Starch Nanoparticles: Synthesis, Characterisation, and Potential Applications

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ABSTRACT

The biocompatibility, biodegradability, and non-toxicity of starch nanoparticles (SNPs) have made them an adaptable and sustainable material with a wide range of uses across many industries. The synthesis, characterisation, and possible applications of SNPs are covered in detail in this article. Numerous techniques, including as enzymatic hydrolysis, high-pressure homogenization, and nanoprecipitation, can be used to synthesize SNPs; each has unique benefits and drawbacks. Determining the size, shape, and surface characteristics of SNPs requires the use of characterization techniques such dynamic light scattering (DLS), transmission electron microscopy (TEM), and scanning electron microscopy (SEM). Exploration of SNPs in several domains has been prompted by their unique features. SNPs improve the bioavailability and regulated release of medications in drug delivery devices. They extend the shelf life and texture of items in the food sector. SNPs have potential for use in environmentally friendly applications including water filtration and biodegradable packaging. Their potential to increase crop output and sustainability is highlighted by their use in agriculture as pesticide and fertilizer carriers.

KEYWORDS: *Starch nanoparticles, Starch, Hydrolysis, Precipitation, SEM, TEM, SNP, DLS, medical treatments, molecular level.*

INTRODUCTION

With the introduction of nanotechnology, the medical industry has undergone a significant revolution in recent years. Nanoparticles, which typically range in size from 1 to 100 nanometres, have emerged as formidable tools with numerous uses in diagnostics, therapeutics, drug transport, imaging, and tissue engineering. Because of their small size and high surface area-to-volume ratio, nanoparticles have special physicochemical features that make them very adaptable and useful for solving complicated biomedical problems.

Nanoparticles have several distinct benefits over traditional medical treatments. Their small size enables precise targeting at the cellular and molecular levels, resulting in personalized interactions with biological systems. Nanoparticles can encapsulate or combine medicinal compounds to improve their stability, bioavailability, and targeted delivery to specific tissues or organs. This feature is especially useful for crossing biological barriers, such as the blood-brain barrier, and boosting therapy efficacy while avoiding negative effects on healthy tissues [1,2].

Nanoparticles have great potential to transform healthcare delivery and personalized medicine, which makes them indispensable in the medical field in addition to their use in diagnosis and therapy. Development of personalized treatments based on a patient's genetic profile, illness features, and response to treatment is made possible by platforms based on nanotechnology.

HISTORY OF STARCH NANOPARTICLES

Starting in the late 20th century, scientists started investigating the composition and characteristics of natural starch granules, which is when starch nanoparticles originated. Native starch was widely used in food, medicine, and industrial purposes. It was sourced from a variety of plant sources and functioned as a basic carbohydrate reserve in plants. Early research showed that starch granules may be broken down into tiny pieces by chemical or mechanical processes, resulting in the creation of what would become known as starch nanoparticles. These early findings paved the way for additional research into the special qualities and possible uses of these starch granules at the nanoscale [1].

To alter and engineer materials at the nanoscale, researchers started to apply the concepts and methods of nanoscience as nanotechnology grew in prominence in the latter half of the 20th century. A growing number of biomedical applications have shown interest in starch nanoparticles because of their biocompatibility, biodegradability, and flexibility. The ability to carefully control the size, shape, and surface characteristics of starch nanoparticles created new opportunities for biomedical applications such as scaffolds for tissue engineering, medication delivery, and imaging agents. This signalled the start of a period of vigorous research and development aimed at examining the potential of starch nanoparticles in biomedicine [1].

Early in the twenty-first century, the need for novel drug delivery methods, diagnostic tools, and regenerative therapies prompted a shift in research priorities toward the medicinal uses of starch nanoparticles. Research findings have indicated that starch nanoparticles had the capability to function as efficient delivery systems for therapeutic substances, augmenting contrast in imaging for diagnostic reasons, fostering tissue regeneration in regenerative medicine, and enhancing wound healing results. These results demonstrated how revolutionary starch nanoparticles can be in transforming healthcare delivery and meeting unmet medical requirements [3].

STARCH

Starch, a biocompatible and biodegradable polysaccharide produced from plants, has been widely used in pharmaceutical applications. In recent years, researchers have investigated starch nanoparticles as potential carriers for medication delivery and therapeutic purposes. These starch nanoparticles have various advantages, including biocompatibility, low toxicity, ease of modification, and the capacity to encapsulate a variety of therapeutic compounds.

The two primary polysaccharides that make up starch are amylose and amylopectin. Whereas amylopectin has branching chains with extra α-(1→6) linkages, amylose is made up of linear chains of α-(1→4) linked glucose units. Using a variety of processing methods, natural starch is normally converted into starch nanoparticles, which have diameters in the nanometer range. These nanoparticles possess the semi-crystalline structure of natural starch, with amorphous and crystallinity-filled areas. Starch nanoparticles' crystalline areas, which are mainly made up of densely packed amylose molecules, add to their mechanical strength and stability. Amorphous areas, which are characterized by irregular starch molecule configurations, facilitate drug loading and diffusion by offering accessible locations for therapeutic agent encapsulation and release [4].

Starch nanocrystals (SNC) are crystalline nanoparticles with dimensions usually between 10 and 100 nanometres that are produced from starch by enzymatic treatment or acid hydrolysis. These nanocrystals are great candidates for use in drug administration, tissue engineering, and diagnostic imaging because of their high aspect ratio, outstanding crystallinity, mechanical strength, and biocompatibility. Starch nanoparticles (SNP) which are produced by techniques like high-pressure homogenization or ultrasonication, cover a wider range of particle sizes and morphologies, such as spherical, ellipsoidal, or irregular forms. These nanoparticles can be used in targeted medication administration, diagnostic imaging contrast agents, and wound healing formulations because of their diverse qualities, which include biocompatibility, biodegradability, and customizable surface characteristics [4].

PREPARATION OF STARCH NANOPARTICLES

HYDROLYSIS

Hydrolysis is a chemical reaction in which a molecule combines with water, breaking chemical bonds and producing two or more products. In the framework of starch nanoparticle synthesis, hydrolysis is the process of breaking down starch molecules into smaller fragments, resulting in the generation of nanoparticles. Hydrolysis can be accomplished through a variety of methods, the choice of which is determined by criteria such as desired nanoparticle properties, reaction circumstances, and scalability.

1. Acid Hydrolysis

Acid hydrolysis is a popular method for producing starch nanoparticles. It entails breaking down starch molecules using acid catalysts, such as sulfuric acid (H_2SO_4) or hydrochloric acid (HCl). This technique involves heating starch while it's dissolved in an acidic solution and experiencing reflux. The starch polysaccharide chain's glycosidic bond breaking is aided by the acid catalysts. Smaller starch fragments are created as a result of acid hydrolysis, and these fragments eventually combine to form nanoparticles. The size and shape of the nanoparticles can be controlled by adjusting the reaction parameters, which include acid concentration, temperature, and reaction duration. Benefits of acid hydrolysis include scalability, high efficiency, and very easy operation. Additionally, this can cause starch molecules to degrade or undergo chemical changes, which can affect the properties of resulting nanoparticles [5].

2. Enzymatic Hydrolysis

Enzymatic hydrolysis breaks down starch molecules into smaller fragments by using enzymes that break down starch, such as α-amylase or glucoamylase. This process involves suspending starch in an enzymatic solution that has the required enzymes in it. Smaller starch fragments and oligosaccharides are formed when the enzymes specifically cleave the α-1,4 glycosidic linkages in the starch polysaccharide chain. Benefits of enzymatic hydrolysis include little chemical changes to starch molecules, gentle reaction conditions, and great specificity. It enables exact regulation of the resultant nanoparticles' size distribution and degree of hydrolysis. In contrast to acid hydrolysis, enzymatic hydrolysis could necessitate longer reaction periods and a greater expense. There may be difficulties with enzyme recovery, stability, and purity while using them.

Both acid and enzymatic hydrolysis procedures can be utilized to create starch nanoparticles with customized characteristics for use in biological, medicinal, and industrial applications. The preferred hydrolysis process is determined by parameters such as desired nanoparticle properties, reaction circumstances, and application requirements [6].

NANOPRECIPITATION

A widely used method for creating starch nanoparticles is nanoprecipitation, sometimes referred to as regeneration or precipitation. With this method, starch nanoparticles are precipitated from a solution by introducing a nonsolvent or anti-solvent, which causes a change in the solvent's properties. Among the many benefits of nanoprecipitation are its ease of use, adaptability, and controllability over the size and characteristics of nanoparticles [7,8].

Solution Preparation: The initial step in nanoprecipitation is to prepare a starch solution. Starch is usually dissolved in a suitable solvent to produce a homogenous solution. Common solvents include water, organic solvents (e.g., dimethyl sulfoxide, dimethylformamide), or a combination of both. The concentration of starch in the solution can be changed to achieve the desired nanoparticle features, including size, shape, and drug loading capacity.

Addition of Nonsolvent: After the starch solution is created, a nonsolvent or antisolvent is added to induce nanoprecipitation. The nonsolvent is usually a liquid in which the starch is insoluble or poorly soluble. Nonsolvent commonly utilized include ethanol, methanol, acetone, and a water-organic solvent mixture. The choice of nonsolvent is determined by factors such as starch solubility and desired nanoparticle properties. The nonsolvent lowers starch's solubility in solution, resulting in the precipitation of starch nanoparticles. The pace and extent of nanoprecipitation are determined by parameters such as solvent concentration, volume ratio, and mixing conditions.

Precipitation and Nanoparticle Formation: Because starch is less soluble in the new solvent environment, starch nanoparticles start to form when the nonsolvent is added. As starch molecules group and self-assemble into nanoscale structures, nucleation and growth of nanoparticles take place. The size, shape, and dispersion of the resultant nanoparticles are influenced by the kinetics of nanoprecipitation. Important factors that affect the properties of nanoparticles include temperature, agitation, and the pace at which solvent and nonsolvent are mixed. The features of nanoparticles, including size, shape, surface charge, and drug encapsulation effectiveness, can be precisely tuned by adjusting these factors.

Nanoparticle Collection and Purification: The suspension containing starch nanoparticles may go through additional processing processes to gather and refine the nanoparticles after nanoprecipitation. The nanoparticles can be separated from the solvent and nonsolvent using methods including centrifugation, filtering, or ultracentrifugation. After the nanoparticles are gathered, any remaining solvents and non-solvents can be removed by washing and drying the particles, producing pure starch nanoparticles that are prepared for additional analysis and use.

Nanoprecipitation is a versatile and efficient approach for producing starch nanoparticles with customized properties suited for a wide range of biological, pharmacological, and industrial applications. Through manipulation of variables including solvent composition, mixing conditions, and precipitation kinetics, scientists may precisely tailor the properties of starch nanoparticles to fulfil particular application needs.

PHYSICAL METHODS

Physical approaches for producing starch nanoparticles include mechanical or physical operations that disrupt starch molecules and promote nanoparticle production. These approaches are suitable for producing nanoparticles because they have benefits such as scalability, ease of use, and lack of harmful chemical reactions [9].

1. High-Pressure Homogenization

A popular technique for creating starch nanoparticles is high-pressure homogenization (HPH), which provides exact control over the size, shape, and dispersion of the particles. This method involves forcing a suspension of starch particles through a small opening at high pressures—typically between 100 to 2000 bar—followed by an immediate decompression. Starch aggregates break up and nanoparticles are formed during homogenization because of the strong shear forces and cavitation. Particle size and distribution are further optimized as a result of the repeated homogenization cycles. One advantage of HPH is its scalability, which enables the large-scale manufacturing of starch nanoparticles appropriate for industrial applications. HPH can be conducted at controlled temperatures, reducing the danger of thermal deterioration while maintaining the functional qualities of starch nanoparticles [10].

HPH is a continuous and efficient technique that produces high yields of homogenous starch nanoparticles with low batch-to-batch variance. The final nanoparticle product's reliability and quality is ensured by HPH's consistency and reproducibility. Furthermore, to improve the stability, encapsulation effectiveness, and controlled release behaviour of starch nanoparticles, HPH can be coupled with other processing methods like ultrasonication or chemical modification.

By including different functional additives or modifiers into the starch nanoparticle matrix, this technique makes it possible to create multifunctional nanocomposites that are ideal for specific applications. In order to improve the solubility, stability, and bioavailability of hydrophobic medications or active substances, HPH makes it easier for them to be encapsulated within the hydrophilic starch nanoparticle matrix [10].

2. Ultrasonication

A further helpful procedure to generate starch nanoparticles is the ultrasonication process, which uses the mechanical energy produced by ultrasonic waves to break up starch clumps and encourage the creation of particles. This technique involves subjecting a starch suspension to high-frequency sound waves produced by an ultrasonic probe or bath, usually in the 20–100 kHz range. The cavitation caused by the ultrasonic waves causes the microbubbles in the suspension to expand and rupture. Starch particles break up into nanoparticles as a result of the extreme shear stresses and microstreaming phenomena produced by the quick expansion and collapse of these bubbles. Power intensity, sonication duration, and sample concentration are examples of ultrasonication parameters that can be changed to regulate the size and shape of the resultant nanoparticles. The use of ultrasonication reduces the possibility of thermal or chemical modification of starch nanoparticles by operating under moderate reaction conditions, such as ambient temperature and air pressure.

Depending on the required particle size and yield, ultrasonication can synthesize starch nanoparticles in a matter of minutes to hours. It is a quick and effective method. For high-throughput screening of nanoparticle formulations and process parameter optimization, this quick turnaround time is particularly beneficial. Ultrasonication can help to stabilize starch nanoparticles by creating stable colloidal dispersions. Stabilizing agents or surfactants may adsorb onto the surface of starch nanoparticles as a result of surface alteration brought about by the acoustic cavitation process [11]. By improving their colloidal stability, these surface modifications prolong the shelf-life of starch nanoparticles by avoiding aggregation or sedimentation over time. To attain particular nanoparticle characteristics or functions, ultrasonication might be coupled with other processing methods as emulsification, precipitation, or solvent evaporation [12].

3. Freeze-Drying (Lyophilization)

Freeze drying, also known as lyophilization, is a popular method for producing starch nanoparticles that preserves their structural integrity and characteristics. This method creates a solid matrix by freezing a dispersion of starch nanoparticles at low temperatures, usually below the freezing point of water. The frozen sample is then placed under vacuum, which causes the frozen water in the matrix to sublimate - that is, it transits directly from the solid to the gas phase without passing through the liquid phase. The removal of ice crystals from the frozen material creates porous structures in which the starch nanoparticles are lodged. The freeze-drying technique preserves the starch nanoparticles' original particle size, shape, and dispersion while retaining their functional capabilities.

Freeze drying lowers the possibility of microbial development, enzymatic breakdown, or chemical reactions that could take place in aqueous conditions by eliminating water from the nanoparticle solution [13]. As a result, the starch nanoparticles become a dry powder that is more stable against chemical and physical deterioration, extending its shelf life and sustaining its functionality over time. The high porosity of freeze-dried starch nanoparticles enables quick rehydration and dispersibility when reconstituted in aqueous solutions. The capacity of starch nanoparticles to rehydrate quickly and uniformly in a variety of formulations and matrices improves their processability and handling ease.

4. Spray Drying

Spray drying is a popular approach for producing starch nanoparticles due to its speed, scalability, and adaptability [14]. This approach involves employing a spray nozzle to atomize a suspension of starch nanoparticles into small droplets, which are then added to a hot drying chamber. When the droplets are subjected to a stream of hot air, the solvent rapidly evaporates, resulting in the formation of dry nanoparticles. Small-sized nanoparticles are formed as a result of the droplets' high surface area-to-volume ratio, which makes solvent removal more effective. The controlled drying conditions, which include temperature, airflow rate, and residence time, provide precise control over the particle size, shape, and dispersion of the resulting starch nanoparticles.

Spray-dried starch nanoparticles can be employed for controlled release, targeted delivery, or enhanced stability of active chemicals in food, medicine, and nutraceuticals by encasing bioactive components within the nanoparticle matrix. Co-spray drying and co-precipitation are two processing methods that can be combined with spray drying to develop hybrid nanoparticle systems that have improved characteristics or functions [15].

The physicochemical characteristics of starch nanoparticles can be preserved during processing with the help of spray drying. The risk of thermal degradation or chemical change of the nanoparticles is decreased due to the quick residence time and rapid drying kinetics in the hot drying chamber, which minimize exposure to high temperatures. The starch nanoparticles are suitable for a range of applications because of the mild processing conditions that maintain their functionality, surface features, and structural integrity. Surface modification approaches, such as coating or conjugation with targeted ligands, enable the customisation of starch nanoparticles for specific biological or pharmacological uses.

EVALUATION PARAMETERS OF STARCH NANOPARTICLES

1. Particle Size and Size Distribution

Dynamic Light Scattering (DLS)

Photon Correlation Spectroscopy, or Dynamic Light Scattering (DLS) is a potent technique used to characterize starch nanoparticles in solution. DLS offers important insights into the size distribution and hydrodynamic characteristics of nanoparticles by taking advantage of the Brownian motion of particles.

Using a laser beam to illuminate a sample containing scattered starch nanoparticles, this non-invasive technique measures the variations in scattered light intensity over time. Particle size is determined by detecting and analysing changes in scattered light intensity caused by starch nanoparticles moving in a Brownian motion. DLS facilitates the estimation of the hydrodynamic diameter and size distribution of starch nanoparticles in solution, which helps to optimize synthesis processes and analyse nanoparticle stability [16].

DLS has been applied, for instance, to assess the size distribution and colloidal stability of starch nanoparticles for drug delivery applications in publications like Gao et al. (2020) and Li et al. (2019). DLS is a useful method for comprehending the physicochemical characteristics of starch nanoparticles and their potential applicability in a variety of industries, such as biomedicine, food science, and materials engineering, because it offers quick and non-destructive observations [17,18].

Transmission Electron Microscopy (TEM)

Transmission Electron Microscopy (TEM) is an effective technique for characterizing starch nanoparticles at the nanoscale. By directly visualizing individual nanoparticles, this technique offers important insights into their size, shape, and internal structure.

Using a concentrated electron beam to pass through a tiny sample, TEM enables atomic-level detail to be seen in high-resolution imaging of nanoparticles [18]. When scattered across a TEM grid and dyed with contrasting chemicals, starch nanoparticles show up beneath the electron beam as discrete objects. It enables precise measurements of the size, form, and surface properties of starch nanoparticles by researchers. It provides the capacity to examine internal structures, including crystalline domains or wrapped payloads, which contributes to our understanding of the characteristics and functions of nanoparticles.

Lin et al. (2021) and Li et al. (2018) used TEM to study the shape and size distribution of starch nanoparticles for drug delivery and biological applications. Because of it's ability to provide high-resolution imaging and quantitative analysis, TEM remains an important technique for understanding the structural features of starch nanoparticles and improving their applications in a variety of industries [19,20].

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) is a useful technique for measuring and characterizing starch nanoparticles, as it provides high-resolution imaging and thorough surface analysis.

SEM creates images by scanning a sample's surface with a focussed electron beam, which causes secondary electrons to be identified. With nanometre-scale resolution, this technique allows researchers to see the morphology, size, and surface characteristics of starch nanoparticles. Under a scanning electron microscope (SEM), the three-dimensional structure and surface morphology of starch nanoparticles can be observed after they have been disseminated onto a conductive substrate and coated with a thin coating of metal. SEM helps with the evaluation of nanoparticle stability and the improvement of synthesis techniques by offering insights into the size distribution, shape, and aggregation behaviour of starch nanoparticles.

SEM has been used in studies like Li et al. (2018) and Liu et al. (2020) to look into the morphology and surface properties of starch nanoparticles for use in food science and medication delivery [20,28]. SEM is still a useful tool for comprehending the structural characteristics of starch nanoparticles and expanding their uses across a range of industries since it can give quantitative analysis and detailed imaging of these particles.

2. Surface Charge and Zeta Potential

Zeta Potential Analysis

Zeta Potential Analysis is an essential method for measuring and characterizing starch nanoparticles, offering important information about their colloidal stability and surface charge. As a crucial marker of particle stability and interparticle interactions, zeta potential is the electrokinetic potential at the sliding plane of charged particles in a dispersion [21]. When distributed in an appropriate solvent, starch nanoparticles pick up an electric double layer made of ions from the surrounding medium, which results in a net surface charge.

In order to compute the zeta potential using electrophoretic mobility, an electric field is applied to the nanoparticle dispersion, and the particle movement velocity is measured. With this method, scientists may evaluate the stability, aggregation behaviour, and surface charge of starch nanoparticles in solution [22,23].

Zeta potential analysis has been used in studies like Lin et al. (2021) and Chen et al. (2019) to look at the stability and surface charge of starch nanoparticles for use in food and medicine delivery. Zeta potential analysis helps to understand the colloidal behaviour of nanoparticles and optimize formulation parameters for a range of applications by giving quantitative information on the surface charge of the particles [19,24].

Electrophoretic Light Scattering (ELS)

Electrophoretic light scattering (ELS) is a useful technique for measuring and characterizing starch nanoparticles, providing information on their surface charge and stability.

ELS measures the electrophoretic mobility of scattered nanoparticles in a sample by subjecting it to an electric field. The surface charge of the nanoparticles and their interactions with the surrounding medium affect their mobility. The electrokinetic potential at the sliding plane of charged particles is represented by the zeta potential, which can be calculated using ELS's analysis of particle movement velocity under an electric field. When dispersed in an appropriate solvent, starch nanoparticles develop an electric double layer that gives rise to a net surface charge that influences their colloidal behaviour. By giving quantitative details about the surface charge and colloidal stability of starch nanoparticles, ELS enables researchers to evaluate the zeta potential of these particles [25].

ELS has been used in studies like Cheng et al. (2020) and Li et al. (2018) to look into the stability and surface charge of starch nanoparticles for a variety of uses [20,31]. ELS helps design successful nanoparticle-based systems and optimize formulation parameters in medication delivery, food science, and materials engineering by providing insights into the surface properties of nanoparticles.

3. Crystallinity and Structural Analysis

X-ray Diffraction (XRD)

X-ray diffraction (XRD) is an effective technique for measuring and characterizing starch nanoparticles, providing information about their crystalline structure and phase composition.

In order to do X-ray radiography (XRD), a sample is exposed to X-rays, and the dispersed X-rays' diffraction pattern is examined. The arrangement of atoms within the sample is revealed by this pattern, which makes it possible to identify the crystalline phases and calculate crystallographic parameters. When starch nanoparticles are analysed using X-ray reflectometry, they show diffraction peaks that represent the crystalline domains within the nanoparticles. Researchers can ascertain the nanoparticles' crystalline structure, degree of crystallinity, and index of crystallinity by examining the locations, intensities, and forms of these peaks. XRD also makes it possible to identify the crystallographic phases that are present in the sample, which helps to clarify the characteristics and behaviour of nanoparticles [26].

X-ray diffraction (XRD) has been used in studies like Zhang et al. (2016) and Li et al. (2020) to look into the crystalline structure and phase composition of starch nanoparticles for different purposes [6,30]. In domains like medicine delivery, food science, and materials engineering, X-ray reflectance (XRD) provides information on the crystallinity and structure of nanoparticles, which helps optimize synthesis techniques and build nanoparticle-based systems with customized characteristics.

Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) is a potent technique for measuring and characterizing starch nanoparticles, revealing their chemical composition, functional groups, and molecular structure.

In order to measure the absorption and transmission of the resulting spectrum of wavelengths, FTIR involves first irradiating a material with infrared light. When starch nanoparticles undergo Fourier Transform Infrared (FTIR) analysis, they display distinctive absorption bands that are indicative of the stretching and bending vibrations of the functional groups that are present in the nanoparticles. Researchers can determine particular chemical bonds and functional groups, such as hydroxyl groups (O-H), carbonyl groups (C=O), and glycosidic bonds (C-O-C), within the nanoparticles by examining these absorption bands [27]. In addition, chemical alterations or surface coatings on the nanoparticles can be found using FTIR, which sheds light on their surface chemistry and reactivity.

FTIR has been used in studies like Cheng et al. (2020) and Li et al. (2018) to look into the molecular structure and chemical makeup of starch nanoparticles for a variety of uses. In domains like medicine delivery, culinary science, and materials engineering, FTIR helps optimize synthesis procedures and build nanoparticle-based systems with customized features by providing comprehensive information about the chemistry and structure of nanoparticles.

4. Thermal Properties

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is an essential technique for measuring and characterizing starch nanoparticles, providing information on their thermal behaviour and stability.

Thermal diffusivity analysis (DSC) measures the heat flux resulting from temperature-dependent changes in a sample's chemical and physical characteristics. In DSC estimation, starch nanoparticles show typical thermal changes such melting, crystallization, and disintegration. The crystalline phase transitions and thermal stability of the nanoparticles are shown by the melting temperature (Tm), whilst the energy needed for melting is indicated by the enthalpy of fusion (ΔH). Also, the glass transition temperature (Tg), which is impacted by variables including chain flexibility and molecule mobility, denotes the change from a rigid to a rubbery state [28].

DSC analysis helps with the evaluation of nanoparticle stability and the optimization of synthesis techniques by allowing researchers to evaluate the thermal stability, crystallinity, and phase transitions of starch nanoparticles under various conditions. DSC has been used in studies like Lin et al. (2021) and Cheng et al. (2020) to look into the stability and thermal behaviour of starch nanoparticles for a variety of uses [19,31]. DSC helps developers of nanoparticle-based systems with customized thermal properties in domains including medicine delivery, food science, and materials engineering by providing insights into the thermal properties of nanoparticles.

APPLICATIONS OF STARCH NANOPARTICLES

1. Drug Delivery

Starch nanoparticles provide several benefits for drug delivery applications, making them a desirable choice for pharmaceutical formulation.

Therapeutic Agent Encapsulation: A variety of therapeutic agents, such as tiny molecules, proteins, peptides, and nucleic acids, can be encapsulated by starch nanoparticles. Encapsulation keeps the medications stable, prevents them from breaking down, and lengthens the amount of time they spend in the body's circulation [29].

Improvement of Solubility and Bioavailability: By offering a large surface area for drug dispersion, starch nanoparticles can increase the solubility of medications that are not very water soluble. A higher percentage of the provided dose reaches the systemic circulation when a substance is more soluble, which increases bioavailability and boosts therapeutic efficacy.

Targeted Drug Delivery: To deliver drugs to particular cells or tissues, targeting ligands, including peptides or antibodies, can be functionalized with starch nanoparticles. Targeting ligands help the nanoparticles bind more selectively to the receptors that are overexpressed in sick cells, which improves drug accumulation at the target site and reduces off-target effects.

Controlled and Sustained Release: Starch nanoparticles allow for the long-term, controlled release of medications. Drug release kinetics can be adjusted to match particular therapeutic requirements by adjusting the composition, size, and surface characteristics of the nanoparticles. This minimizes variations in drug plasma levels and lowers the frequency of dosing.

Protection of Labile Drugs: Proteins and peptides, which are susceptible to enzymatic breakdown and premature release, are shielded from these effects by starch nanoparticles. Drugs are protected from abrasive physiological circumstances by being encapsulated within the nanoparticle matrix, which maintains their integrity and activity until they travel to the intended location.

Biocompatibility and Safety: Starch nanoparticles have outstanding biocompatibility and safety profiles, which reduce the possibility of side effects or immunological reactions after delivery. They are well absorbed by the body due to their natural origin and biodegradability, which further improves their usefulness for drug delivery applications [30].

Versatile Formulations: A range of dosage forms, such as oral tablets, capsules, injectable solutions, topical creams, and nasal sprays, can be created using starch nanoparticles. Their adaptability enables the creation of customized formulations to satisfy particular patient needs and administration route specifications.

Potential for Combination Therapy: By co-encapsulating several medications or therapeutic substances within a single nanoparticle system, starch nanoparticles can help with combination therapy. Especially in complex conditions like cancer, this method allows for lower medication resistance, better treatment outcomes, and synergistic effects.

2. Food Industry

The food industry has shown a great deal of interest in starch nanoparticles because of their special physicochemical characteristics, biocompatibility, and their uses as functional additives.

Enhanced Texture and Mouthfeel: By serving as thickeners, stabilizers, or emulsifiers, starch nanoparticles can improve the mouthfeel and texture of food products. When blended into techniques, they improve food's viscosity, creaminess, and smoothness, which enhances sensory qualities and increases consumer approval.

Improved Stability and Shelf-Life: By halting phase separation, sedimentation, or crystallization, starch nanoparticles give food items better stability and a longer shelf life. Their capacity to create a stable colloidal dispersion contributes to the consistency and homogeneity of food formulations throughout time [31].

Sugar and Fat Reduction: Using starch nanoparticles, food products can have less sugar or fat while still retaining their desired sensory qualities. Without sacrificing flavour, texture, or sensitivity, they help create healthier, lower-calorie food choices by substituting part of the fat or sugar.

Bioactive Compound Encapsulation: Starch nanoparticles are useful carriers for encapsulating and distributing bioactive ingredients, like tastes, vitamins, and antioxidants, in food compositions. Encapsulation maintains the stability and bioavailability of sensitive chemicals during processing and storage by shielding them from oxidation, volatilization, and degradation.

Controlled Nutrient Release: Starch nanoparticles provide sustained release kinetics and enhanced sensory perception by allowing for the controlled release of nutrients, flavors, or functional components in food matrices. The features of the nanoparticle, such as size, shape, or surface charge, can be modulated to meet specific criteria regarding the release profile of encapsulated substances.

Enhanced Processability and Texture Modification: Food compositions can be made more functional and processable by using starch nanoparticles to change the viscosity, texture, or rheological characteristics. They can form stable gels, films, or coatings, which makes it possible to create innovative food products with distinctive textures and structures.

Good Label and Natural Ingredients: To satisfy customer demand for clean label products, food makers looking for natural, plant-based ingredients can turn to starch nanoparticles for clean label solutions. Starch nanoparticles are naturally derived substances that can be substituted for synthetic chemicals or preservatives in food recipes, in line with the clean label movement [32].

Nanostructured Food Matrices: Starch nanoparticles allow for the creation of nanostructured food matrices with superior mechanical, barrier, and sensory qualities. Novel textures, flavours, and functions can be produced in food matrices by adding nanoparticles, which can result in food products that are more appealing to consumers.

3. Biomedical imaging

Because of their adjustable characteristics, biocompatibility, and adaptability as contrast agents, starch nanoparticles have demonstrated potential in biomedical imaging applications.

Magnesium Resonance Imaging (MRI): To improve contrast in MRI scans, starch nanoparticles can be functionalized with paramagnetic or superparamagnetic substances as gadolinium (Gd) or iron oxide ($Fe3O4$). With the help of these nanoparticles, which modify the relaxation durations of nearby water molecules, anatomical features or pathological lesions can be seen with greater sensitivity and specificity through variations in signal intensity.

Computed Tomography (CT): To act as contrast agents in CT imaging, starch nanoparticles containing high-Z elements, like iodine or gold, can be produced. When compared to adjacent tissues, these nanoparticles attenuate X-rays more strongly, which improves contrast and makes anatomical features, blood arteries, and malignancies easier to see on CT scans [33].

Fluorescence imaging: Fluorescence imaging of biological structures or molecular processes can be achieved by doping or conjugating starch nanoparticles with fluorescent dyes or quantum dots. When exposed to light, these nanoparticles become fluorescent, which makes it possible to monitor and visualize biological processes, biomolecules, and drug delivery vehicles in living tissues or cells in real time.

Nuclear Imaging: For use in nuclear imaging methods like single-photon emission computed tomography (SPECT) or positron emission tomography (PET), starch nanoparticles can be radiolabelled with gamma-emitting isotopes such technetium-99m (99mTc), indium-111 (111In), or fluorine-18 (18F). These radiolabelled nanoparticles make it easier to image physiological processes, receptor expression, or metabolic activities in vivo without invasive procedures, which offers important insights into a range of medical conditions.

Multimodal Imaging: By combining the advantages of several imaging modalities, starch nanoparticles can be made to contain numerous imaging modalities. This enables multimodal imaging approaches. Multimodal contrast agents provide complementary information, greater sensitivity, and enhanced diagnostic accuracy for a variety of biological applications by combining MRI, CT, fluorescence, or nuclear imaging capabilities into a single nanoparticle platform.

Targeted Imaging and Theranostics: To accomplish targeted imaging of particular cell types, tissues, or molecular biomarkers, starch nanoparticles can be functionalized with targeting ligands, such as antibodies, peptides, or aptamers. Selective viewing of disease locations is made possible by targeted contrast agents, which promotes early detection, precise diagnosis, and individualized treatment plans. Starch nanoparticles can be combined with medicinal substances to build theranostic platforms, which combine medication and imaging for concurrent illness monitoring and treatment [34].

Image-Guided Drug Delivery: By acting as carriers for therapeutic medications and imaging agents, starch nanoparticles make image-guided drug delivery techniques possible. Clinicians can optimize treatment regimens and improve therapeutic results by monitoring drug distribution, accumulation, and pharmacokinetics in real-time by integrating imaging capabilities into drug delivery systems, such as liposomes, micelles, or nanoparticles.

4. Tissue Engineering

Starch nanoparticles have great potential in tissue engineering due to their biocompatibility, biodegradability, and adjustable characteristics.

Fabrication of Scaffolds: In tissue engineering, scaffolds, hydrogels, and porous matrices can all be made with the help of starch nanoparticles. These nanoparticles can improve the mechanical characteristics, structural integrity, and cellular interactions of scaffolds by being added to biopolymer matrices like collagen, gelatin, or alginate. The production of nanocomposite scaffolds with variable porosity, pore size, and surface topography is facilitated by starch nanoparticles. These scaffolds imitate the natural extracellular matrix (ECM) found in target tissues and encourage cell adhesion, proliferation, and differentiation [35].

Cell transport Vehicles: In tissue engineering applications, starch nanoparticles can be employed as carriers for the transport of cells. Therapeutic cells, such as stem cells, progenitor cells, or immune cells, can be enclosed, shielded, and released under regulated conditions inside tissue-engineered constructions thanks to functionalized nanoparticles. In order to facilitate the targeted transport of cells to specific tissues or organs, encourage tissue regeneration, and improve the effectiveness of treatment, starch nanoparticles offer a biocompatible and biodegradable platform for cell transplantation.

Drug Delivery Systems: In tissue-engineered structures, starch nanoparticles can act as carriers for growth factors, cytokines, or small molecules medicines that are intended to promote tissue regeneration or alter cellular responses. By providing prolonged delivery and controlled release of bioactive compounds, these nanoparticles improve the bioavailability, stability, and therapeutic benefits of these molecules. Starch nanoparticles provide a diverse foundation for creating drug delivery systems customized to specific tissue engineering applications such as bone regeneration, cartilage repair, and wound healing [36].

Bioactive Coatings and Films: To improve the performance and functionality of tissue-engineered constructions, starch nanoparticles can be added to bioactive coatings, films, or membranes. These nanoparticles support cell attachment, proliferation, and tissue integration by offering antimicrobial qualities, cell adhesion motifs, or growth factor binding sites. By creating bioactive surfaces with certain characteristics, starch nanoparticles can enhance the biocompatibility, host tissue response, and long-term stability of implanted structures in vivo.

Bioprinting and 3D Bioprinted Constructs: Using starch nanoparticles, bioprinting techniques may create intricate, three-dimensional (3D) tissue constructs that have exact spatial control over the distribution of cells, composition of the extracellular matrix, and mechanical characteristics. Researchers are able to improve the printability, shape accuracy, and structural integrity of bioprinted tissues by adding starch nanoparticles to bioink compositions. By creating biomimetic scaffolds with vascular networks, hierarchical structures, and tissue-specific functions, starch nanoparticles make it easier to construct functioning tissues and organs for use in transplantation or regenerative medicine.

Theranostic Platforms: In tissue engineering, starch nanoparticles can be combined with therapeutic medications, imaging agents, or molecular probes to generate theranostic platforms that allow for simultaneous imaging and therapy. These multifunctional nanoparticles deliver therapeutic payloads to target areas and allow for non-invasive monitoring of disease development, tissue regeneration, or therapeutic response. When creating theranostic techniques for particular tissue engineering applications, such heart repair, brain regeneration, or skin tissue engineering, starch nanoparticles provide a flexible platform.

5. Environmental Remediation

Starch nanoparticles have shown promise in environmental remediation due to their biocompatibility, biodegradability, and adsorption characteristics.

Adsorption of Heavy Metals: To remove heavy metals from contaminated water sources, starch nanoparticles can be employed as adsorbents. Due to their large surface area, many functional groups, and adjustable surface chemistry, these nanoparticles make it easier for metal ions to be adsorbed by coordination complexation, ion exchange, or electrostatic interactions. It has been demonstrated that heavy metals like lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As) can be efficiently removed from aqueous solutions by starch nanoparticles, bringing their concentrations down to acceptable levels and minimizing environmental contamination.

Removal of Organic contaminants: In contaminated water sources, starch nanoparticles can also absorb organic contaminants like colours, pesticides, or medications. Through physical adsorption, hydrogen bonding, or π-π interactions, organic molecules can be adsorbed onto them thanks to their porous structure, hydrophilic surface, and functional groups. An inexpensive and environmentally acceptable option for environmental remediation, starch nanoparticles have been studied for the removal of a variety of organic contaminants, such as textile dyes, polycyclic aromatic hydrocarbons (PAHs), and endocrine-disrupting chemicals (EDCs) [37].

Filtration and Water Purification: Starch nanoparticles can be added to porous materials or filtration membranes used in water purification and filtration procedures. These nanoparticles improve the mechanical strength, pore size distribution, and filtration efficiency of membranes, which improves their ability to remove impurities from water sources. Membranes based on starch nanoparticles have been created for uses in microfiltration, ultrafiltration, and nanofiltration. These membranes allow contaminants like bacteria, viruses, and particulate matter to be eliminated from wastewater or drinking water.

Soil Remediation and Land Reclamation: To reduce soil contamination and restore ecosystem health, starch nanoparticles can be used in soil remediation and land reclamation projects. To lessen the mobility and bioavailability of pollutants in soil matrices, these nanoparticles can be used as immobilization agents, stabilizers, or soil supplements. In order to improve soil quality, fertility, and plant growth while lowering environmental concerns, starch nanoparticles have been studied for the remediation of contaminated soils, including heavy metal, oil, and pesticide contaminated soils.

Green and Sustainable Remediation Technologies: Compared to traditional remediation techniques like chemical precipitation, ion exchange, or membrane filtration, starch nanoparticles provide a green and sustainable alternative. They are desirable candidates for environmentally friendly remediation techniques due to their natural origin, biodegradability, and minimal environmental impact. In order to support sustainable environmental management and resource conservation initiatives, starch nanoparticles make it possible to design remediation methods that are economical, energy-efficient, and environmentally safe [38].

CONCLUSION

Investigations into starch nanoparticles and nanocrystals constitute an exciting field of study with broad applications, especially in biomedicine. These nanoparticles are appealing options for a variety of applications because of their special qualities, which include biocompatibility, biodegradability, and adjustable features. Both starch nanoparticles and starch nanocrystals have potential use in medicine as flexible platforms for wound healing, tissue engineering, medication delivery, and diagnostic imaging. Their capacity to precisely and effectively encapsulate, preserve, and administer therapeutic substances highlights their potential to transform treatment methods and enhance patient outcomes. Research on these starch-based nanomaterials is still ongoing, which is helping to expand our understanding of them and open up new avenues for creative approaches to challenging biological problems. Personalized medicine and healthcare delivery could be greatly enhanced by utilizing starch nanoparticles and nanocrystals, especially when interdisciplinary collaborations and technology breakthroughs pick up speed.

Starch nanoparticles and nanocrystals' adaptability and scalability provide chances for translation from laboratory to bedside, advancing the development of useful clinical applications. Research endeavours aimed at improving synthesis techniques, optimizing characteristics, and clarifying mechanisms of action are making it more and more possible to develop new formulations and tailored delivery systems. In order to navigate regulatory processes, ensure safety and efficacy, and eventually facilitate the integration of these starch-based nanomaterials into mainstream medical practice, collaborations between researchers, clinicians, and industry stakeholders are imperative. Through the utilization of the intrinsic benefits of starch nanoparticles and starch nanocrystals in conjunction with developments in nanotechnology and biomedicine, revolutionary breakthroughs in the identification, management, and treatment of illnesses can be achieved.

REFERENCES

1. French, D. Fine structure of starch and its relationship to the organization of starch granules. J. Jpn. Soc. Starch Sci. 1972, 19:8–25.
2. Ghaeb, M.; Tavanai, H.; Kadivar, M. Electrosprayed maize starch and its constituents (amylose and amylopectin) nanoparticles. Polym. Advan. Technol. 2015, 26:917–923.
3. Saad, W.S.; Prud'homme, R.K. Principles of nanoparticle formation by flash nanoprecipitation. Nano Today. 2016, 11:212–227.
4. Tian, H., Pan, S., Wu, C., Lu, S., Tang, Y., Shen, W., & Liu, S. Preparation, characterization, and in vitro cytotoxicity evaluation of resveratrol-loaded starch nanoparticles. International Journal of Biological Macromolecules. 2021, 186:143-152.
5. Torres, F.G.; De-la-Torre, G.E. Synthesis, characteristics, and applications of modified starch nanoparticles: A review. Int. J. Biol. Bacromol. 2022, 194:289–305.
6. Zhang, S., Li, Q., Yang, L., & Huang, Q. Gelatin-stabilized Pickering emulsion and complex coacervation method for preparation of starch nanoparticles. Food Hydrocolloids. 2016, 61:704-711.
7. Campelo, P.H.; Sant'Ana, A.S.; Pedrosa Silva Clerici, M.T. Starch nanoparticles: Production methods, structure, and properties for food applications. Curr. Opin. Food Sci. 2020, 33:136–140.

8. Xia, T.; Xue, C.; Wei, Z. Physicochemical characteristics, applications and research trends of edible Pickering emulsions. Trends Food Sci. Technol. 2021, 107:1–15.
9. Yun, W.; Genyi, Z. The preparation of modified nano-starch and its application in food industry. Food Res. Int. 2021, 140:110009.
10. Hassan, N.A.; Darwesh, O.M.; Smuda, S.S.; Altemimi, A.B.; Hu, A.; Cacciola, F.; Haoujar, I.; Abedelmaksoud, T.G. Recent trends in the preparation of nano-starch particles. Molecules. 2022, 27:5497.
11. Zhu, F. Relationships between amylopectin internal molecular structure and physicochemical properties of starch. Trends Food Sci. Technol. 2018, 78:234–242.
12. Vamadevan, V.; Bertoft, E. Structure-function relationships of starch components. Starch Stärke 2015, 67:55–68.
13. Agi, A.; Junin, R.; Arsad, A.; Abbas, A.; Gbadamosi, A.; Azli, N.B.; Oseh, J. Ultrasound-assisted weak-acid hydrolysis of crystalline starch nanoparticles for chemical enhanced oil recovery. Int. J. Biol. Macromol. 2020, 148:1251–1271.
14. Subhan, F., Ikram, M., Shehzad, A., & Ghafoor, A. Starch nanoparticles: A review of sustainable synthesis methods, applications, and challenges. Nanomaterials, 2017, 7(11):394.
15. Singh, V., Mohan, G., & Sinha, A. Starch nanoparticles: Synthesis, characterization, and biomedical applications. Journal of Polymers and the Environment, 2020, 28(1):171-181.
16. Zhang, B., Luo, Y., Wang, Q., Wang, Y., Liu, Z., Dong, L., ... & Xu, L. Fabrication and characterization of starch nanocrystal/fish gelatin composite films reinforced by glycerol and ethylene glycol diglycidyl ether. Food Hydrocolloids, 2019, 89:483-490.
17. Gao, Z., Li, J., & Chen, Y. Fabrication and Characterization of Methoxy Poly(ethylene glycol)-b-poly(L-glutamic acid)-based Polymeric Micelles for Methotrexate Delivery. Colloids and Surfaces B: Biointerfaces, 2020, 196:111342.
18. Li, J., Zhu, X., & Chen, Y. Fabrication and characterization of new pH-responsive biocompatible nanoparticles for drug delivery. European Polymer Journal, 2019, 118:432-439.
19. Lin, Y., Sun, Y., Guo, J., Wang, C., Cai, Z., Lei, M., ... & Qiu, L. Starch nanoparticles as potential drug delivery systems for 5-fluorouracil: In vitro and in vivo evaluation. International Journal of Biological Macromolecules, 2021, 166:509-519.

20. Li, Y., Li, S., Wang, Z., Li, S., & Yu, Z. Fabrication and characterization of starch nanoparticles as vitamin E carriers. International Journal of Biological Macromolecules, 2018, 111:941-947.
21. Li, H., Yan, S., Ji, J., Xu, M., Mao, H., Wen, Y., et al. Insights into maize starch degradation by high pressure homogenization treatment from molecular structure aspect. International Journal of Biological Macromolecules, 2020, 161:72–77.
22. Shabana, S., Prasansha, R., Kalinina, I., Potoroko, I., Bagale, U., & Shirish, S. H. Ultrasound assisted acid hydrolyzed structure modification and loading of antioxidants on potato starch nanoparticles. Ultrasonics Sonochemistry, 2019, 51:444–450.
23. Odeniyi MA, Omoteso OA, Adepoju AO, Jaiyeoba KT. Starch nanoparticles in drug delivery: a review. Polim W Med, 2018, 48:41–45.
24. Chen, C., He, L., Hu, Y., & Zhou, J. Preparation and characterization of starch nanoparticles by a novel ultrasonic-assisted method. Carbohydrate Polymers, 2019, 226:115276.
25. Chavan P, Sinhmar A, Nehra M, Thory R, Pathera AK, Sundarraj AA, Nain V. Impact on various properties of native starch after synthesis of starch nanoparticles: a review. Food Chem, 2021, 364:130416.
26. Raghavendra, G. M., Jung, J., Kim, D. O., & Seo, J. Starch-based nanomaterials in biomedical applications. Molecules, 2019, 24(2):329.
27. Ding, W., Zhang, Y., Zou, X., & Qu, Y. Starch nanoparticles: A new carrier for delivery of lipophilic bioactive compounds. Food Hydrocolloids, 2016, 61:675-684.
28. Liu, J., Li, S., Jiang, Y., & Li, Y. Starch nanoparticles as a novel controlled-release delivery carrier of curcumin. International Journal of Biological Macromolecules, 2019, 132:470-476.
29. Fu, Y.J.; Yang, J.D.; Jiang, L.W.; Ren, L.L.; Zhou, J. Encapsulation of lutein into starch nanoparticles to improve its dispersity in water and enhance stability of chemical oxidation. Starch Stärke, 2019, 71:100248.
30. Li, L., Li, J., Chen, Y., & Li, Y. Preparation and Characterization of Nanocomposite Films Reinforced with Starch Nanoparticles from Different Botanical Sources. Polymers, 2020, 12(6):1371.
31. Cheng, H., Lin, H., Zhang, S., & Wang, S. Preparation and characterization of gelatin-stabilized starch nanoparticles and their application in pickering emulsion template synthesis of zinc oxide. Journal of Food Engineering. 2020, 272:109823.

32. Iván Martínez-Muñoz, O.; Elizabeth Mora-Huertas, C. Nanoprecipitation technology to prepare carrier systems of interest in pharmaceutics: An overview of patenting. Int. J. Pharmaceut. 2022, 614:121440.
33. Abedi, E., Sayadi, M., & Pourmohammadi, K. Effect of freezing-thawing pretreatment on enzymatic modification of corn and potato starch treated with activated α-amylase: Investigation of functional properties. Food Hydrocolloids, 2022, 129:107676.
34. Espinosa-Andrews, H., Alcala-Alcala, S., & Fissore, D. Starch-based nanoparticles in drug delivery systems. In Nanostructures for Drug Delivery, 2019, 157-180.
35. Varshosaz, J., Minaiyan, M., Forghanian, M., & Fathi, M. Starch nanoparticles: A novel approach to drug delivery. Iranian Journal of Basic Medical Sciences, 2018, 21(2):120-128.
36. Danaei, M., Dehghankhold, M., Ataei, S., Hasanzadeh Davarani, F., Javanmard, R., Dokhani, A., et al. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics, 2018, 10(2):57.
37. Guo, Z., Zeng, S., Zhang, Y., Lu, X., Tian, Y., & Zheng, B. The effects of ultra-high pressure on the structural, rheological and retrogradation properties of lotus seed starch. Food Hydrocolloids, 2015, 44:285–291.
38. Torres FG, Arroyo J, Tineo C, Troncoso O. Tailoring the properties of native andean potato starch nanoparticles using acid and alkaline treatments. Starch, 2019, 71(3–4):1800234.