



Formulation factors of starch-based nanosystems preparation and their pharmaceutical application

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Abstract

Starch-based nanosystems are considered a talented nanocarrier for drug delivery owing to their small particle size, biodegradability, and biocompatibilities. Starch-based nanosystems showed enhancement in biological activity, solubility, entrapment efficiency, and in-vitro release of several drugs. Starch-based nanosystems are categorized into two types; starch nanocrystals and starch nanoparticles. The difference between starch nanocrystals and starch nanoparticles will be summarized. Numerous techniques are employed to formulate starch-based nanosystems including chemical and physical methods. This review summarizes the existing knowledge on; a number of techniques used to formulate starch-based nanosystems, factors affecting each technique, and the advantages of combining both physical and chemical methods on the formulation time and physicochemical properties of the starch-based nanosystems. Besides, most innovative information regarding starch-based nanosystems modification on increasing entrapment efficiency will be discussed. Furthermore, applying starch-based nanosystems as effective drug delivery nanocarriers for delivering drugs and bioactive elements to improve their bioavailability will be abridged in this review.

Keywords: Starch-based nanosystems; acid hydrolysis; nanoprecipitation; ultrasound; high-pressure homogenizer

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1. Introduction

Starch is a semi-crystalline natural polysaccharide, renewable, and biodegradable polymer created by many plants. The basic formula of this polymer is $(C_6H_{10}O_5)_n$. It entails two glucosidic macromolecules: linear amylose (18-28%) and branched amylopectin (72-82 %). Amylose is made

up of α -1, 4 glucan units linked by glycoside bonds. Amylopectin is made of short linear α -1, 4 glucan chains which are linked by α -1, 6 glycosidic bonds. It is prearranged in crystalline clusters of double helices forming stacks of interchanging crystalline and amorphous lamellae with even repeat distance. Starch has been commonly used in

the pharmaceutical manufacturing as a binder, disintegrate and filler in tablet formulation (Mahkam 2010, Odeku 2013, Lawal 2019, Marinopoulou, Papastergiadis et al. 2019). It is also reported that starch acted as reducing and stabilizing agents for silver nanoparticle preparation (Khan, Singh et al. 2013). Furthermore, starch was widely used to encapsulate and deliver a wide variety of food ingredients (Zhu 2017).

Recently, Starch-based nanosystems attracted focus due to their distinctive properties that are dissimilar from their bulk ingredients. Another fascinating feature of starch-based nanosystems is its capability to encapsulate various bioactive compounds, like testosterone, caffeine, ciprofloxacin, 5-fluorouracil, and curcumin. Starch-based nanosystems provide advantages of higher surface area, lower viscosity, and higher entrapment of active components (Santander-Ortega, Stauner et al. 2010, Chin, Yazid et al. 2014, Athira and Jyothi 2015, Najafi, Baghaie et al. 2016, Acevedo-Guevara, Nieto-Suaza et al. 2018, Shi, Hopfer et al. 2019). Starch-based nanosystems have been reported from different botanical sources e.g. waxy maize starch (Putaux, Molina-Boisseau et al. 2003), potato starch (Chen, Wei et al. 2008, Zheng, Ai et al. 2009, LeCorre, Vahanian et al. 2012, Shabana, Prasansha et al. 2019), cassava (García, Ribba et al. 2009, Athira and Jyothi 2015), tapioca (Hedayati, Niakousari et al. 2020), Breadfruit starch of the *Apocynaceae* (Andrade, Otoni et al. 2020), Banana Starch (Nieto-Suaza, Acevedo-Guevara et al. 2019), wheat starch (Momenpoor, Danafar et al. 2019), Lotus seed starch (Guo, Zhao et al. 2019), corn and yam starches (Minakawa, Faria-Tischer et al. 2019).

At this review, we will discuss the two categories of starch-based nanosystems, also, different chemical and physical methods used to formulate starch-based nanosystems, and factors affecting their characters. Moreover, the starch-based nanosystems pharmaceutical application will be discussed.

2. Starch-based nano-systems classification

Starch-based nanosystems can be categorized according to their crystallinity into two types; starch nanocrystals (SNCs) and starch nanoparticles (SNPs). Starch nanocrystals (SNC) are crystal-like nanoparticles arising from the disorder of the semi-crystalline assembly of starch granules at a temperature below their gelatinization temperature. SNCs are frequently attained through acid hydrolysis. SNCs are commonly used in the food

and pharmaceutical manufacturing. It was used for emulsion stabilization (Li, Sun et al. 2012, Haaj, Thielemans et al. 2014) and as nanofillers for reinforcement of nanocomposites (González, Retegi et al. 2015, Hao, Chen et al. 2018). In contrast, SNPs are amorphous (crystallinity <10%) spherical particles with variable sizes at the nanoscale. SNPs have been studied as a drug delivery carrier for several drugs. For instance, SNPs showed an enhancement in penetration studies on human skin when loaded with testosterone, flufenamic acid, and caffeine (Santander-Ortega, Stauner et al. 2010). Several methods were utilized to prepare SNPs including nanoprecipitation, ultrasonication, and high-pressure homogenization.

Recently several studies reported that SNPs modification increases the entrapment efficiency of several drugs. Xiao et al reported that dialdehyde SNPs conjugated with 5-fluorouracil have been documented to have improved inhibition of breast cancer cells (MF-7) in vitro relative to free 5-fluorouracil (Xiao, Liu et al. 2012). SNPs acetylation was found to increase EE % of curcumin, ciprofloxacin (Najafi, Baghaie et al. 2016) and decrease PDI which was illuminated by the acetylation role in increasing hydrogen bonding positions in starch molecules permitting interaction with more drug molecules (Tan, Xu et al. 2009, Acevedo-Guevara, Nieto-Suaza et al. 2018).

In addition, acetylation showed an insignificant increase in PS of SNPs, which was credited to aggregation caused by intermolecular hydrogen bonding. Studies conducted by several researchers found that the acetylated SNPs allowed more controlled release than SNPs which was claimed to presence of acetyl group in their chemical structure (Acevedo-Guevara, Nieto-Suaza et al. 2018).

3. Methods of preparation

The methods of starch-based nanosystems are classified into either chemical methods (acid hydrolysis and nanoprecipitation) or physical methods (ultrasonication and high-pressure homogenization). Chemical methods focused on opening the starch assembly. Once the starch structure unwrapped, the formation of the hydrogen bonds can be fast-tracked, through which SNPs are formed. By comparison, the physical methods were focused on the physical disruption of starch structure.

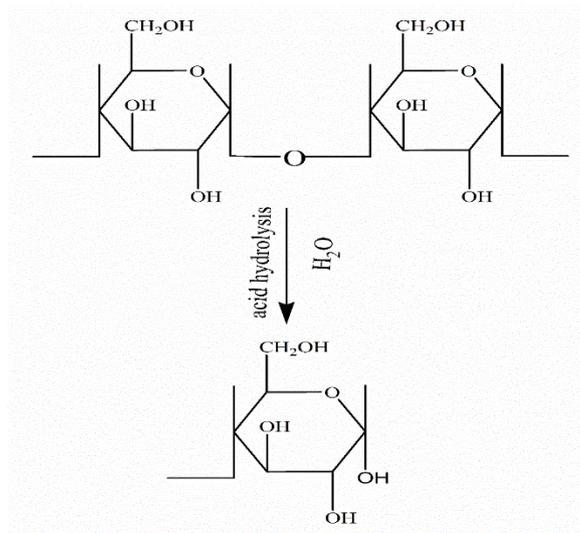


Figure 1: a schematic presentation of the acid hydrolysis mechanism.

3.1 Acid Hydrolysis methods

Acid hydrolysis is a simple method that has been used for SNCs preparation for many years. It involves using mild acids and temperature below temperature of the starch gelatinization. Mineral acids like Sulfuric acid and hydrochloric acid are commonly used, but recently several acids were used including citric acid ([Agi, Junin et al. 2020](#)) and organic acids like oxalic acids ([Zhou, Fang et al. 2020](#)). Acids cause scission of the glucosidic bonds, thus altering the structure and characteristics of the native starch (**Figure 1**). Acids only dissolve the amorphous region while crystalline remains. The main advantage of this method is increasing the overall crystallinity and solubility of the SNCs. However, the main weaknesses of such a method remained the extended duration, along with the low-yield being in the range of 2–15%. Extra problem also arises from the existence of a huge number of OH groups, which incline to reform the supra-molecular interactions that are characters of starch, yielding aggregates that limits its practical industrial utilization ([Dufresne 2008](#)).

Starch hydrolysis involves two stages, initial fast stage corresponding to hydrolysis of the amorphous part, and slow stage and corresponding to hydrolysis of the crystalline part and double helices, which is slowly eroded ([LeCorre, Bras et al. 2011](#), [Li, Yan et al. 2020](#), [Soler, Valenzuela-Díaz et al. 2020](#)). Two theories have been anticipated to explain the reason for the slow hydrolysis. First, the

compact packaging of starch crystallites with starch chains does not permit penetration easily of H₃O⁺ into the regions. Second, acid hydrolysis of a glucosidic bond may necessitate an alteration in conformation (chair to half chair) of the D-glucopyranosyl part. This transition will be impossible if the crystalline structure halts the sugar conformation ([Hoover 2000](#)).

Several factors are affecting the characters of SNCs prepared by the acid hydrolysis process like the amylose content, concentration, and type of acid, the hydrolysis duration, and the hydrolysis temperature. The effect of acid type, hydrolysis temperature, and duration of hydrolysis on the yield, the size of SNCs, and degree of crystallinity from the different botanical origins are illustrated in Table 1.

It was first stated that the size and crystallinity of acid hydrolysis SNCs is depending on the starch botanical source ([Xu, Ding et al. 2010](#)). However, a study published by LeCorre et al ([LeCorre, Bras et al. 2011](#)) concluded that the SNCs size and crystallinity were dependent on amylose content rather than the botanical source. They scrutinized the effect of starch botanical source and amylose content on SNCs size and crystallinity. They used three botanical sources (maize, potato, and wheat) and three concentrations of maize amylose (0, 25, and 70%). The results of that study concluded that increasing amylose content was accompanied by a significant decrease in crystallinity of SNCs and a

Table 1: the effect of acid type, hydrolysis temperature, and duration of hydrolysis on the yield, the size of SNCs, and degree of crystallinity from different botanical origin ₁

Starch origin	Temp.	Hydrolysis duration	Acid type	Yield %	Particle Size	Degree of crystallinity	Reference
Normal maize starch	40°C	5 days	3.16 M H ₂ SO ₄	-	47 ± 42 nm	48	(LeCorre, Bras et al. 2011)
waxy maize starch				-	58 ± 36 nm	42	
Amylomaize				-	118 ± 53 nm	35	
Potato starch				-	52 ± 4 nm	43	
Wheat starch				-	100 ± 50 nm	35	
taro starch	40°C	3 days	2.2 N HCL 3.16 N H ₂ SO ₄	34.443 40.592	586,1 nm 395,1 nm	87.3%	(Winarti, Surono et al. 2019)
	40°C	5 days	2.2 N HCL 3.16N H ₂ SO ₄	30.428 21.644	695,5 nm 358,0 nm		
arrowroot starch	40°C	3 days	2.2 N HCL 3.16 N H ₂ SO ₄	51.220 40.010	10,48 µm 648,4 nm	51.3%.	
	40°C	5 days	2.2 N HCL 3.16 N H ₂ SO ₄	38.056 40.129	938,1 nm 382,2 nm		
Quinoa starch	30°C	5 days	3.16 M H ₂ SO ₄	35.8	1056.7 nm	34.3	
	35°C			22.8	369.8 nm	34.8	
	40°C			6.8	243.4 nm	36.2	
Waxy maize starch	40°C	5 days	3.16 M H ₂ SO ₄	14.1	394.8 nm	48.0	
waxy maize starch	130 °C	15 h	6 M of oxalic acid	89.6%	46.58-197.15	29.52%-42.44%	(Zhou, Fang et al. 2020)

mild increase in PS. It was reported in another study (Cheetham and Tao 1998) that the crystallinity of SNCs was due to double helix packing of amylopectin side chains so increasing amylose content contributes to lower the crystallinity of the SNCs. While the mild increase in PS with increasing amylose content was explained by that increasing amylose content could jam the hydrolysis pathway giving chance for particle aggregation or large particle formation. Furthermore, the study concluded that there is no correlation between botanic origin and amylose content with the SNCs shape. The type and concentration of acid were found to have a significant effect on SNCs properties. Winarti et al analyzed the influence of the form of acid and hydrolysis duration on SNCs prepared from Taro starch and Arrowroot starch.

They used 2.2 N HCL and 3.16 M H₂SO₄ for hydrolysis of starch, which incubated at 40°C for 3 and 5 days. The SNCs obtained showed solubility improvement, a decrease in swelling power, and a decrease in temperature of gelatinization. The result of that study concluded that using HCL in hydrolysis provided a higher yield and large particle size than H₂SO₄. However, using H₂SO₄, produced a final suspension more stable than that obtained from HCL, which was attributed to the existence of sulfate group on the surface of the nanoparticles. The results also revealed that increasing H₂SO₄ hydrolysis duration decreased particle size in contrast to HCL, which increased PS by increasing hydrolysis duration. Furthermore, They claimed that the yield of SNCs had decreased due to the long time of the hydrolysis process

consequently the extra components of starch were dissolved in the acidic medium and decrease the yield of the SNCs (Winarti, Surono et al. 2019). These data were in agreement with that reported by Li, Yan et al. who concluded that increasing hydrolysis time, decreases the molecular size and amylose content which subsequently decrease the SNCs yield (Li, Yan et al. 2020). Wang, Truong et al treated the corn starch with three concentrations of HCL 0.06, 0.14, and 1.0N at 50°C. They announced that the rate of hydrolysis and crystallinity were increased with increasing acid concentration (Wang, Truong et al. 2003).

Temperature is another factor affecting SNCs properties. A study conducted by Velásquez-Castillo, Leite et al used three different hydrolysis temperatures (30, 35, and 40°C) to study the effect of hydrolysis temperature on the yield and PS of quinoa SNCs. They claimed that rising hydrolysis temperature did not influence the crystallinity index. of quinoa SNCs, however, resulted in lowering the obtained yield, thermal stability, as well as decreasing PS of SNCs (Velásquez-Castillo, Leite et al. 2020).

In general, SNCs gained by the conventional mineral acid hydrolysis technique are restricted because of long time required and low yield obtained. This tendency hinders the industrial application of SNCs. For the aforementioned reasons, several procedures with physical treatments or a combination of different methods were attempted. It was conveyed that the waxy maize SNCs properties were improved after dialdehyde modification. The waxy maize SNCs modified with dialdehyde showed Higher stability and more water dispersibility compared with waxy maize SNCs prepared without dialdehyde modification (Chen, Hao et al. 2019). In addition, enzymatic pretreatment was innovated to minimise the acidic hydrolysis period and increase the yield of SNCs of waxy maize; the final yield of SNCs of waxy maize obtained was 15% (LeCorre, Vahanian et al. 2012). To expand the SNCs yield, Kim, Han et al prepared waxy maize SNCs with a high yield of 78% using ultrasonication after cold sulfuric acid hydrolysis for 6 days (Kim, Han et al. 2013). Recently, Shabana et al (Shabana, Prasansha et al. 2019) reported that the combination of ultrasonication and acid hydrolysis allows the development of smaller particles and increased the antioxidant loading capacity. Zhou, Fang et al. prepared waxy maize SNCs using dry-heated oxalic acid hydrolysis. They obtained a high yield of SNCs (89.6%) with PS ranged from 46.58 to 197.15 nm, and the PDI was

0.28-0.52 (Zhou, Fang et al. 2020).

3.2. Nanoprecipitation method

Nanoprecipitation, also defined as the solvent displacement method, which involves two solvent systems that are miscible with each other. Nanoprecipitation is a simple method that not requires specialized equipment or complex operating conditions (Chong, Chin et al. 2020, Gutiérrez, Morán et al. 2020, Liu, Yang et al. 2020). It has been extensively used in pharmaceutical industry to prepare SNPs (Joye and McClements 2013). It involves the slow addition of a dilute polymer solution to a non-solvent or sequential addition of non-solvent into the polymer solution, which leads to the formation of nano-scale polymer particles (Acevedo-Guevara, Nieto-Suaza et al. 2018). The process is primarily based on the interfacial biopolymers deposition and displacement of water miscible semi-polar solvent from a lipophilic solution. Qin et al prepared SNPs from different botanical sources including; corn, tapioca, sweet potato, potato, and pea starch by dropwise addition of ethanol into a dilute solution of gelatinized starch under stirring. They reported that the PS of SNPs was between 30–75 nm (Qin, Liu et al. 2016). The properties of SNPs can be controlled by several factors including; starch concentration, the addition of surfactants, and the ratio of starch solution to non-solvent used in the precipitation. The effect of these factors on PS and morphology of SNPs are illustrated in Table 2.

Starch concentration was found to have a great role in determining the PS and encapsulation efficiency of the SNPs. An rise in the concentration of waxy maize starch acetate has been recorded from 1 to 20 mg/ml resulted in increasing the PS from 249 to 720 nm (Tan, Xu et al. 2009). Also, an increase in corn starch concentration was reported to increase the PS of SNPs from 132 to 220 nm (Hebeish, El-Rafie et al. 2014). Similar findings were reported by Hedayati and nikaousari et al whom used tapioca starch (Hedayati, Niakousari et al. 2020). The reported increase in the PS with increasing starch concentration arises from the higher viscosity and aggregation obtained that lead to the formation of a large diameter. It is also reported by Fu et al that increasing starch concentration decreased the lutein content. However, encapsulating lutein into SNPs increased lutein stability against chemical oxidation and enhanced its water dispersity (Fu, Yang et al. 2019).

Table 2: The effect of the ratio of starch solution to non-solvent used in the precipitation on particle size and morphology of starch nanoparticles

Starch origin	Starch concentration	Solvent system	Starch solution: non solvent	PS	Morphology	ref
Debranched waxy corn starch	10 mg/ml	Water: ethanol	1:3 1:4 1:5	80-170 20-100 50-140	Spherical Spherical Spherical	(Qiu, Yang et al. 2016)
Amylose Potato starch	10 mg/ml	Water: ethanol	1:3 1:4 1:5	100–200 30-60 70-100	Spherical Spherical Spherical	(Qiu, Qin et al. 2016)
Normal corn starch	10 mg/ml	Dimethyl-sulfoxide	1:5 1:10 1:20 1:30	208.1- 213.1	not clear not clear irregular spherical irregular spherical	(Wu, Chang et al. 2016)
native sago starch	10 mg/ml	NaOH/urea (NU) (0.8:1 wt%)	1:10 1:15 1:20	300-400	fibrous mixture of spherical and elongated fiber spherical	(Chin, Pang et al. 2011)

The presence of surfactant during the nanoprecipitation process was found to have a significant effect on decreasing the PS of SNPs. Chin and Pang et al synthesized SNPs between 300 nm and 400 nm by controlled drop-wise precipitation of 1ml 1 % native sago starch solution to excess absolute alcohol (10 mL, 15 mL, and 20 mL). in contrast, when they used 4% tween 80 as a Surfactants during precipitation they obtained SNPs with a mean diameter of about 150 nm (Chin, Pang et al. 2011). Putro and ismadji et al studied the effect of ionic surfactant (Cetyl trimethylammonium bromide and Sodium dodecyl sulfate) and non-ionic surfactant (Tween 20) on the crystalline structure of SNPs prepared from potato starch. They reported that surfactants increase the crystallinity of SNPs, which was contributed to the ability of surfactants to penetrate the starch internal cavity of the single helix part. The study concluded that the ionic surfactant gave higher drug uptake than the non-ionic surfactant, which was explained by ionic surfactant charges that increase the affinity of surfactant molecules toward starch particles (Putro, Ismadji et al. 2020). It is believed that the existance of surfactants during the precipitation process limits the aggregation of the SNPs and hence reduces their PS. (Chin, Pang et al. 2011). The ratios of starch solution to non-solvent used

were reported to have a significant impact on the PS and morphology of SNPs. Qiu et al investigated the effect of starch solution to the ethanol ratio on the PS of potato amylose SNPs. They prepared spherical amylose SNPs by dropwise adding a fixed quantity of absolute ethanol (30, 40, 50 mL) into 10 ml gelatinized amylose solution (1% W/V). The PS of SNPs decreased as ethanol amount increased from 30 to 40 ml then the PS was slightly increased when the amount of ethanol increased from 40 to 50 ml (Qiu, Qin et al. 2016). Similar findings have been documented by Qiu, Yang et al. (Qiu, Yang et al. 2016) who prepared SNPs by adding the same quantities of ethanol (30, 40, 50 mL) into 10 ml of short linear glucan solution (1%W/V) obtained from debranched waxy corn starch. The stated increase in PS was due to the decrease in the solvent power of starch solution and nucleation induced by increasing ethanol amount. Also, could be due to collision among particles leads to aggregation (Joye and McClements 2013, Qiu, Qin et al. 2016). There is a linear dependence between PS and the polarity of the mixture. It was found that the PS decreased as the solubility of the solvent mixture decreased (Tan, Xu et al. 2009, Qiu, Yang et al. 2016, Wu, Chang et al. 2016). Regarding the effect of the ratio of starch solution to non-solvent used on the morphology of SNPs.

Chin, Pang, et al prepared SNPs by addition of 1 ml of sago starch solution (10mg/ml) into different volumes of absolute ethanol (10, 15, and 20 ml) at a constant stirring rate. The findings of that analysis concluded that the morphology of the SNPs was dependent on the volume of ethanol used in precipitation. SNPs fibrous in shape were obtained when the ethanol volume was 10 ml. A mixture of spherical and elongated fiber-like SNPs was reported at a volume of 15 ml. However, when the ethanol volume ratio was 20 ml, spherical-shaped SNPs with PS between 300 and 400 nm were obtained (Chin, Pang et al. 2011). In Another study conducted by Wu. et al, an increase in the ethanol from 5 to 30 ml at precipitation of 1 ml of corn starch-dimethylsulfoxide solution (10mg/ml) has been significantly changed the morphology of the SNPs. At 5 and 10 ml volume of ethanol, the shape of SNPs was not clear because of the aggregation. An irregular spherical shape with distinct surface SNPs was observed at ethanol volume 20 ml and a further increase in ethanol volume to 30ml did not show any changes in the particle size and morphology of SNPs (Wu, Chang et al. 2016).

Recently it was reported that the combination of nanoprecipitation and another method or chemicals will faster the process. El-sheikh et al synthesized SNPs based on blending NaOH and glycerol in an aqueous solution during the synthesis progression while the precipitation of the SNPs is performed using ethanol under homogenization at ambient environment. The obtained nanoparticles were reported to be round in shape and uniformly distributed with a size of about 62.5 nm. The FT-IR findings revealed that the strength of the SNPs OH stretching band was higher than that of the native starch; this was due to the power of sodium hydroxide gelatinization and to the effect of homogenization throughout precipitation on damaging the crystalline structure of the starch molecules. The X-ray result confirmed the amorphous structure which was due to the swelling effect of sodium hydroxide on the starch and using high pressure homogenization (El-Sheikh 2017). Despite the nanoprecipitation advantages, it requires high levels of non-solvents such as isopropanol, ethanol, and acetone, which hinder its industrial application.

3.3. Ultrasound technique

The ultrasound technique is an eco-friendly method for the physical disruption of starch structure. It splits the covalent bonds in polymeric material through mechanical effects associated with the

collapse of micro bubbles by sound waves. Exposing the starch solution to ultrasonic waves results in a reduction of the molar mass and provides more channels for water dispersion through the starch granules. Izidoro et al explored the effect of ultrasound on the physical properties of starch suspensions. The outcome of this investigation revealed an improvement in starch solubility and water absorption ability after ultrasound treatment at a frequency of 20 kHz. (24 W power with 40% amplitude) for 1 h (Izidoro, Sierakowski et al. 2011).

It was reported that the ultra-sonication is affected by the temperature of the preparation. Zhu et al. reported that ultrasonic treatment of starch suspension for 30 min at temperatures ranging from 20 to 30°C resulted in a reduction of the molecular order in crystalline lamellae affecting the supra-molecular structure of starch without any reduction in particle size (Zhu, Li et al. 2012). In contrast, at a temperature around 5°C, the ultrasound treatment for the same time resulted in damage to the surface of the starch granules (Zuo, Hébraud et al. 2012). The ultra-sonication treatment was reported to decrease the crystallinity and degradation temperature of the starch producing SNPs with amorphous characters. Andrade et al prepared SNPs by submitting a 0.5% (w/v) breadfruit starch suspension to 75 min of ultra-sonication (a frequency of 20 kHz using a 50-W probe ultrasonic processor) at a temperature between 8 and 10 °C. The SNPs obtained were 145 nm in diameter and had a low zeta potential (-17 mv) which did not prevent SNPs aggregation. The x-ray results revealed a break of the crystalline assembly of native starch, and thus SNPs with amorphous characters obtained. The thermal analysis result indicated that the native starch had a degradation temperature higher than SNPs (Andrade, Otoni et al. 2020).

Several studies reported that the crystallinity of SNPs not only depends on the ultra-sonication but also depends on the source of starch and the ratio between amylose and amylopectin present in the starch (Bel Haaj, Magnin et al. 2013, Minakawa, Faria-Tischer et al. 2019). Minakawa et al, prepared starch nanoparticles from three different types of starch (cassava, corn, and yam) differ in amylose content. They subjected a solution of 10% starch for 30 minutes sonication at 25°C and the yield for all starch used was 12 ± 1 % starch nanoparticles. The reported results revealed that starch with high amylose content produced particles with smaller size and low crystallinity

while starch with low amylose content produces large particles size and amorphous particles. The results also revealed a decrease in crystallinity and thermal stability of nanoparticles compared with native starch from different sources which was attributed to the effect of ultra-sonication on decreasing polymerization and increase number of OH groups on the surface of nanoparticles (Minakawa, Faria-Tischer et al. 2019). Bel Haaj et al. prepared SNPs from standard starch (70% amylopectin) and waxy maize (99% amylopectin) by 75-minute sonication at 80% output at temperature ranged from 8 to 10°C. The results revealed that the particle size was sharply decreased at the first 30 minutes and 45 minutes for the waxy starch and the standard starch respectively then continued to decrease more slowly. The nanoparticles obtained from the waxy maize were less aggregated than those obtained from standard starch were. It was observed that SNPs obtained from waxy maize had lower crystallinity than those obtained from the standard starch. (Bel Haaj, Magnin et al. 2013).

It was reported that the combination of ultra-sonication and chemical process produced nanoparticles with more desired properties. Shabana et al studied the effect of combining ultra-sonication and acid hydrolysis on SNPs preparation. They prepared starch nanoparticles by sonication, sonication assisted with acid hydrolysis, and conventional acid hydrolysis method. Diluted sulfuric acid was used in the hydrolysis process and the temperature was maintained at 10°C during the experiment. The reported result of PS analysis showed that the PS decreased with increasing sonication time and particles obtained from ultrasound-assisted acid treatment were the smallest one (40 nm) compared to that obtained from ultra-sonication only (80 nm) and conventional acid hydrolysis method (1596 nm). The molecular weight of starch was decreased in ultrasound-assisted acid treatment more than ultrasound, which was attributed to increasing molecules structural breakdown by using sulfuric acid. Despite the role of acid in increasing the crystallinity of SNPs, it was found that acid treatment has not increased the crystalline pattern of nanoparticles, which was attributed to the modification of amylose to amylopectin associated with acid treatment (Shabana, Prasansha et al. 2019).

The effect of acid hydrolysis on the crystallinity of SNPs that was prepared by ultra-sonication was studied twice by Kim et al. in different conditions.

The results of the two studies concluded that ultra-sonication during the acid hydrolysis process was coupled with an increase in crystallinity (Kim, Han et al. 2013). In contrast, when ultra-sonication was performed after the acid hydrolysis at 4 °C the crystalline pattern was decreased (Kim, Park et al. 2013).

Mudasir et al produced SNPs from different starch sources by mild alkali hydrolysis and ultra-sonication. The nanoparticles obtained were ranged from 402 to 606 nm in diameter. The difference in particle size was attributed to the difference in the branching pattern of amylopectin within the starch. The study also revealed a notable increase in water absorption capacity and loss of crystallinity of all the prepared SNPs (Mudasir, Adil et al. 2020).

3.4. High-Pressure Homogenization

High-pressure homogenization is another physical and eco-friendly technique used for SNPs preparation. It involves passing the starch slurry through a high-pressure homogenizer under a certain pressure to decrease PS from micro to Nano size. A 5 % starch slurry was passed through the chambers of a Microfluidizer at a rate of 133 ml/min under the persistent pressure of 207 MPa several times. The starch PS was reduced from 3–6 µm to 10–20 nm without any change in crystal structure or thermal stability of starch granules (Liu, Wu et al. 2009). Liu et al. reported the use of a high-pressure homogenization method to prepare corn SNPs with a yield of almost 100%. However, the high yield gained, the method does not allow appropriate control of PS (Liu, Wu et al. 2009). Sodium trimetaphosphate cross-linked SNPs were produced by combining a high-pressure homogenization technique with mini-emulsion cross-linking method (Shi, Li et al. 2011). However, the efficiency of the technique, its use is limited owing to low yield obtained as only low concentration starch slurry can be processed for homogenization.

4. Starch-based Nanosystem pharmaceutical application

Recently, Starch-based Nanosystems are talented as nanocarriers of different bioactive molecules for different routes. It was reported that starch-based Nanosystem was successfully used as a bioactive carrier for several drugs including; Diclofenac sodium (El-Naggar, El-Rafie et al. 2015), curcumin (Acevedo-Guevara, Nieto-Suaza et al. 2018), two antioxidant: gallic acid and butylated

hydroxytoluene (de Oliveira, Fornaciari et al. 2018), Doxorubicin HCl (Yang, Li et al. 2017), Catechin (Ahmad, Mudgil et al. 2019), Ascorbic Acid and Oxalic Acid (Shabana, Prasansha et al. 2019), 5-fluorouracil (Norul Nazilah, Nagarjun Konduru et al. 2018), Vitamin D3 (Hasanvand, Fathi et al. 2018), and Quercetin (Farrag, Ide et al. 2018)

Ismail and Gopinath enhanced antibacterial activity and decreased resistance complication of penicillin and streptomycin against streptococcus pyogenes by loading on SNPs. They prepared SNPs using nanoprecipitation method, which produced spherical nanoparticles with uniform size distribution. The reported result showed a significant increase in the inhibition zone of antibiotic-loaded SNPs than antibiotics alone (Ismail and Gopinath 2017). Jong, Ju, and Zhang prepared SNPs loaded with doxorubicin, they reported that the SNPs protected the doxorubicin in the acidic conditions and showed good in-vitro drug release under neutral conditions (Jong, Ju et al. 2017).

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