, pea)	Water	Ethanol	30-75 nm	N/A	N/A	V-shaped crystalline structure for enhanced stability and functionality in nanoparticle applications.	No agent loaded
	[26]	Quercetin	Hydrophobic	Sago starch	NaOH/urea/H_2O (1:1:98)	HCL	292.1 nm	80±2%	42.5±1.2%	Release: 96.12±1.8% in 12 hours	Dietary bioactive delivery (antioxidant)
	[27]	Quercetin	Amphipathic	Unripe banana starch	NaOH/Urea/H_2O (1:1:98)	HCl/H_2O	67.67–133.27 nm	39.6–85.28%	N/A	Variable release of 30.71–98% over 12 hours for tailored drug delivery kinetics.	Dietary bioactive delivery (antioxidant)
	[28]	Piroxicam	Hydrophobic	Quinoa starch	NaOH, glycerin, and distilled water in the ratio of (0.8: 1: 98.2 w/w)	HCl/H_2O	282-870 nm	N/A	N/A	Rapid release of 98.8% within 2 hours for efficient drug delivery.	Dietary bioactive delivery (NSAID analgesic/anti-inflammatory)
	[29]	(No drug loaded)	(No agent loaded)	Normal, high amylose, and waxy maize starches	NaOH+urea+H_2O	Ethanol	29.7 ± 77.4 nm	N/A	N/A	Tween 20-stabilized, enhanced aqueous dispersion with smaller sizes using waxy starch.	No drug loaded
	[30]	Quercetin	Amphipathic	Corn starch	90 DMSO/H_2O ratio	10 ethanol/solvent ratio	166.35 nm	N/A	N/A	Controlled release: 96.12–98%	Dietary bioactive delivery (antioxidant)
	[31]	Piperine	Hydrophobic	Sago starch	NaOH: urea (NU) (0.8:1 wt%)	Ethanol	52–154 nm	N/A	2.268 mg/mL	Uniform size, compact structure	Dietary bioactive delivery (pharmacoenhancer)
	[32]	Lutein	Hydrophobic	Lotus root starch	N/A	N/A	N/A	84.60%	N/A	Controlled release of 86.5% for optimized drug delivery kinetics.	Dietary bioactive delivery (ocular health)

Variables	Ref.	Agent	Physical Chemistry	Starch Type	Aqueous Solvent	Organic Solvent	Particle Size (nm)	EE (%)	LE (%)	Property	Proposed General Application (Specific Application)
Emulsion/microemulsion	[33]	Penicillin, streptomycin	Hydrophilic	Corn starch	NaOH/Urea/H_2O (8:4.6:5.4)	Sunflower oil	N/A	N/A	N/A	Tween-20 surfactant stabilization	Drug delivery (antibiotic delivery)
	[34]	Curcumin	Hydrophobic	Rice starch modified by OSA	Water	Sunflower oil	N/A	91.73%	N/A	Thermodynamically stable structure	Dietary bioactive delivery (anti-inflammatory/antioxidant effects)
	[35]	Epigallocatechin gallate	Amphiphilic	Corn and OSA, and shells	Water	Soybean oil	413–841 nm	41.43–63.89%	N/A	Contains Span 80 surfactant	Dietary bioactive delivery (external genital/perianal warts [HPV])
	[36]	CG-1521	Amphiphilic	Corn starch	Water	DMSO	200 nm	N/A	N/A	Contains PVA surfactant	Drug delivery (investigated as an anticancer agent)
	[37]	β-carotene	Hydrophobic	Various kinds of modified OSA-starch	Water	Ethyl acetate	300–600 nm	70%	N/A	Enhances solubility and stability for food fortification and nutraceutical delivery	Dietary bioactive delivery (food fortification)
	[38]	Resveratrol	Hydrophobic	Corn starch	Water	ODO and glyceryl triacetate (1:1)	145.20±1.37 nm	N/A	98.81±2.34%	Contains Tween 20, 40, 60, and 80 surfactants	Dietary bioactive delivery (antioxidant)
	[29]	(No agent loaded)	(No agent loaded)	Maize starches (normal, high amylose, waxy)	Water	Soybean or sunflower	35-147 nm	N/A	N/A	Contains Tween 20 and Span 60 surfactants	No agent loaded
Emulsion cross-linking	[39]	5-fluorouracil	Hydrophilic	Resistant starch type 3	Potassium hydroxide solution	Cyclohexane	300 nm	N/A	49.25%	Contains Span-80, Tween-80 surfactants, and MBAA cross-linking agent	Drug delivery (anticancer chemotherapy delivery)
	[40]	Methylene blue	Hydrophilic	Acid-treated starch	Water	Butan-1-ol/ cyclohexane	94.3 nm	N/A	80.27%	Contains $C1_6$mimBr surfactant for enhanced viscoelastic and hydrogel-forming properties.	Drug delivery (antidote in methemoglobinemia- antimicrobial)
	[41]	Paclitaxel	Hydrophobic	Acid-modified cassava starch	Water	Cyclohexane	326–775 nm	N/A	14.56–32.07 mg/g	Contains Span 80 and Tween 60 surfactants, and $POCl_3$ cross-linking agent	Drug delivery (anticancer chemotherapy delivery)
	[42]	Insulin	Hydrophilic	Potato starch	Water	Liquid paraffin	194.2±6.3-229.5±7.2 nm	N/A	N/A	Contains Span 80 surfactant, epichlorohydrin, and $POCl_3$ cross-linking agents, with sustained drug release over 12 hours	Drug delivery (therapy for type 1 and type 2 diabetes mellitus)

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Variables	Ref.	Agent	Physical Chemistry	Starch Type	Aqueous Solvent	Organic Solvent	Particle Size (nm)	EE (%)	LE (%)	Property	Proposed General Application (Specific Application)
Dialysis	[43]	Curcumin	Hydrophobic	Oxidized SNPs	Phosphate-buffered saline (PBS)	DMSO	212 nm	N/A	N/A	Exhibits pH-responsive drug release	Dietary bioactive delivery (anti-inflammatory/antioxidant effects)
	[43]	Cholesterol-imidazole	Hydrophobic	Oxidized SNPs	Phosphate-buffered saline (PBS)	DMSO	213 nm	N/A	N/A	Exhibits pH-responsive drug release	Drug delivery (anti-fungal drugs)
	[44]	Benzo[a] pyrene	Hydrophobic	OSA-BS-starch	Water	Water and DMSO	5 nm	N/A	28%	Small nanoparticles with 28% Benzo[a]pyrene loading capacity	Model payload (hydrophobic model of high toxicological concern)
	[45]	Potassium Sorbate (PS)	Hydrophilic	Tapioca starch	Water	DMSO	<450 nm	N/A	N/A	Retains up to 6889 ppm potassium sorbate with modified starch for antimicrobial applications	Dietary bioactive delivery (food preservative)
Sacrificial template	[46]	Doxorubicin	Hydrochloride	Hollow starch	Water	(One phase used)	30–300 nm	N/A	97.56%	Exhibits a hollow nanoparticle structure	Drug delivery (anti-cancer chemotherapy delivery)
	[47]	Phenolic acids	Hydrophilic	Corn starch	Water	(One phase used)	87–123 nm	95.26%	N/A	Hollow nanospheres with a large cavity for phenolic acid encapsulation	Dietary bioactive delivery (antioxidant/anti-inflammatory)
Ball milling	[48]	Camel milk probiotics	Hydrophilic	Hazelnut starch	(Dried condition)	(Dried condition)	271 nm	N/A	N/A	Zeta potential of -19.9 mV for stable nanoparticle dispersion.	Dietary bioactive delivery (co-administered with antibiotics to reduce the risk of antibiotic-associated diarrhea)
	[49]	(No agent loaded)	(No agent loaded)	Corn starch	Water with H_2SO_4	(One phase used)	66–320 nm	N/A	N/A	Reduced crystallinity for enhanced solubility and EE.	No agent loaded
	[49]	(No agent loaded)	(No agent loaded)	Waxy maize starch	Water with H_2SO_4	(One phase used)	320.6±10.3 nm to 66.7±3.6 nm	41.6±2.3% to 13.5±0.7%	N/A	Disrupted crystalline structures with retained crystalline properties, ideal for aqueous-phase processing.	No agent loaded
	[50]	(No agent loaded)	No agent loaded	Potato starch	(Dried condition)	(Dried condition)	120 nm		N/A	Spherical morphology for uniform particle structure and enhanced functionality.	No agent loaded

Variables	Ref.	Agent	Physical Chemistry	Starch Type	Aqueous Solvent	Organic Solvent	Particle Size (nm)	EE (%)	LE (%)	Property	Proposed General Application (Specific Application)
Ultrasound	[51]	L-ascorbic acid, oxalic acid	Hydrophilic	Potato starch	Water with H_2SO_4	(One phase used)	80–40 nm	N/A	N/A	Enhanced dispersion and uniformity for effective encapsulation of hydrophilic compounds.	Dietary bioactive delivery (supplementation)
	[52]	Rutin	Hydrophilic	Quinoa and corn starch	Water with NaOH	Ethanol	107–222 nm	63.1–67.4%	N/A	Rough, plush-like particle surface with sixfold enhanced adsorption compared to native starch.	Dietary bioactive delivery (venoactive agent)
	[8]	Resveratrol	Hydrophilic	Water chestnut	Water (0.1 M NaOH)	Ethanol	606 nm	79.37%	N/A	Porous structures with reduced crystallinity for improved solubility and EE.	Dietary bioactive delivery (antioxidant)
				Horse chestnut			420 nm	81.46%	N/A		
				Lotus stem			535 nm	75.83%	N/A		
	[53]	(No agent loaded)	(No agent loaded)	Normal and waxy starch	Water	Isopropanol	600 nm	N/A	N/A	Platelet-like, thin morphology (5 nm thick) for enhanced surface area and functionality.	No agent loaded

Abbreviation: EE: Encapsulation efficiency; LE: Loading Efficiency; N/A: Not available; NaOH: Sodium hydroxide; HCl: Hydrochloric acid; DMSO: Dimethyl sulfoxide; OSA: Octenyl succinic anhydride; ODO: Octadecene; H_2O: Water; H_2SO_4: Sulfuric acid; $C1_6$mimBr: 1-Hexadecyl-3-methylimidazolium Bromide; MBAA: N,N'-Methylenebisacrylamide; $POCl_3$: Phosphorus oxychloride; PVA: Polyvinyl alcohol.

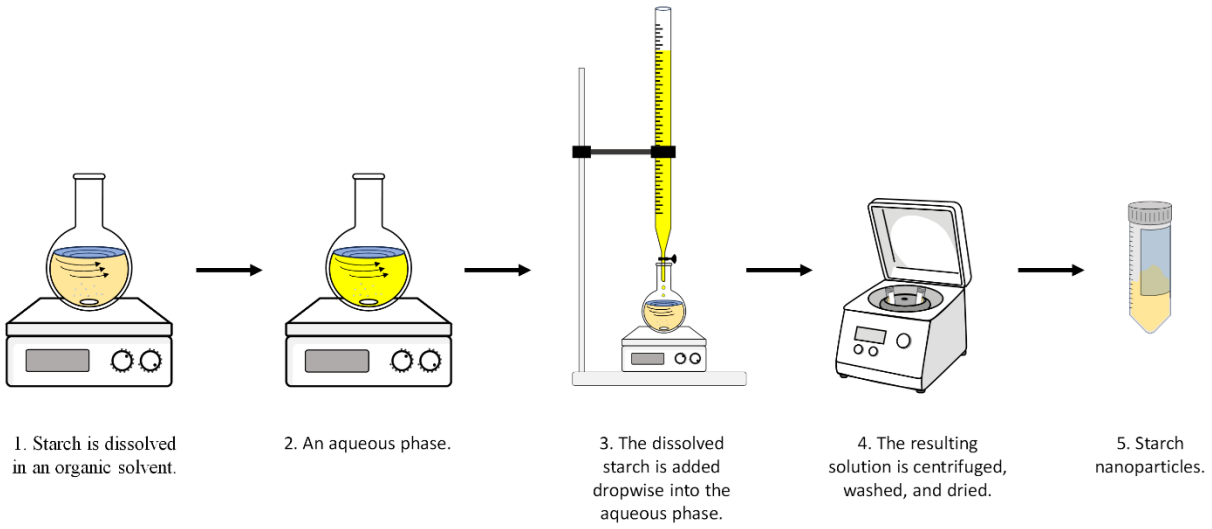

Figure 1. Nanoprecipitation process for snps. a diagram showing the mixing of aqueous and organic phases to form SNPs via controlled precipitation

Note: Original artwork by the authors; no prior publication or third-party content was used.

The water-repelling nature of these compounds drives tighter clustering in the organic solvent, resulting in smaller, more compact particles with higher drug loads. Acetylation enhances starch compatibility with the organic phase, explaining the high encapsulation efficiencies and stability observed. Similarly, Jaízia dos Santos Alves et al. encapsulated propolis extract, a hydrophobic compound, in potato and cassava SNPs, yielding 8–340 nm particles with 65–73% loading [24]. Wan-Hong et al. encapsulated piperine, a hydrophobic alkaloid, in sago SNPs, achieving 52–154 nm particles and 2.268 mg/mL loading capacity [31]. Zhang et al. encapsulated lutein into lotus root SNPs, achieving 84.6% EE and 86.5% controlled release in simulated intestinal fluid, attributed to hydrogen bonding and hydrophobic interactions [32]. Kumar et al. loaded quercetin, another hydrophobic compound, into Sago SNPs using a modified nanoprecipitation method. The nanoparticles had a Z-average size of 292.1 nm (dynamic light scatter [DLS]) and 113.51±43.24 nm (scanning electron microscope [SEM]), with an EE of 80±2% and a loading capacity of 42.5±1.2%. In vitro release reached 96.12±1.8% within 12 hours [26]. Bhatia et al. prepared piroxicam, a hydrophobic anti-inflammatory agent, loaded in quinoa SNPs. Particle sizes ranged from 282-870 nm with a PDI of 0.339-0.772, and in vitro release reached 98.8% within 2 hours, indicating efficacy for compounds with mixed characteristics [28]. Wang et al. compared direct loading and nanoprecipitation for paclitaxel, a hydrophobic drug, in porous corn starch. Nanoprecipitation outperformed the direct method with drug loading of 14.13±0.27% and EE of 73.92±0.54% vs 9.79±0.31% and 71.17±0.67%. SEM confirmed paclitaxel in starch pores, with MTT assays showing IC50 values of 85.68±7.38 μM for SNPs [21]. These consistent results for hydrophobic compounds, like curcumin and lutein, exhibit enhanced compatibility with organic solvents, such as acetone or ethanol, promoting compact particle assembly and higher encapsulation efficiencies driven by their water-repelling properties.

Amphipathic compounds

Kumar et al. used unripe banana starch to encapsulate quercetin, an amphipathic compound, producing spherical SNPs (67.67–133.27 nm) with encapsulation efficiencies of 39.6–85.28% and drug release of 30.71–98% over 12 hours [27]. Jiang et al. encapsulated quercetin, an amphipathic compound, in corn SNPs using DMSO/ethanol, achieving 166.35 nm particles and enhanced stability [30]. Amphipathic compounds can partition into both organic and aqueous phases; consequently, nanoprecipitation outcomes (size, PDI, EE) become highly sensitive to solvent/antisolvent ratios and mixing conditions that set supersaturation, nucleation, and growth [60]. Optimizing these phase conditions is therefore essential to balance the compound's dual affinities and reduce variability in particle characteristics [62]. In parallel, chemical modification of starch (e.g. acetylation or OSA-substitution) increases hydrophobic character and interfacial activity [63], improving compatibility with organic phases and consistently enhancing the encapsulation and delivery of hydrophobic actives [22].

General trends

Qin et al. utilized seven starch types (e.g. waxy corn, potato, pea) with amylose content ranging from 0.8% to 69% to form SNPs. Particle sizes reduced from 15-49 μm (original starch) to 30-75 nm, all exhibiting a V-shaped crystalline structure, demonstrating the method's adaptability across starch types [25]. Gutiérrez et al. used normal, high amylose, and waxy maize starches, observing that an organic phase addition rate of 4 ml/h yielded optimal SNPs (29.7±77.4 nm, PDI 0.43±0.04) for normal starch. Waxy starch produced smaller SNPs, suggesting that amylopectin aids in hydrophobic compound encapsulation [29]. The smaller sizes of the waxy starch suggest that amylopectin's branched structure aids in the encapsulation of hydrophobic compounds by enhancing precipitation efficiency in organic phases. Future research could focus on optimizing solvent compositions to stabilize amphipathic compounds or developing novel starch modifications to improve encapsulation across diverse polarities.

Emulsion/microemulsion

Emulsion and microemulsion methods emulsify an aqueous phase containing starch with an organic phase, stabilized by surfactants [11, 54]. Native starch's hydrophilic nature and modified starches' hydrophobic properties (e.g. octenyl succinylation) facilitate stable droplet formation [35]. In emulsions, vigorous homogenization (e.g. microfluidization, ultrasonication) creates droplets, while microemulsions form spontaneously due to thermodynamic stability, yielding smaller, more uniform SNPs [12]. The hydrophilic-lipophilic balance (HLB) of surfactants influences droplet size and particle structure. A visual depiction of this method is provided in Figure 2a.The studies below illustrate how compound polarity and emulsion type shape outcomes.

Hydrophilic compounds

Ismail et al. encapsulated hydrophilic antibiotics (penicillin, streptomycin) in corn SNPs via water-in-oil (W/O) emulsions, achieving stable particles with antibacterial activity [33]. Hydrophilic compounds, like penicillin, align effectively with W/O emulsions, where their aqueous compatibility supports stable particle formation. However, the dominance of the water phase often results in larger particles, as hydrophilic compounds disperse broadly rather than forming tight clusters.

Hydrophobic compounds

Gong et al. encapsulated curcumin, a hydrophobic agent, in rice starch modified with octenyl succinic anhydride, achieving 91.73% EE with Tween 20 [34]. De Paz et al. encapsulated β-carotene, a hydrophobic compound, in various modified OSA-starch, reporting particle sizes of 300–600 nm with an EE of 70% [37]. Bi et al. encapsulated resveratrol, another hydrophobic compound, in corn starch microemulsions, achieving a particle size of 145.20±1.37 nm and a PDI of 0.096±0.006, with a loading efficiency of 98.81±2.34% [38]. These hydrophobic compounds, such as curcumin and β-carotene, thrive in oil-in-water (O/W) emulsions or microemulsions, where surfactants, like Tween 20, facilitate their integration into the starch matrix. The high efficiencies and smaller particle sizes result from the compounds' preference for the oil phase, enhanced by modified starches and the thermodynamic stability of microemulsions.

Amphiphilic compounds

Gao et al. encapsulated epigallocatechin gallate (EGCG), an amphiphilic catechin, in corn and modified SNPs, yielding particle sizes of 413–841 nm with encapsulation efficiencies of 41.43–63.89% [35]. Alp et al. encapsulated CG-1521, an amphiphilic histone deacetylase inhibitor, in corn SNPs, achieving particle sizes of 200 nm and extended release [36]. The dual-phase affinities of these compounds complicate emulsion stability, as they interact with both water and oil phases, leading to larger, less uniform particles and moderate efficiencies. This variability highlights the need for fine-tuned surfactant and phase conditions.

General trends

Gutiérrez et al. synthesized SNPs from maize starches (normal, high amylose, waxy), achieving sizes ranging from 35 to 147 nm. Waxy and high amylose starches with Tween 20 (hydrophilic surfactant) produced smaller SNPs, with the type of oil having little effect. This suggests their suitability for encapsulating hydrophobic compounds with oil type having little effect, suggesting suitability for hydrophobic compounds [29]. The smaller sizes associated with waxy starch indicate its appropriateness for hydrophobic compounds, as amylopectin enhances emulsion stability in oil-rich systems.

These methods rely on the stabilization of aqueous and organic phases through surfactants, with the HLB dictating particle size and uniformity. Microemulsions, benefiting from thermodynamic stability, offer superior con-

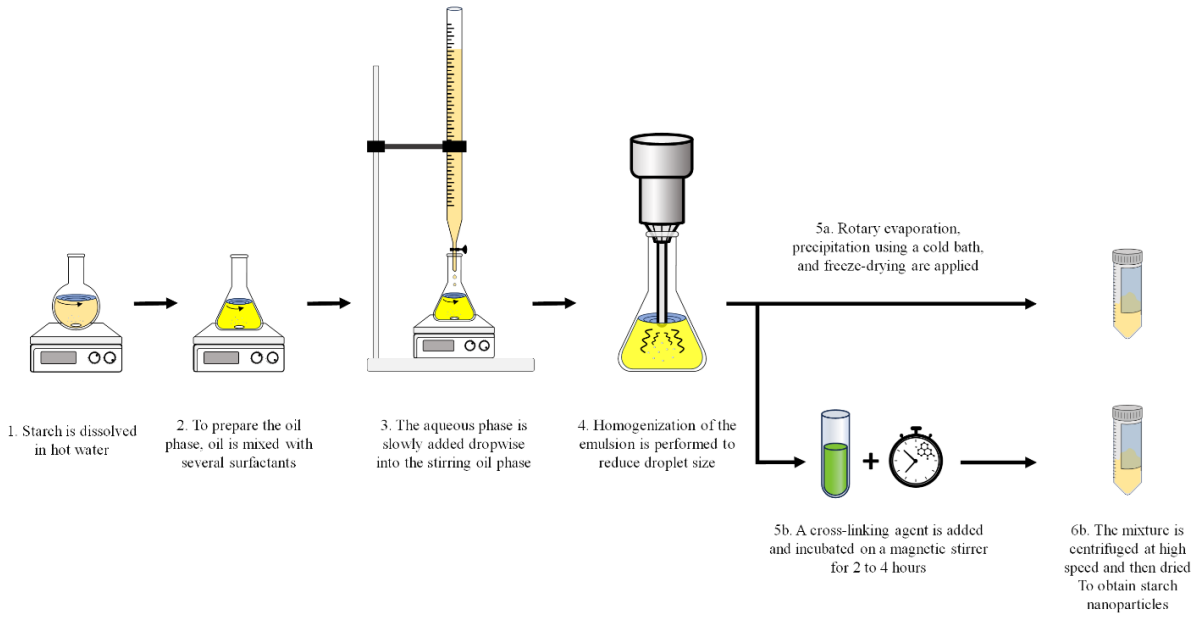

Figure 2. Emulsion/microemulsion and emulsion cross-linking method for SNPs

a) Illustration of starch emulsification with an organic phase, stabilized by surfactants; b) Schematic depicting the formation of networked SNPs using cross-linking agents in emulsified droplets

Note: Original artwork by the authors; no prior publication or third-party content was used.

trol for hydrophobic compounds. Further studies could explore surfactant formulations tailored to amphiphilic compounds or investigate the influence of phase dielectric properties on emulsion stability across varied polarities.

Emulsion cross-linking

Emulsion cross-linking combines an aqueous phase with cross-linking agents and starch, which is emulsified in an organic phase with surfactants [11, 54]. This process forms networked nanoparticles through cross-linking reactions within emulsified water droplets, with particle size dependent on emulsion type [12]. This process is schematically shown in Figure 2b.

Hydrophilic native starch and hydrophobic modified starches (e.g. OSA-modified) stabilize emulsions, while the amylose/amylopectin ratio and the type of cross-linker (e.g. epichlorohydrin, $POCl_3$) influence SNP structure and biocompatibility.

The studies below show the method's effectiveness, particularly for hydrophilic compounds.

Hydrophilic compounds

Ding et al. encapsulated 5-fluorouracil, a hydrophilic drug, in resistant starch type 3 SNPs, achieving particle sizes of 300 nm with controlled release in simulated gastrointestinal conditions and a loading efficiency of 49.25% [39]. Wang et al. encapsulated methylene blue, another hydrophilic compound, in acid-treated starch granules with epichlorohydrin, resulting in particle sizes of 94.3 nm and a loading efficiency of 80.27% [40]. Jain et al. encapsulated insulin in potato SNPs, reporting particle sizes ranging from 194.2±6.3 to 229.5±7.2 nm based on the concentration of epichlorohydrin as a cross-linking agent, along with sustained release over 12 hours [42]. Hydrophilic compounds, like 5-fluorouracil, which are compatible with aqueous phases, interact effectively with cross-linkers, such as epichlorohydrin, resulting in well-structured particles with high loading capacities.

Hydrophobic compounds

Xie et al. encapsulated paclitaxel as a hydrophobic drug in acid-modified cassava SNPs with $POCl_3$, yielding particle sizes ranging from 326 to 775 nm with loading efficiencies of 14.56 to 32.07 mg/g [41]. Hydrophobic compounds, like paclitaxel, face challenges in water-dominant emulsions, where their organic-phase preference leads to reduced loading and larger particle sizes due to phase incompatibilities. The choice of cross-linker, such as the potentially toxic phosphorus oxychloride ($POCl_3$), impacts biocompatibility and process safety. Nanoemulsions enhance particle size control, while modified starches improve hydrophobic compound integration.

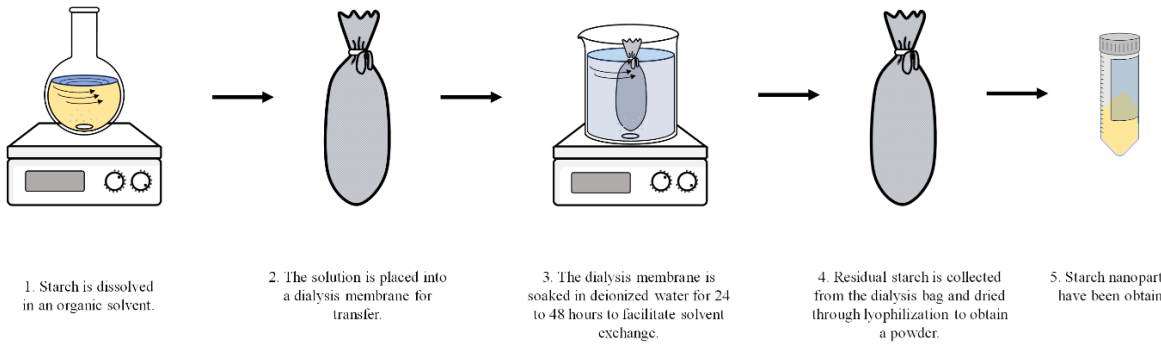

Figure 3. Dialysis method for starch nanoparticle synthesis

Note: Schematic diagram illustrating starch aggregation through polarity changes across a dialysis membrane. Redesigned by the authors based on Morán et al. 2021 [65].

Emulsion cross-linking integrates cross-linking agents within emulsified systems to form networked nanoparticles, with compound polarity shaping the efficacy of the process. Future research could prioritize biocompatible cross-linkers to enhance safety for hydrophobic compounds or adjust emulsion compositions to better accommodate diverse polarities.

Dialysis

Dialysis is a bottom-up method for synthesizing SNPs, where starch dissolved in an organic phase within a dialysis bag is submerged in an aqueous phase, inducing aggregation and precipitation through polarity changes [11, 54]. Figure 3 displays a schematic outline of this approach.

The method leverages hydrophilic native starch and hydrophobic modified starches, with amylose content and phase ratios critically affecting particle uniformity [12]. High-amylose starches enhance structural stability, while optimizing the phase ratio ensures controlled precipitation.

The studies below emphasize the method's success with hydrophobic compounds.

Hydrophobic compounds

Xu et al. encapsulated curcumin and cholesterol-imidazole conjugates as hydrophobic compounds in oxidized SNPs, achieving particle sizes of approximately 212 nm and pH-responsive release [43]. Delsarte et al. encapsulated Benzo[a]pyrene, another hydrophobic compound, in OSA-BS-SNPs, achieving particle sizes of 5 nm with a loading efficiency of 28% [44]. The low water solubility of these compounds drives compact particle formation under organic phase influence, explaining the small sizes and precise control. Modified starches enhance compatibility, supporting stimuli-responsive release.

Hydrophilic compounds

Alzate et al. encapsulated potassium sorbate (PS), a hydrophilic antimicrobial, in tapioca starch using dialysis within a microemulsion. Nanoparticles (<450 nm) derived from diluted solutions retained up to 6889 ppm PS, significantly exceeding the retention in microparticles (20-200 µm, up to 1243 ppm), with acetylated starch demonstrating the highest retention at 2564 ppm [45]. The larger particle sizes result from broader dispersion in the aqueous phase, although modified starches improve stability and retention.

Dialysis facilitates nanoparticle formation through controlled polarity transitions across a membrane, with compound properties governing aggregation dynamics. The method's reliance on phase polarity gradients underscores its suitability for hydrophobic compounds, while high-amylose starches bolster structural integrity for hydrophilic ones. Further investigations could optimize diffusion parameters to improve particle uniformity for hydrophilic compounds or explore membrane compositions to enhance precipitation control across polarities.

Sacrificial template

The sacrificial template method involves coating a template (e.g. silica, calcium carbonate) with starch, followed by template removal to create hollow nanoparticles [11, 54]. A graphical representation of this method is shown in Figure 4.

The method leverages hydrophilic starch for aqueous phase coating and hydrophobic modifications for organic phase compatibility, with template porosity and amy-

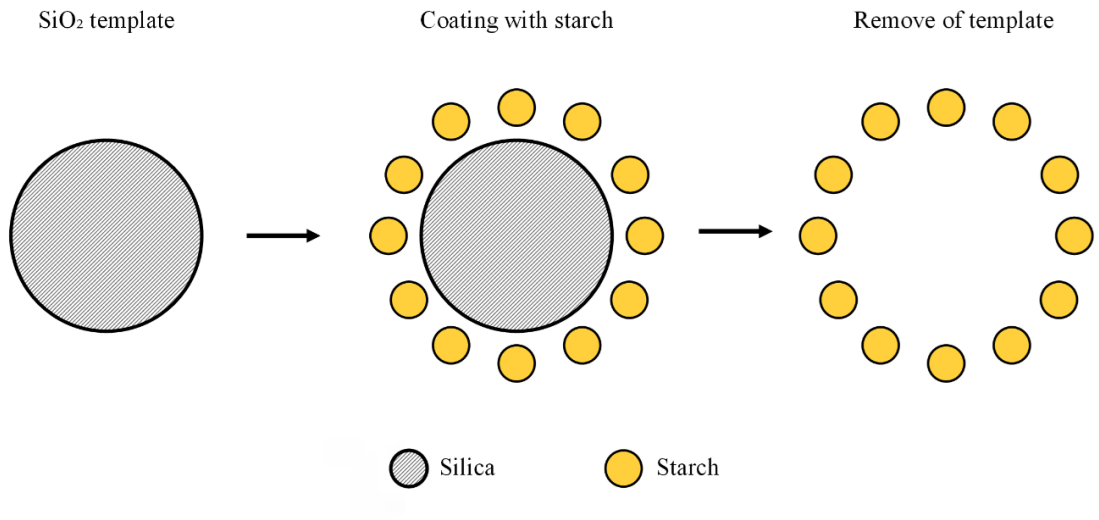

Figure 4. Sacrificial template method for hollow nanoparticles

Note: Representation of starch coating on a template, followed by removal to create hollow nanoparticles. Redesigned by the authors based on Morán et al. 2021 [64].

lose content affecting loading capacity and particle size [12]. High-amylose starches enhance structural integrity, while porous templates increase EE. The studies below focus on hydrophilic compounds.

Hydrophilic compounds

Yang et al. encapsulated doxorubicin hydrochloride in hollow SNPs using $CaCO_3$ templates, achieving particle sizes ranging from 30 to 300 nm and a loading efficiency of 97.56% [46]. Li et al. encapsulated phenolic acids, another hydrophilic compound, in corn starch with short linear glucan, achieving particle sizes of 87 to 123 nm with an EE of 95.26% [47].

The sacrificial template method excels in producing hollow nanoparticles for hydrophilic compounds, leveraging aqueous-phase interactions to coat templates, such as calcium carbonate. Hydrophilic compounds, such as doxorubicin hydrochloride, integrate seamlessly

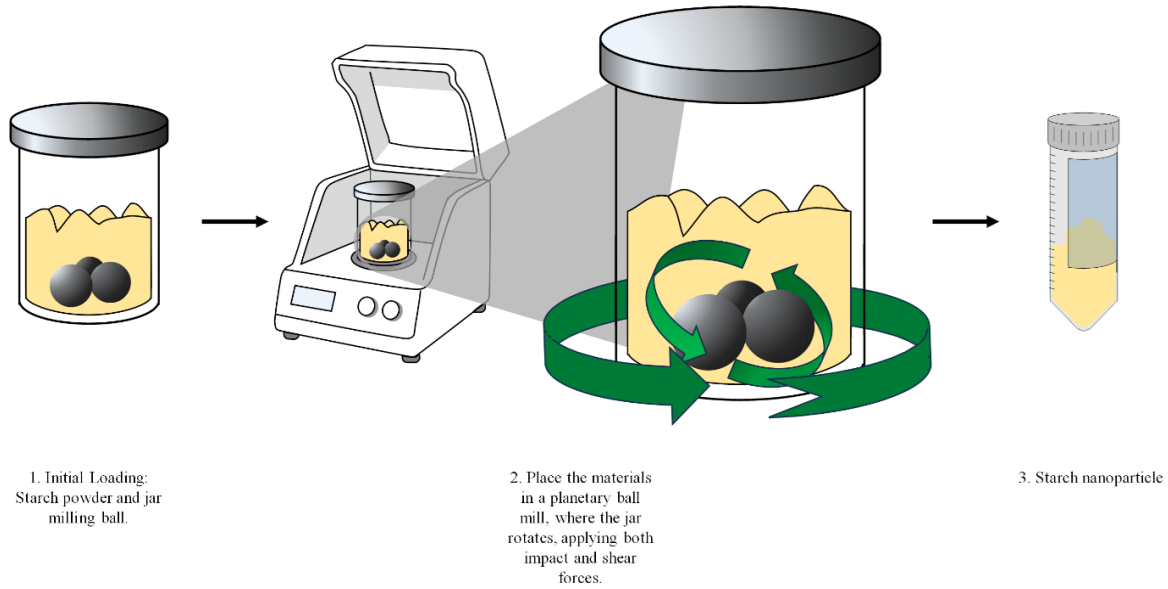

Figure 5. Ball milling for starch particle reduction

Note: Diagram of mechanical size reduction of starch particles via high-energy impact and friction. Original artwork by the authors; no prior publication or third-party content was used.

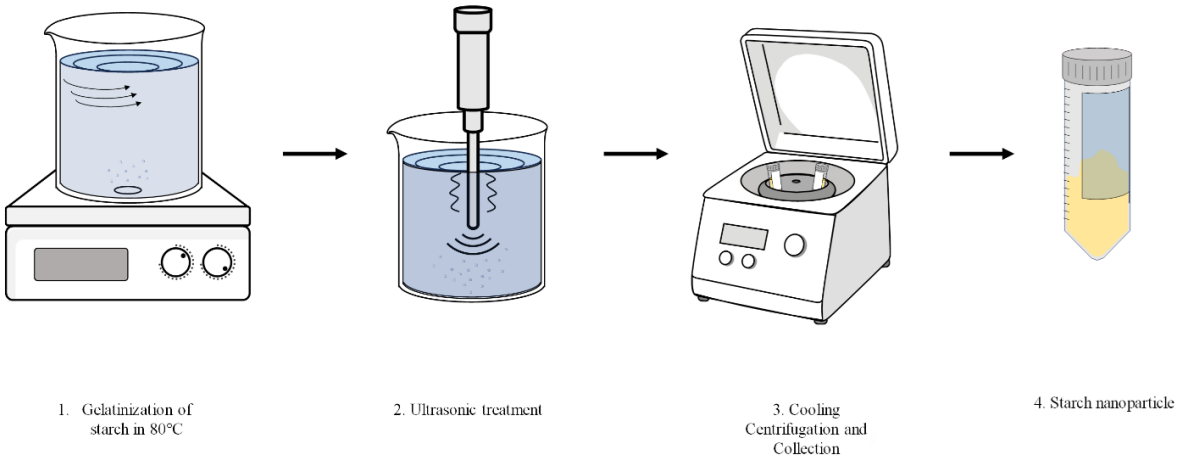

Figure 6. Ultrasonication for Starch Nanoparticle Production

Note: Illustration of sound wave-induced cavitation to produce SNPs. Original artwork by the authors; no prior publication or third-party content was used.

into starch matrices, achieving high encapsulation efficiencies due to favorable hydrogen bonding and phase compatibility. The method's applicability to hydrophobic compounds remains limited, as their organic-phase preferences challenge aqueous-based template coating. Template porosity and starch amylose content enhance loading capacity, though the complexity of template removal restricts scalability. Future studies could simplify template dissolution processes or investigate hydrophobic starch modifications to expand the method's utility for water-repelling compounds.

Top-down methods

Top-down methods are distinguished from bottom-up methods, which synthesize nanoparticles by assembling smaller molecular units. Instead, top-down approaches focus on size reduction, leveraging mechanical energy (e.g. grinding, shear forces) or chemical degradation (e.g. radiation-induced bond cleavage) to achieve nanoscale particles [65]. These methods are versatile and can be tailored to produce SNPs with specific sizes, morphologies, and functional properties, depending on the starch source and processing conditions. The resulting nanoparticles often exhibit increased surface area, improved solubility, and enhanced encapsulation capabilities, making them ideal for various applications [66]. These techniques are particularly advantageous for processing hydrophilic starches due to their ability to disrupt hydrogen bonding and crystalline structures without requiring complex molecular assembly.

Ball milling

Ball milling reduces starch particle size through high-energy impact and friction, suitable for dry or wet conditions without chemical additives [11, 54]. This technique is illustrated diagrammatically in Figure 5.

The method leverages starch's hydrophilic nature for effective size reduction, with milling time and energy affecting particle size. The studies below focus on hydrophilic starches.

Hydrophilic starches

Ahmad et al. encapsulated camel milk probiotics (*Pediococcus acidilactici*), which are considered hydrophilic, in hazelnut SNPs, achieving particles with a size of 271 nm and a zeta potential of -19.9 mV [48]. Dai et al. produced corn SNCs with ball milling and acid hydrolysis, yielding particles sized between 66 and 320 nm [49]. Dai et al. milled waxy maize starch at 300 rpm, which reduced crystallinity over time. Following acid treatment after 30 minutes of milling, particle sizes were reduced from 320.6±10.3 nm to 66.7±3.6 nm, with yields decreasing from 41.6±2.3% to 13.5±0.7% over five days [49]. Lin et al. produced spherical potato SNPs (120 nm) after 90 min of grinding [50].

Ball milling employs mechanical energy to reduce starch particle size, proving effective for hydrophilic starches due to their compatibility with aqueous-phase processing. The method's high-energy impacts disrupt

starch granules, producing particles with retained crystalline properties, making them well-suited to water-compatible materials. Its application to hydrophobic or amphipathic compounds is less explored, as their phase incompatibilities may hinder effective size reduction. Milling parameters, such as duration and energy input, critically influence particle morphology. Future research could adapt milling conditions to incorporate modified starches for hydrophobic compound encapsulation or optimize energy inputs to enhance particle uniformity.

Ultrasound

Ultrasonication uses high-frequency sound waves to generate cavitation and shear forces, reducing starch particle size, with acid hydrolysis enhancing disruption [11, 54]. A diagram illustrating this process is depicted in Figure 6.

The method suits hydrophilic starches, with ultrasound intensity and hydrolysis conditions affecting outcomes. The studies below highlight outcomes for both hydrophilic and hydrophobic compounds.

Hydrophilic compounds

Shabana et al. encapsulated hydrophilic antioxidants (L-ascorbic acid and oxalic acid) in potato SNPs, achieving particle sizes of 80 nm with ultrasonication alone and 40 nm with hydrolysis [51]. Ahmad et al. loaded resveratrol, a hydrophilic compound, into water chestnut (691 nm), horse chestnut (419 nm), and lotus stem (797 nm) starches. The encapsulation efficiencies were 79.37%, 81.46%, and 75.83%, respectively, with porous or film-like structures and reduced crystallinity. Without loading, the sizes were 606 nm, 420 nm, and 535 nm, achieved using ultrasonication and alkaline hydrolysis [8]. Hydrophilic compounds, like L-ascorbic acid, with their affinity for the aqueous phase, form well-dispersed particles that benefit from hydrogen bonding within the starch matrix.

Hydrophobic compounds

Remanan et al. encapsulated rutin, a hydrophobic flavonoid, in quinoa and corn SNPs, yielding particle sizes between 107 and 222 nm with encapsulation efficiencies of 63.1% to 67.4% [52]. Hydrophobic compounds, like rutin, which are less compatible with aqueous systems, tend to result in larger particles with reduced encapsulation efficiencies, reflecting weaker phase interactions.

General trends

Boufi et al. reduced the sizes of normal and waxy SNPs from 600 nm (after 15 minutes) to 40 nm (after 75 minutes) via ultrasonication, producing platelet-like shapes (5 nm thick) and demonstrating consistent efficacy across starch types [53].

Ultrasonication utilizes high-frequency sound waves to generate cavitation and shear forces, effectively reducing particle size, especially for hydrophilic starches. The method's high energy requirements pose challenges for industrial scalability. Further studies could develop energy-efficient ultrasonication protocols or explore modified starches to improve compatibility with hydrophobic compounds, broadening the method's applicability.

Conclusion

The fabrication of SNPs reveals a dynamic interplay between the properties of encapsulated compounds and the inherent mechanisms of each method. The polarity of the compound—whether hydrophilic, hydrophobic, or amphipathic—serves as a fundamental driver of particle formation, influencing how effectively the starch matrix can adapt to the compound's behavior. Methods that leverage aqueous environments tend to favor hydrophilic compounds, allowing their water-compatible nature to integrate smoothly into the process, often yielding particles with robust structural integrity. Conversely, hydrophobic compounds thrive in systems where organic phases or stabilizing agents bridge their aversion to water, promoting tighter aggregation and enhanced encapsulation. Amphipathic compounds, with their dual characteristics, challenge the adaptability of any given approach, often requiring fine-tuned conditions to balance their competing tendencies. Starch modifications emerge as a critical factor, offering a means to adjust the matrix's compatibility with diverse polarities, while process parameters, such as phase interactions or energy inputs, dictate the precision and scalability of the outcomes. Looking ahead, exploring tailored modifications or hybrid techniques could unlock greater versatility, enabling these methods to accommodate a wider spectrum of compounds with improved consistency and efficiency.

Ethical Considerations

Compliance with ethical guidelines

This narrative review adhered to the ethical principles outlined in the Declaration of Helsinki, ensuring integrity in the synthesis of existing research on SNP fabrication

for drug delivery. As a literature-based study, no human or animal subjects were directly involved, negating the need for institutional review board approval or informed consent. No conflicts of interest exist among the authors.

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Authors contribution's

Conceptualization: Maryam Sadat Nabavinia; Data Curation and investigation: Pooya Javaherchian; Methodology, Maryam Sadat Nabavinia and Pooya Javaherchian; Supervision: Maryam Sadat Nabavinia; Writing the original draft: Pooya Javaherchian and Farid Mahinizadeh; Review and editing: All authors

Conflict of interest

The authors declared no conflict of interest.

References

[1] Sobeih MO, Sawalha S, Hamed R, Ali F, Kim MP. Starch-derived bioplastics: Pioneering sustainable solutions for industrial Use. Materials. 2025; 18(8):1762. [DOI:10.3390/ma18081762] [PMID]

[2] Waterschoot J, Gomand SV, Fierens E, Delcour JA. Production, structure, physicochemical and functional properties of maize, cassava, wheat, potato and rice starches. Stärke. 2015; 67(1-2):14-29. [DOI:10.1002/star.201300238]

[3] Marta H, Rizki DI, Mardawati E, Djali M, Mohammad M, Cahyana Y. Starch nanoparticles: Preparation, properties and applications. Polymers. 2023; 15(5):1167. [DOI:10.3390/polym15051167] [PMID]

[4] Santhosh R, Ahmed J, Thakur R, Sarkar P. Starch-based edible packaging: rheological, thermal, mechanical, microstructural, and barrier properties-A review. Sustain Food Technolo. 2024; 2(2):307-30. [DOI:10.1039/D3FB00211J]

[5] Koshenaj K, Ferrari G. A comprehensive review on starch-based hydrogels: From tradition to innovation, opportunities, and drawbacks. Polymers. 2024; 16(14):1991. [DOI:10.3390/polym16141991] [PMID]

[6] Kojić I, Bechtel A, Aleksić N, Životić D, Trifunović S, Gajica G, et al. Study of the synergetic effect of co-pyrolysis of lignite and high-density polyethylene aiming to improve utilization of low-rank coal. Polymers. 2021; 13(5):759. [DOI:10.3390/polym13050759] [PMID]

[7] Le Corre D, Bras J, Dufresne A. Starch nanoparticles: A review. Biomacromolecules. 2010; 11(5):1139-53. [DOI:10.1021/bm901428y] [PMID]

[8] Ahmad M, Gani A, Hassan I, Huang Q, Shabbir H. Production and characterization of starch nanoparticles by mild alkali hydrolysis and ultra-sonication process. Sci Rep. 2020; 10(1):3533. [DOI:10.1038/s41598-020-60380-0] [PMID]

[9] Buzea C, Pacheco II, Robbie K. Nanomaterials and nanoparticles: Sources and toxicity. Biointerphases. 2007; 2(4):MR17-1. [DOI:10.1116/1.2815690] [PMID]

[10] Le Corre D, Angellier-Coussy H. Preparation and application of starch nanoparticles for nanocomposites: A review. React Funct Polymers. 2014; 85:97-120. [DOI:10.1016/j.reactfunctpolym.2014.09.020]

[11] Pattekari P, Zheng Z, Zhang X, Levchenko T, Torchilin V, Lvov Y. Top-down and bottom-up approaches in production of aqueous nanocolloids of low solubility drug paclitaxel. Phys Chem Chem Phys. 2011; 13(19):9014-9. [DOI:10.1039/c0cp02549f] [PMID]

[12] Yu M, Ji N, Wang Y, Dai L, Xiong L, Sun Q. Starch-based nanoparticles: Stimuli responsiveness, toxicity, and interactions with food components. Compr Rev Food Sci Food Saf. 2021; 20(1):1075-100. [DOI:10.1111/1541-4337.12677] [PMID]

[13] Bel Haaj S, Magnin A, Pétrier C, Boufi S. Starch nanoparticles formation via high power ultrasonication. Carbohydr Polym. 2013; 92(2):1625-32. [DOI:10.1016/j.carbpol.2012.11.022] [PMID]

[14] Zhang W, Liu L, Cheng H, Zhu J, Li X, Ye S, et al. Hydrogel-based dressings designed to facilitate wound healing. Mater Adv. 2024; 5(4):1364-94. [DOI:10.1039/D3MA00682D]

[15] Davari N, Nourmohammadi J, Mohammadi J. Nitric oxide-releasing thiolated starch nanoparticles embedded in gelatin sponges for wound dressing applications. Int J Biol Macromol. 2024; 265(Pt 2):131062. [DOI:10.1016/j.ijbiomac.2024.131062] [PMID]

[16] Lu Y, Sathiyaseelan A, Zhang X, Zhang L, Han K, Wang MH. Synthesis of Starch-Based Ag(2) [Fe (CN)(5)NO] Nanoparticles for Utilization in Antibacterial and Wound-Dressing Applications. Antioxidants (Basel). 2024; 13(2):154. [DOI:10.3390/antiox13020154] [PMID]

[17] Angellier h, molina-boisseau s, lebrun l, dufresne a. processing and structural properties of waxy maize starch nanocrystals reinforced natural rubber. Macromolecules. 2005; 38(9):3783-92. [DOI:10.1021/ma050054z]

[18] Amiryaghoubi N, Jahanban Esfahlan R. Applications of hydroxyapatite-based polymeric scaffolds in bone tissue engineering: An update. Adv Pharm Bull. 2024; 14(4):794-806. [DOI:10.34172/apb.43818] [PMID]

[19] Vicentini FC, Silva LRG, Stefano JS, Lima ARF, Prakash J, Bonacin JA, et al. Starch-based electrochemical sensors and biosensors: A review. Biomed Mater Devices. 2023;1(1):319-38. [DOI:10.1007/s44174-022-00012-5] [PMID]

[20] Mahmoudi Najafi SH, Baghaie M, Ashori A. Preparation and characterization of acetylated starch nanoparticles as drug carrier: Ciprofloxacin as a model. Int J Biol Macromol. 2016; 87:48-54. [DOI:10.1016/j.ijbiomac.2016.02.030] [PMID]

[21] Wang L, Zhao X, Yang F, Wu W, Wu M, Li Y, et al. Loading paclitaxel into porous starch in the form of nanoparticles to improve its dissolution and bioavailability. Int J Bioll Macromol. 2019; 138:207-14. [DOI:10.1016/j.ijbiomac.2019.07.083] [PMID]

[22] Acevedo-Guevara L, Nieto-Suaza L, Sanchez LT, Pinzon MI, Villa CC. Development of native and modified banana starch nanoparticles as vehicles for curcumin. Int J Biol Macromol. 2018; 111:498-504. [DOI:10.1016/j.ijbiomac.2018.01.063] [PMID]

[23] Fu Y, Yang J, Jiang L, Ren L, Zhou J. Encapsulation of lutein into starch nanoparticles to improve its dispersity in water and enhance stability of chemical oxidation. Stärke. 2018; 71(5-6):1800248. [DOI:10.1002/star.201800248]

[24] Jaízia dos Santos Alves M, Rodrigues Monteiro A, Ayala Valencia G. Antioxidant nanoparticles based on starch and the phenolic compounds from propolis extract: Production and physicochemical properties. Stärke. 2022; 74(7-8):2100289. [DOI:10.1002/star.202100289]

[25] Qin Y, Liu C, Jiang S, Xiong L, Sun Q. Characterization of starch nanoparticles prepared by nanoprecipitation: Influence of amylose content and starch type. Indust Crop Prod. 2016; 87:182-90. [DOI:10.1016/j.indcrop.2016.04.038]

[26] Kumar M, Kumar D. Formulation and evaluation of quercetin loaded sago starch nanoparticles. Cur Nanomed. 2025; 15(5):637-45. [DOI:10.2174/2210681213666230524145559]

[27] Kumar D, Sharma PK. Formulation and evaluation of quercetin-loaded banana starch nanoparticles. Nanosci Nanotechnol Asia. 2023; 13(4):79-87. [DOI:10.2174/2210681213666230524145559]

[28] Bhatia M, Rohilla S. Formulation and optimization of quinoa starch nanoparticles: Quality by design approach for solubility enhancement of piroxicam. Saudi Pharm J. 2020; 28(8):927-35. [DOI:10.1016/j.jsps.2020.06.013] [PMID]

[29] Gutiérrez G, Morán D, Marefati A, Purhagen J, Rayner M, Matos M. Synthesis of controlled size starch nanoparticles (SNPs). Carbohydr Polym. 2020; 250:116938. [DOI:10.1016/j.carbpol.2020.116938] [PMID]

[30] Jiang F, Du C, Zhao N, Jiang W, Yu X, Du Sk. Preparation and characterization of quinoa starch nanoparticles as quercetin carriers. Food Chem. 2022; 369:130895. [DOI:10.1016/j.foodchem.2021.130895] [PMID]

[31] Wan-Hong C, Chin S, Pang SC, Kok KY. Synthesis and Characterisation of Piperine-loaded Starch Nanoparticles. J Phys Sci. 2020; 31(1):57-68.[DOI:10.21315/jps2020.31.1.4]

[32] Zhang Y, Song J, Wu C, Deng G. Lutein-loaded lotus root starch nanoparticles: Preparation, release, and in vitro anti-inflammatory activity. Int J Biol Macromol. 2025; 304(Pt 1):140785. [DOI:10.1016/j.ijbiomac.2025.140785] [PMID]

[33] Ismail NS, Gopinath SC. Enhanced antibacterial effect by antibiotic loaded starch nanoparticle. J AssocArab Univ Basic Appl Sci. 2017; 24:136-40. [DOI:10.1016/j.jaubas.2016.10.005]

[34] Gong H, Lin S, Ren H, Song X, Zhao Q. Pickering emulsion stabilised by double-modified starch particles and its delivery property for curcumin. Int J Food Sci Technol. 2022; 57(12):7751-62. [DOI:10.1111/ijfs.16135]

[35] Gao W, Zhu J, Liu P, Cui B, Abd El-Aty AM. Preparation and characterization of octenyl succinylated starch microgels via a water-in-oil (W/O) inverse microemulsion process for loading and releasing epigallocatechin gallate. Food Chem. 2021; 355:129661. [DOI:10.1016/j.foodchem.2021.129661] [PMID]

[36] Alp E, Damkaci F, Guven E, Tenniswood M. Starch nanoparticles for delivery of the histone deacetylase inhibitor CG-1521 in breast cancer treatment. Int J Nanomedicine. 2019; 14:1335-46. [DOI:10.2147/IJN.S191837] [PMID]

[37] de Paz E, Martín Á, Mateos E, Cocero MJ. Production of water-soluble β-carotene micellar formulations by novel emulsion techniques. Chemical Engineering and Processing: Proc Intensification. 2013; 74:90-6. [DOI:10.1016/j.cep.2013.09.004]

[38] Bi W, Liyuan G, Wenjuan W, Qiang X. Skin targeting of resveratrol-loaded starch-based Pickering emulsions: Preparation, characterization, and evaluation. Colloid Polym Sci. 2021; 299(8):1383-95. [DOI:10.1007/s00396-021-04856-z]

[39] Ding Y, Lin Q, Kan J. Development and characteristics nanoscale retrograded starch as an encapsulating agent for colon-specific drug delivery. Colloids Surf B Biointerfaces. 2018; 171:656-67. [DOI:10.1016/j.colsurfb.2018.08.007] [PMID]

[40] Wang X, Chen H, Luo Z, Fu X. Preparation of starch nanoparticles in water in oil microemulsion system and their drug delivery properties. Carbohydr Polym. 2016; 138:192-200. [DOI:10.1016/j.carbpol.2015.11.006] [PMID]

[41] Xie X, Zhang Y, Zhu Y, Lan Y. Preparation and drug-loading properties of amphoteric cassava starch nanoparticles. Nanomaterials. 2022; 12(4):598. [DOI:10.3390/nano12040598] [PMID]

[42] Jain AK, Khar RK, Ahmed FJ, Diwan PV. Effective insulin delivery using starch nanoparticles as a potential transnasal mucoadhesive carrier. Eur J Pharm Biopharm. 2008; 69(2):426-35. [DOI:10.1016/j.ejpb.2007.12.001] [PMID]

[43] Xu Y, Zi Y, Lei J, Mo X, Shao Z, Wu Y, et al. pH-Responsive nanoparticles based on cholesterol/imidazole modified oxidized-starch for targeted anticancer drug delivery. Carbohydr Polym. 2020; 233:115858. [DOI:10.1016/j.carbpol.2020.115858] [PMID]

[44] Delsarte I, Delattre F, Rafin C, Veignie E. Investigations of benzo[a]pyrene encapsulation and Fenton degradation by starch nanoparticles. Carbohydr Polym. 2018; 186:344-9. [DOI:10.1016/j.carbpol.2018.01.037] [PMID]

[45] Alzate P, Gerschenson L, Flores S. Micro/nanoparticles containing potassium sorbate obtained by the dialysis technique: Effect of starch concentration and starch ester type on the particle properties. Food Hydrocoll. 2019; 95:540-50. [DOI:10.1016/j.foodhyd.2019.04.066]

[46] Yang J, Li F, Li M, Zhang S, Liu J, Liang C, et al. Fabrication and characterization of hollow starch nanoparticles by gelation process for drug delivery application. Carbohydr Polym. 2017; 173:223-32. [DOI:10.1016/j.carbpol.2017.06.006] [PMID]

[47] Li X, Li M, Liu J, Ji N, Liang C, Sun Q, et al. Preparation of hollow biopolymer nanospheres employing starch nanoparticle templates for enhancement of phenolic acid antioxidant activities. J Agric Food Chem. 2017; 65(19):3868-82. [DOI:10.1021/acs.jafc.7b01172] [PMID]

[48] Ahmad M, Gani A, Hamed F, Maqsood S. Comparative study on utilization of micro and nano sized starch particles for encapsulation of camel milk derived probiotics (Pediococcus acidolactici). Lebensm Wiss Technol. 2019; 110:231-8. [DOI:10.1016/j.lwt.2019.04.078]

[49] Dai L, Li C, Zhang J, Cheng F. Preparation and characterization of starch nanocrystals combining ball milling with acid hydrolysis. Carbohydr Polym. 2018; 180:122-7. [DOI:10.1016/j.carbpol.2017.10.015] [PMID]

[50] Lin H, Qin L, Hong H, Li Q. Preparation of starch nanoparticles via high-energy ball milling. J Nano Res. 2016; 40:174-9. [DOI:10.4028/www.scientific.net/JNanoR.40.174]

[51] Shabana S, Prasansha R, Kalinina I, Potoroko I, Bagale U, Shirish SH. Ultrasound assisted acid hydrolyzed structure modification and loading of antioxidants on potato starch nanoparticles. Ultrason Sonochem. 2019; 51:444-50. [DOI:10.1016/j.ultsonch.2018.07.023] [PMID]

[52] Remanan MK, Zhu F. Encapsulation of rutin using quinoa and maize starch nanoparticles. Food Chem. 2021; 353:128534. [DOI:10.1016/j.foodchem.2020.128534] [PMID]

[53] Boufi S, Bel Haaj S, Magnin A, Pignon F, Impéror-Clerc M, Mortha G. Ultrasonic assisted production of starch nanoparticles: Structural characterization and mechanism of disintegration. Ultrason Sonochem. 2018; 41:327-36. [DOI:10.1016/j.ultsonch.2017.09.033] [PMID]

[54] Kim H-Y, Park SS, Lim S-T. Preparation, characterization and utilization of starch nanoparticles. Colloids and Surfaces B: Biointerfaces. 2015; 126:607-20. [DOI:10.1016/j.colsurfb.2014.11.011] [PMID]

[55] Lu H, Tian Y. Nanostarch: Preparation, Modification, and Application in Pickering Emulsions. J Agric Food Chem. 2021; 69(25):6929-42. [DOI:10.1021/acs.jafc.1c01244] [PMID]

[56] Tagliapietra BL, de Melo BG, Sanches EA, Plata-Oviedo M, Campelo PH, Clerici MTPS. From micro to nanoscale: A critical review on the concept, production, characterization, and application of starch nanostructure. Stärke. 2021; 73(11-12):2100079. [DOI:10.1002/star.202100079]

[57] Zarski A, Bajer K, Kapuśniak J. Review of the most important methods of improving the processing properties of starch toward non-food applications. Polymers. 2021; 13(5):832. [DOI:10.3390/polym13050832] [PMID]

[58] El-Naggar ME, El-Rafie MH, El-sheikh MA, El-Feky GS, Hebeish A. Synthesis, characterization, release kinetics and toxicity profile of drug-loaded starch nanoparticles. Int J Biol Macromol. 2015; 81:718-29. [DOI:10.1016/j.ijbiomac.2015.09.005] [PMID]

[59] Barichello JM, Morishita M, Takayama K, Nagai T. Encapsulation of hydrophilic and lipophilic drugs in PLGA nanoparticles by the nanoprecipitation method. Drug Dev Ind Pharm. 1999; 25(4):471-6. [DOI:10.1081/DDC-100102197] [PMID]

[60] Lepeltier E, Bourgaux C, Couvreur P. Nanoprecipitation and the "ouzo effect": Application to drug delivery devices. Adv Drug Deliv Rev. 2014; 71:86-97. [DOI:10.1016/j.addr.2013.12.009] [PMID]

[61] Massella D, Celasco E, Salaün F, Ferri A, Barresi AA. Overcoming the limits of flash nanoprecipitation: Effective loading of hydrophilic drug into polymeric nanoparticles with controlled structure. Polymers. 2018; 10(10):1092. [DOI:10.3390/polym10101092] [PMID]

[62] Huang R, Song H, Li S, Guan X. Selection strategy for encapsulation of hydrophilic and hydrophobic ingredients with food-grade materials: A systematic review and analysis. Food Chem. 2025; 25:102149. [DOI:10.1016/j.fochx.2024.102149] [PMID]

[63] Subroto E, Cahyana Y, Indiarto R, Rahmah TA. Modification of starches and flours by acetylation and its dual modifications: a review of impact on physicochemical properties and their applications. Polymers. 2023; 15(14):2990. [DOI:10.3390/polym15142990] [PMID]

[64] Morán D, Gutiérrez G, Blanco-López MC, Marefati A, Rayner M, Matos M. Synthesis of starch nanoparticles and their applications for bioactive compound encapsulation. Appl Sci. 2021; 11(10):4547. [DOI:10.3390/app11104547]

[65] Huston M, DeBella M, Dibella M, Gupta A. Green Synthesis of Nanomaterials. Nanomaterials. 2021; 11(8):2130. [DOI:10.3390/nano11082130] [PMID]

[66] Baig N, Kammakakam I, Falath W. Nanomaterials: A review of synthesis methods, properties, recent progress, and challenges. Materials Adv. 2021; 2(6):1821-71. [DOI:10.1039/D0MA00807A]

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