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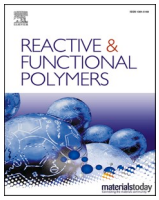

Perspective Article

Preparation methods and applications of chitosan nanoparticles; with an outlook toward reinforcement of biodegradable packaging

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ABSTRACT

Chitosan nanoparticles (NPs) are promising polymeric and bio-based NPs, which have received a lot of attention in the last decades. They have great potential as nanocarriers that encapsulate substances such as drugs or active compounds, deliver them to a specific place or site, and provide a controlled release. In the present review, we give a complete overview of the preparation methods, including novel and green procedures, and compile developed applications in medicine, agriculture, and wastewater treatment. Moreover, we highlight the future perspective of chitosan NPs use in PLA-based biodegradable polymers which can be one of the solutions for reducing plastic pollution in nature. Properties of chitosan NPs can be tuned in such a way that they can serve as reinforcement elements in biodegradable plastics leading to much-needed improvements, and also as functional elements that make the application in food packaging with e.g., enhanced antimicrobial activity possible.

1. Introduction

Nanosized materials may have improved or unexpected properties compared to the base material they stem from. Inorganic and organic NPs have been researched intensely, and numerous preparation routes (top-down, crosslinking, microbial) and possible fields of use (electronics, textile, and medicine) have been identified. Although it is good to point out that their effect on nature and the human body have been questioned. Polysaccharide-based NPs, are however known to be environmentally-benign, much less linked to concerns over toxicity, biodegradability, and physiological stability.

For example, chitosan a natural polysaccharide, is extensively used in medical formulations [1,2]. Chitosan, is derived from chitin and found as the primary component of cell walls of fungi, the exoskeletons of crustaceans and insects, and scales of fish. It is a cationic polymer composed of (1–4)-2-amino-2-deoxy-β-D-glucan that due its' pH sensitivity, biocompatibility, and bioactive functions has attracted more attention than its base polymer chitin [3,4].

From literature, it is clear that the properties of chitosan NPs can vary considerably depending on the preparation methods that are used, and the surface modification techniques that are applied, which can lead to applications in completely different fields. The field of medicine has been reviewed extensively, e.g. in the following reviews [5–9]. In addition to the great advances made in the field of medicine, researchers have concentrated on diverse applications over the last decades such as in agriculture, wastewater treatment, and cosmetics.

In addition, chitosan NPs may be used as filler material for biodegradable plastic matrixes which are in need of improvement in terms of mechanical and barrier properties [10–12]. In order to take steps in this field, more research is needed on the interaction strength between particle and based polymer, and that depends greatly on the size, and surface properties (which is a resultant of among others preparation method), that may be tailored by modification (chemical, physical, etc.).

This study aims to review recent developments in the preparation and application of chitosan NPs, and gives short overviews of the main fields of application, medicine/pharma, agriculture, water, and cosmetics. We bring this knowledge together for our main application field of interest: the preparation of nanoparticle reinforced packaging materials.

We first describe the preparation methods that are used for chitosan particle production and highlight the differences in the methods and particle properties that are obtained. The next section is dedicated to applications that are most recently described in different areas, and the modification techniques that lead to a. adjustment of surface hydrophobicity, b. surface charge, c. additional effects related to functionality. In the last section, we bring all insights together and give an outlook on how these particles can be best applied in packaging materials (for which aggregation and prevention thereof is an important point), and be

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instrumental in improving the properties of packaging materials in a more general sense.

2. Preparation of chitosan nanoparticles

Chitosan NPs were first characterized by Ohya et al., (1994) for the circulatory delivery of 5-fluorouracil, a chemotherapy medication. [13]. After this, researchers have studied chitosan NPs extensively and developed different methods considering diverse factors such as size, stability, drug loading capacity, and retention time. The basic approaches used to form chitosan NPs revolve around emulsification, precipitation, ionic or covalent crosslinking, or combinations thereof.

Emulsification and crosslinking was the first method described in the literature for the preparation of chitosan NPs using the amino group of chitosan and the aldehyde group of a crosslinking agent [13]. An emulsion consisting of an aqueous chitosan solution and an oil phase is made using Span 80 as a stabilizer, toluene, and glutaraldehyde as the crosslinker [13,14]. The phases are mixed intensely, and droplets form the basis of the NPs are formed after crosslinking. The separation of NPs from the emulsion can typically be done through centrifugation, multiple washing steps (with petroleum ether, acetone, sodium metabisulphite, and water) and vacuum- or freeze-drying. It is possible to obtain small size NPs with a narrow distribution. However, this method is no longer used since glutaraldehyde was noticed to cause overt toxicity and drug integrity issues.

Similar to the emulsification and crosslinking, the reversed micelles (microemulsion) method is another technique that based on covalent crosslinking; albeit that now water-in-oil reverse micelle structures assist the production of chitosan NPs. The aqueous phase including chitosan and glutaraldehyde is mixed with the organic phase that contains a lipophilic surfactant and an organic solvent. Usually, cetyltrimethylammonium (CTAB) bromide or sodium bis (2-ethylhexyl) sulfosuccinate (AOT) are used as surfactants, and *n*-hexane as an organic solvent is preferred [15,16]. The core of the micelle which contains chitosan works as a nanoreactor where chitosan NP are formed by crosslinking. Fig. 1 illustrates the preparation of chitosan NPs with the reversed micelles method. The isolation of NPs happens in three steps; the precipitation of surfactant with $CaCl_2$, dialysis for the elimination of unreacted materials, and freeze-drying [17]. It is possible to obtain ultrafine nanoparticles that have size below 100 nm, which is an important feature for many applications in which the specific surface area plays a role (loading capacity and sustained release). Lately, the preparation procedure has been adapted making use of non-harmful solvents and crosslinker which mitigates the issues with the classic method based on glutaraldehyde [16,18].

Chitosan NPs can also be produced by precipitation-based methods. The phase inversion precipitation method is based on emulsification combined with precipitation. The oil-in-water emulsion is prepared with an organic phase (dichloromethane and acetone) and an aqueous solution of chitosan, in the presence of a stabilizer (poloxamer). High-pressure homogenization is applied to obtain nanometer-sized well-dispersed emulsion droplets. Then methylene chloride is separated from the emulsion by evaporation at low pressure and room temperature, leading to acetone diffusing out of the droplets and concurrent precipitation of NPs [19]. Alternatively, the emulsion-droplet coalescence method, also called desolvation has been described, and which is based on the coalescence of two water-in-oil emulsions which induces precipitation of NPs because NaOH in one of the emulsions serves as a precipitation agent. Liquid paraffin and sorbitan sesquioleate are first mixed together, and serve as the continuous phase for the two emulsions, one with chitosan and one with NaOH. High-speed homogenization is applied to prepare emulsion containing chitosan. After two emulsions are combined, NaOH diffuses into the ultrafine droplets which decrease chitosan solubility, leading to nanoparticle formation and precipitation. NPs are obtained in three steps: centrifugation, washing with different solvents; toluene, ethanol, and water, respectively and freeze-drying [20,21]. In general, NPs obtained by precipitation methods are larger than 600–800 nm. Although both methods are not very preferred due to the use of organic solvents and high energy required homogenization applications and there are only a few studies in the literature, chitosan nanoparticles obtained by the phase inversion precipitation method have high encapsulation efficiency for hydrophobic drugs such as Cyclosporin A [18,19].

Chitosan nanoparticles have been investigated for more than two decades and ionic gelation is one of the most preferred preparation methods, which has first been described by Calvo et al., (1997) [22]. It is based on ionic crosslinking that happens in the presence of inversely charged groups; for example the protonated amino groups of chitosan and negatively charged groups of the polyanion such as sodium tripolyphosphate (TPP) [23]. Chitosan is added to an aqueous acidic solution (acetic acid solution in general), and then the aqueous solution of TPP is added under vigorous stirring. Anionic molecules diffuse into the mixture of positively-charged chitosan molecules and crosslinking occurs leading to nanoparticle formation. Fig. 2 shows the electrostatic interaction between chitosan and TPP, which ultimately forms spherical shaped nanoparticles. After a couple of centrifugation and washing processes with water, chitosan NPs can be obtained by oven-drying or freeze-drying. It is a straightforward technique without any harmful crosslinker or solvents. Besides, the process can be carried out at room temperature and the final nanoparticle size can be adjusted by changing the chitosan/TPP ratio, which is a crucial property that directly affects drug encapsulation efficiency and delivery [24,25].

Ionic gelation can also be used in combination with radical polymerization, which induces gelation of chitosan simultaneously with polymerization of acrylic or methacrylic acid [26]. Potassium persulfate is used as an initiator for the polymerization reaction which requires 6 h

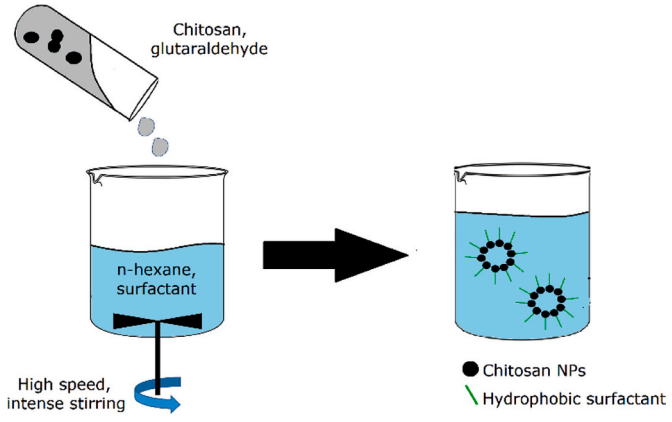

Fig. 1. Schematic illustration of chitosan nanoparticle forming via reversed micelles method.

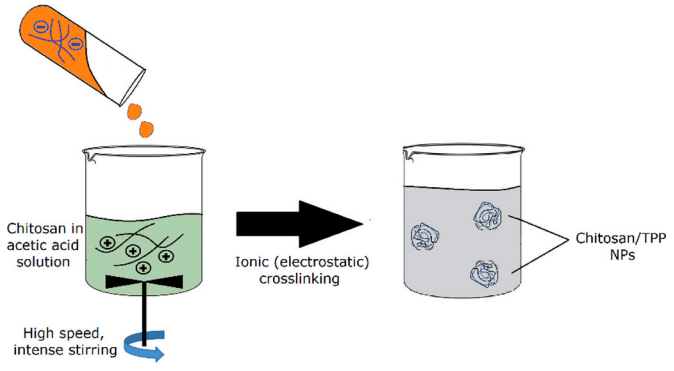

Fig. 2. Schematic illustration of chitosan nanoparticle forming via ionic gelation.

stirring at 60–70 °C [27,28]. As schematic representation of the interaction between chitosan and (meth)acrylic acid, and nanoparticle formation through radical polymerization can be seen in Fig. 3. The unreacted substances are removed by dialysis or multiple washing steps with water. This method has been used to successfully administrate insulin, silk peptide, and serum albumin through the oral route [18,28,29]. A limited number of applications are available today most probably due to long production process.

NP production can be occur by self-assembly which is a widely used method based on multiple simultaneous interactions that may be electrostatic, or hydrophobic in nature, or related to hydrogen bonding, and/or van der Waals forces between chitosan and other molecules [30,31]. The chitosan polyelectrolyte may form complexes with natural anionic materials such as hyaluronic acid or alginate, and this is mostly carried out by combining polymer solutions under stirring. Alternatively, the hydrophobicity of chitosan can be modified by grafting, which acyl-chitosan [32], stearic acid grafted chitosan [33], and PEGylated chitosan [34], that influences mostly the hydrophobic interactions during self-assembly. NPs obtained by self-assembly are especially favorable for encapsulating hydrophilic and lipophilic drugs [30] which allows the active to remain stable in the biocompatible matrix that can be adjusted readily with this mild process.

The top-down approach is also possible for the preparation of NPs, which includes two steps; acid hydrolysis of chitin to form chitin NPs and deacetylation (changing the acetyl group of chitin with an amino group). Basically, acid hydrolysis is applied with a strong acid such as hydrochloric acid for breaking glycosidic bonds and the amorphous part is removed by a couple of centrifugation and washing steps. Chitin nanocrystals are isolated after several centrifugation steps. Deacetylation is done by alkaline treatment with NaOH leading to chitin NPs that are called chitosan NPs above 60% degree of deacetylation [4,35]. Fig. 4 demonstrates chitosan NP production with top-down method. Unlike other methods where drug loading occurs simultaneously with NP formation, this method requires an extra loading step.

In recent years, green preparation routes and the use of 'mild' compounds have become popular among researchers. Spray drying is one these methods; chitosan is mostly dissolved in the aqueous acetic acid and NPs are formed by passing this solution through a nozzle using air temperatures from 120 °C-150 °C [27,36]. Magnetic chitosan NPs may also be produced by spray drying [37]. Generally, this method is used frequently in the production of chitosan microparticles and in the isolation of nanoparticles obtained by other methods. Supercritical-CO_2-assisted solubilization and atomization (SCASA) is one of the pioneering green methods as it is a process that is free of acid- or harmful solvent and uses only water and CO_2 during preparation. The dissolution of chitosan in water occurs through the acidifying effect of pressurized CO_2 under high pressure. After a relatively long dissolution step (48 h), the chitosan solution is fed to a fluidized bed by a spraying nozzle which

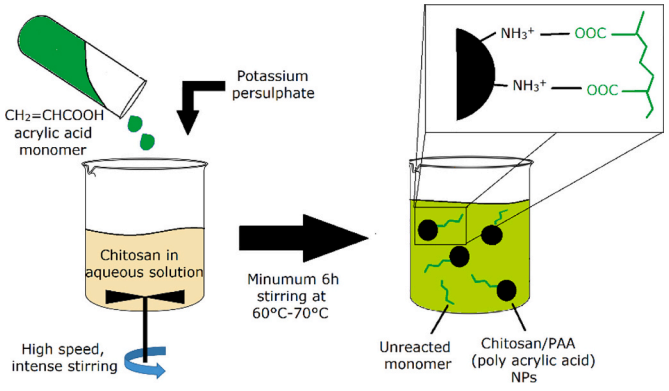

Fig. 3. Schematic illustration of chitosan nanoparticle forming via ionic gelation with radical polymerization.

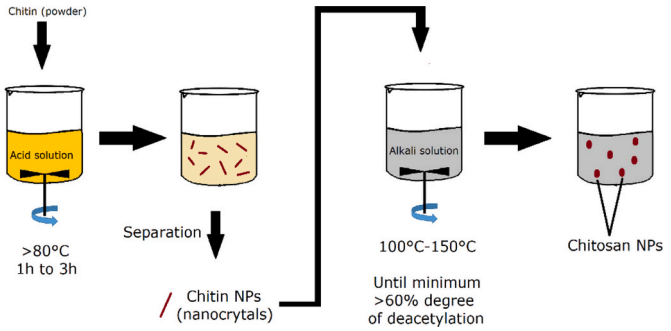

Fig. 4. Schematic illustration of chitosan nanoparticle forming via top-down method.

leads to atomization. NPs form due to the drying process, and are collected by a filter that is positioned on top of the fluidized bed [11,38]. The long processing time and the large particles and their distribution are seen as the disadvantages of this method.

Table 1 indicates the overall evaluation of preparation methods including advantages and drawbacks of each method in terms of ease of preparation, the use of harmful chemicals, and characteristics of NPs. Although it is not possible to nominate a particular method or principle as the best for all applications, methods that follow mild processes and produce NPs in a short time such as ionic gelation, self-assembly, and spray drying seem the most significant options from the points of view of human health and sustainable future.

3. Applications of chitosan nanoparticles

3.1. Medicine and pharmaceutics

Researchers have extensively studied chitosan NPs for various applications in medicine and pharmaceutics. The material is biocompatible and allows encapsulation and chain grafting of the drugs and active ingredients. Remarkable features such as preventing enzymatic degradation of drugs [40], and reducing the damage of non-targeted tissue or cells [41] make their use a great asset in drug delivery, cancer treatment and biological imaging and diagnosis [42]. Besides, the slow biodegradation of chitosan NPs has been reported to ensure controlled and continuous drug release [43]. The highly positive surface charge provides stable NPs that carry substances using various mechanisms in the human body [44,45].

The preparation of drug-loaded chitosan nanoparticle derivatives is generally done by two main techniques; nanoencapsulation and chemical modification. Nanoencapsulation relates to the formation of a nanostructure that contains absorbed drug at the surface or within the nanoparticle [46]. Table 2 shows chitosan NPs applications in medicine, NP properties and the performed modifications. Usually, the drug is encapsulated through a phase exchange process during which chitosan solidifies into NPs. This process helps to increase drug efficiency, specificity and accessibility to the target site while minimizing toxicity and side effects [47,48]. Studies on nanoencapsulation with chitosan NPs are mostly related to the delivery of therapeutic peptides such as insulin [49–51] and Cyclosporin A [46,47] and DNA [52–54] for gene therapy.

Chemical modification of chitosan NPs can be done starting from the base polymers or from the particles. The reactive amino and hydroxyl groups of chitosan are used for this purpose, and different alkaline conditions or temperatures have been reported. Examples are: thiolation [55,56], quaternization [57], carboxylation [52], PEGylation [53,58], and alkylation [59]. Even though chemical modifications are mostly performed as an auxiliary process for increasing encapsulation efficiency, solubility, enzymatic inhibition, and adhesive property, some applications also use direct grafting of the drug or active ingredient onto the polymer chain.

Table 1
The general overview of chitosan NPs preparation methods.

Method	Main Principle(s)	Advantage(s)	Drawback(s)	Ref.
Emulsification and crosslinking	Covalent crosslinking	• Simple process steps	• Use of harmful chemicals	[13,14,39]
Reversed micelles	Covalent crosslinking	• Ultrafine NPs below 100 nm	• Time-consuming process • Complex application • Use of harmful chemicals	[15–17]
Phase inversion precipitation	Precipitation	• High encapsulation capacity for specific compounds	• Requires high shear force • Use of harmful chemicals	[18,19]
Emulsion-droplet coalescence	Precipitation		• Requires high shear force • Use of harmful chemicals	[20,21]
Ionic gelation	Ionic crosslinking	• Use of mild chemicals • Simple process • Ease of adjusting NP size		[22,23]
Ionic gelation with radical polymerization	Polymerization and crosslinking		• Time-consuming process • Complex application	[26,28,29]
Self-assembly	Electrostatic and/or hydrophobic interaction	• Highly stable NPs • Use of mild chemicals • Adjustable procedure	• Hard to control when carried out a large scale	[30–32,34,40]
Top-down	Acid hydrolysis and deacetylation		• Time-consuming process • Complex application • Need an extra step for drug loading	[4]
Spray drying	Atomization	• Simple and fast process • Does not require another separation or drying steps	• Large particle size • Not suitable for use with temperature-sensitive substances	[27,36]
SCASA	Atomization	• Acid- or harmful solvent-free method • Does not require another separation or drying steps	• Time-consuming process • Requires a specially designed system • Large particle size	[11,38]

Table 2
Application of chitosan NPs in medicine and pharmaceutics.

Purpose of use	Compounds	NP production method	Particle size (nm)	Surface charge (mV)	Modification(s)	Ref
Insulin (INS) delivery	CsNPs, hydroxypropyl methylcellulose phthalate (HPMCP), INS	Ionic gelation	255	+30.1 ± 0.8	Spontaneous nanoencapsulation	[60]
	CsNPs, INS	Ionic gelation	289 ± 0.20–404 ± 18	+26 ± 2.4 – +32 ± 0.6	Spontaneous nanoencapsulation	[49]
	CsNPs, INS (with different mass ratios)	Self-assembly	210.1–526.5	+2.83 – +24.69	Spontaneous nanoencapsulation	[61]
	CsNPs, INS	Ionic gelation	346 ± 7	+36 ± 0.8	Spontaneous nanoencapsulation	[50]
	CsNPs, INS	Ionic gelation* (with termed flash nanocomplexation (FNC) system)	46.2 ± 2.7	+9.4 ± 1.2	Spontaneous nanoencapsulation	[51]
Cyclosporin A (CsA) delivery	CsNPs, CsA	Ionic gelation	293 ± 9	+37.5 ± 0.9	Spontaneous nanoencapsulation	[62]
	CsNPs, CsA	Spray drying	317.20 ± 78.69–681.30 ± 75.45	+22.0 ± 0.3 – +30.5 ± 0.5	Spontaneous nanoencapsulation	[63]
DNA delivery (gene therapy)	Glycol chitosan NPs, 5β-cholanic acid, plasmid DNA (pDNA) (hydrophobized)	Self-assembly	277 ± 30–731 ± 51	−1.1 ± 1.1 – +3.3 ± 0.9	Direct grafting and spontaneous nanoencapsulation	[54]
	CsNPs, pDNA	Ionic gelation	190.51 ± 19.05–287.25 ± 14.12	+17.09 ± 0.71 – +41.45 ± 0.43	Spontaneous nanoencapsulation	[53]
	Cs-N-2-hydroxypropyl trimethyl ammonium chloride NPs, pDNA	Phase inversion precipitation	91.8	~ −1	Quaternization and spontaneous nanoencapsulation	[57]
Cancer therapy	Thiolated CsNPs, curcumin (CRC)	Ionic gelation	150 ± 20	+48.2 ± 5	Thiolation and spontaneous nanoencapsulation	[55]
	Thiolated CsNPs, 5-fluorouracil (5-FU)		150 ± 40	+35.7 ± 3		
	Linoleic acid-modified carboxylated-Cs NPs, adriamycin	Self-assembly	417.8 ± 17.8	No information	Carboxylation and acid grafting	[64]
Circulatory system regulator	Thiolated CsNPs, heparin	Ionic gelation	323.1	+35.5	Thiolation and spontaneous nanoencapsulation	[56]
Gene silencing	Cs, methoxy PEG succinimidyl ester (mPEG-NHS), siRNA	Self-assembly	126.6 ± 2.18–175.6 ± 2.76	+19.2 ± 0.41 – +26.7 ± 0.42	PEGylation and spontaneous nanoencapsulation	[34]

3.2. Agriculture

Studies on the use of chitosan NPs for agricultural applications have increased rapidly motivated by the need for sustainable and eco-friendly agrochemicals such as fertilizers and pesticides. Similar as in medicine, chitosan NPs are used mostly as nanocarriers that enhance the stability of active ingredients and as a means to create controlled release [65]. Through these effects, agrochemicals can be applied in lower doses and fewer treatments are needed, thus contamination risk of the environment and toxic effects to other non-targeted organisms are decreased

[64,66].

Table 3 shows a general overview of chitosan NPs applications in agriculture. In general, medium-size and highly positive charged NPs which provide better stability in aqueous environments are preferred to ensure the slow and continuous release of active ingredients in soil. Nanoencapsulation that occurs spontaneously during ionic gelation has been used to encapsulate agrochemical- or active ingredients e.g. essential oils in chitosan NPs [67–70]. Typical applications of chitosan NPs are for herbicide delivery for weed eradication [67,69,71], in insecticide [68,70,72], and fungicide treatment [72–74] and various deliveries such as plant growth regulator [75,76], and fertilizer for balanced nutrition of plants [77–81]. Besides, chitosan derivatives e.g. chitosan-poly(acrylic acid) (CS-PAA) [72], chitosan-poly(methacrylic acid) (CS-PMAA) [80] and alginate/chitosan (ALG/CS) NPs [75,76] have been applied.

3.3. Wastewater treatment

The lack of a cost-efficient, sustainable, and effective sorbent as alternative for the widely used activated carbon has motivated the study of bio-based alternatives [82]. Chitosan includes functional amino and hydroxyl groups, which makes these NPs interesting for the removal of a range of pollutants such as heavy metals, pesticides, and dyes [83]. Besides, NPs may exhibit higher capacity than conventionally used micro-sized sorbents due to their higher surface area [84].

The applications and particle properties of chitosan NPs in wastewater treatment are shown in Table 4. Unlike applications in other fields, ultrafine nanoparticles that are smaller than 100 nm are preferred for wastewater treatment, which leads to a higher surface area that can absorb more pollutants. Chitosan nanoparticle derivatives with increased electrostatic and magnetic properties have generally been suggested for wastewater treatment. Amination is carried out by grafting e.g. ethylenediamine, hexanediamine, or diethylenetriamine of which the NH_2 group(s) are responsible for the electrostatic interactions with the pollutants [85,86]. When used in conjunction with magnetic properties, chitosan NPs have been applied to improve heavy metal and hazardous dye removal [87–89].

3.4. Other applications

Studies have shown that chitosan NPs and their derivatives can bring innovative solutions and new approaches to various scientific fields. Although the progress and use are not as widespread and advanced as in medicine and agriculture, studies have also been carried out in cosmetics, food technology, and dentistry.

Chitosan NPs have been suggested as carriers of active ingredients that are used for skin and hair care. The use of chitosan NPs to deliver minoxidil sulfate (hair growth agent for which concerns consist of side effects) ensured a sustained release without dermal exposure [95,96]. Nanoencapsulation of retinol led to protection against degradation [97], and complexation of retinol in succinic-chitosan NPs increased the antioxidant activity compared to pure retinol [98].

A pioneering study was carried out by del Carpio-Perochena et al., [99] who used chitosan NPs in root canal treatment instead of EDTA. These researchers showed that the antibacterial and chelating ability of chitosan NPs makes them a proper nanomaterial for dental applications. Furthermore, Atta et al. [100], investigated amidated chitosan NPs that may be used for corrosion protection of steel.

Chitosan NPs have also been considered as a filler material in e.g. pectin based edible films to improve the mechanical strength and barrier properties [101–105]. Moreover, there are some studies on the antimicrobial activity of chitosan NPs and their potential use in (edible) food packaging [102,106,107].

4. Future perspective for the use of chitosan nanoparticles in biodegradable food packaging

Petrol-based plastics pose a societal challenge that concerns many. On the one hand, polymeric materials have excellent properties when considering e.g. strength in relation to the amount of material that is used, on the other hand, many of these plastics are not properly disposed of, thus creating a huge environmental issue, which also applied to biomaterials if they do not degrade within an acceptable period of time. For standard plastic degradation, time would need to be expressed in terms of centuries.

In 2020, one trillion food and drink packages are predicted to be thrown away only in Europe [108]. Disposable plastic packaging materials accounted for almost 40% of plastic production in 2018 [109].

Table 3
Application of chitosan NPs in agriculture.

Purpose of use	Compounds	NP production method	Particle size (nm)	Surface charge (mV)	Modification(s)	Ref.
Herbicide delivery	CsNPs, paraquat	Ionic gelation	~300	+45	Spontaneous nanoencapsulation	[67]
	ALG, CsNPs, imazapic (IMC) and imazapyr (IMR)	Ionic gelation	377.70 ± 9.70	−30		[69]
	CsNPs, imazapic (IMC) and imazapyr (IMR)	Ionic gelation	478.60 ± 52.30	+26	Spontaneous nanoencapsulation	
Insecticide delivery	CsNPs, PAA	Polymerization and crosslinking	51.8	no info	–	[72]
	CsNPs, nicotine hydrochloride (NCT), sodium chloride (NaCl)	Ionic gelation	249.9	+35	Spontaneous nanoencapsulation	[70]
	CsNPs, fungal metabolites	Ionic gelation	~200	+24	Spontaneous nanoencapsulation	[68]
Fungicide delivery	CsNPs, *Cymbopogon martinii* essential oil (CMEO)	Self-assembly	455–480	+37.2 – +39.3	Spontaneous nanoencapsulation	[74]
	CsNPs, clove essential oil (CEO)	Emulsification and crosslinking	268.47 ± 0.71	+22.45 ± 0.90	–	[73]
Plant growth agent delivery	ALG, CsNPs, gibberellic acid (GA_3)	Ionic (pre)gelation	~450	29.00 ± 0.3		[75,76]
	CsNPs, gibberellic acid (GA_3)	Ionic gelation	~195	+27.00 ± 3.0	Spontaneous nanoencapsulation	
Fertilizer delivery				+45.3 (with N)		[77–79]
	CsNPs, methacrylic acid, fertilizers (N, P and K)	Polymerization and crosslinking	~500–700	+33.6 (with P) +85.4 (with K)	Nanoencapsulation after NP production	
	CsNPs, fertilizers (N,P and K)	Ionic gelation	~500	+50	Nanoencapsulation after NP production	[81]

Table 4
Application of chitosan NPs in wastewater treatment.*

Purpose of use	Compounds	NP production method	Particle size (nm)	Modification(s)	Ref.
Heavy metal removal	CsNPs, Fe_3O_4	Co-precipitation (for Fe_3O_4 NP production) and crosslinking	~30	Conjunction with magnetic particles	[88]
	CsNPs, acrylic acid, lead (II) nitrate ($Pb(NO_3)_2$)	Crosslinking	50–200	Direct grafting	[90]
	CsNPs, ALG	Ionic gelation (separately for each compound)	396.1	Crosslinking between CS NPs and ALG NPs	[91]
Dye removal	CsNPs, β-cyclodextrin, Fe_3O_4	Co-precipitation (for Fe_3O_4 NP production), Emulsification and crosslinking	~100	Conjunction with magnetic particles	[92]
	CsNPs, ethylenediamine, Fe_3O_4	Co-precipitation (for Fe_3O_4 NP production), Emulsification and crosslinking	15–40	Conjunction with magnetic particles and amination	[93]
	CsNPs, Fe_3O_4	Co-precipitation	78.82	Conjunction with magnetic particles	[94]
		Crosslinking with TPP	68.74		
		Crosslinking with glutaraldehyde	55.93		

* *No information was found related to the surface charges of chitosan NPs.*

These facts have peaked the interest of researchers and different industries, and have made them consider biodegradable plastics that are defined as materials able to completely degrade to water and carbon dioxide by naturally occurring activities of microorganisms such as bacteria, fungi, and algae [110]. Although there is an increasing trend in the production and use of biodegradable plastics; the share of biodegradable plastics was less than 1% of the total plastic production in 2019 [111].

Polylactic acid (PLA), a biodegradable and renewable thermoplastic polyester which is obtained from lactic acid or lactide, seems one of the most promising materials that may be able to replace conventional petrol-based plastics due to its production from renewable sources, the high tensile strength, UV-blocking property, excellent aroma barrier and the processability in standard plastic production lines [112–115]. Interestingly, neat PLA possesses better or comparable O_2 permeability than some conventional plastics such as polystyrene or polyethylene derivatives. Although the price of PLA (2000€/tonne) is still very high compared to conventional plastics (PET: 850–1050€/tonne, HDPE: 1200–1500€/tonne), experts predict that PLA can compete with its petrol-based counterparts in terms of price in the near future considering fluctuating prices of petrol and its finite nature [115].

Currently, PLA-based food packaging materials are for single-use applications: beverage and yoghurt cups, daily meal containers, shopping bags, and cutlery products. Improvements in mechanical and

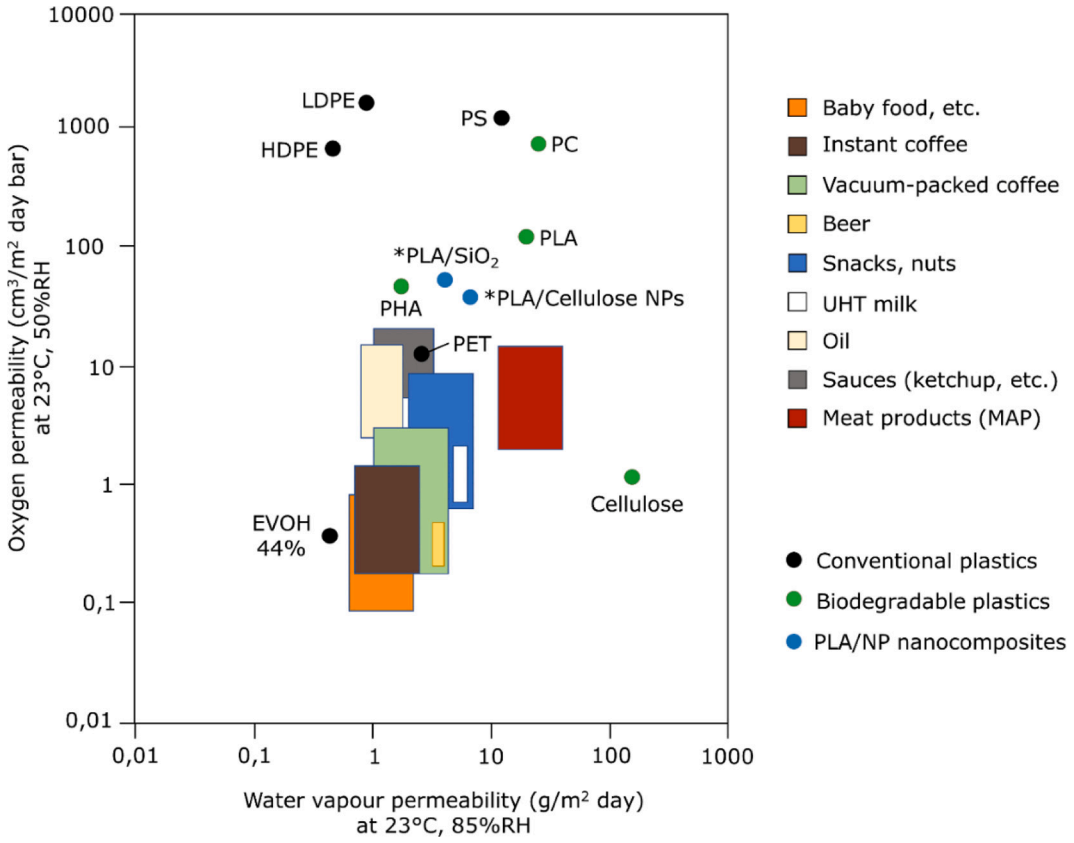

Fig. 5. *Overview of the barrier properties of packaging materials and requirements that need to be met for selected foods* [118–121]
**Approximate values due to different conditions and unit conversion*
LDPE: Low-density polyethylene, HDPE: High-density polyethylene, PS: Polystyrene, PET: Polyethylene terephthalate, EVOH: Ethylene vinyl alcohol, PC: Polycarbonate, PHA: Polyhydroxyalkanoate.

barrier properties are required for the widespread use of PLA in food packaging to become a reality. More specifically water vapor permeability, and brittleness need to be reduced [116,117], as illustrated in Fig. 5 in which an overview is shown of the various materials used in food packaging in the relation of oxygen and water permeability.

Inorganic NPs such as carbon nanomaterials, silica NPs, or metal NPs were extensively studied in the field of nanocomposites [122–125]. These particles can also greatly improve the properties of packaging materials as can be seen in Fig. 5 where nanocomposite properties are very close to the requirements that need to be met for specific food product categories, and quite improved compared to neat PLA for example. The use of inorganic NPs meets growing concerns in terms of environmental pollution; therefore, polysaccharide NPs such as cellulose, starch, chitin, and chitosan are thought to be more suitable fillers for PLA-based nanocomposites. These particles are more or less compatible with the base polymer and have been suggested to improve the mechanical, thermal and barrier properties [126,127]. Furthermore, natural polysaccharide NPs are biodegradable, renewable, versatile, and abundantly available. Besides, some of the polysaccharide NPs such as chitosan possess additional features such as antimicrobial and antioxidant activity, and options for chemical modification due to the presence of primary amino groups [128,129]. Table 5 shows how polysaccharide NPs affect the properties of biodegradable plastics, especially PLA. In general, it can be said that while the thermal properties do not change, the mechanical and barrier properties are improved.

As mentioned before, the compatibility of polysaccharide particles and the base polymer is not always ideal, therefore options to modify they surface properties are of great relevance since the specific surface area of the NPs is very high [135]. It has been suggested that a small amount of NPs (1–5%) will be sufficient for improvements to the matrix, and for this a homogenous distribution of particles inside the nanocomposite is a challenge that needs to be met.

For many nanocomposites, the thermodynamic equilibrium state is that of NPs in the form of aggregates [136,137]. Aggregation between NPs is mostly caused by Van der Waals forces or chemical bonds, and starts just after formation depending on concentration, size, and surface charge. Increasing concentration and smaller size promote aggregation while high surface charge provides more stable NPs [138,139]. Furthermore, (in)compatibility with the polymer matrix may induce aggregation. Keeping aggregation at the lowest levels or ensuring the disruption of aggregates during nanocomposite production is crucial for achieving desired product properties.

Different strategies have been using to manage the aggregation, one of them is breaking up aggregates during extrusion/melt mixing. It has been suggested that the specific mechanical energy (SME: energy given to the system during the process) is an indicative measure for this [140]. On the other hand, the energy that would be needed to break up certain aggregates can be extremely high [141,142], and it would be doubtful if an extruder can generate such energy input, which highlights the importance of surface modification methods to reduce the interaction energy in aggregates. Furthermore, it is good to mention that increasing temperature and long process times can lead to the degradation of PLA.

As mentioned, surface modification is an important tool to increase the hydrophobicity of chitosan NPs and thus facilitate homogeneous distribution in the polymer matrix. Various options are known from [143,144], such as fatty acids and aromatic acids that can be coupled to the amine group of chitosan. Besides, additional features can also be acquired, for instance by phenolic acid grafting that leads to improvements in biological activities (antimicrobial, antioxidant, antitumor, and anti-allergic) [145–147]. In a pioneering study by Salaberria et al. [133], the chloride form of a fatty acid (dodecanoyl chloride acid) was bonded to chitin NPs via acylation. These modified NPs had increased hydrophobicity, and mixed with PLA by extrusion showed higher antifungal activity, which we consider an interesting lead for further development of nanoparticle reinforce packaging materials.

Fig. 6 illustrates the whole production, functionalization, and degradation steps of PLA nanocomposites reinforced with chitosan NPs. Significant progress has been made in industry and academia, especially on PLA production. Moreover, NP production and various functionalization techniques are discussed in detail above, which is illustrative for further functionalization options. However, considering industrial production, some points need to be raised in relation to the origin and characterization of chitosan. Nowadays, shrimp and other crustaceans are the main sources of chitosan, which are allergenic for a part of the world population. The current chitosan production routes include a sequence of treatments for, especially deproteination that is expected to decrease greatly or even omit allergenicity effects. Although there are not many studies in the literature on this subject, no allergic reaction is

Table 5
Studies on polysaccharide NPs reinforced PLA and/or some other biodegradable plastic nanocomposites.

Filler	Matrix	NP preparation method	NP modification	NC preparation method	Main findings	Ref.
Cellulose NPs	•PLA •PLA, PHB •PLA, PHB and plasticizer	•Acid hydrolysis	•Surfactant grafting •L-lactide grafting	Solution casting or melt mixing	+Improvements in oxygen and water vapor permeabilities +Higher UV protection ±Similar thermal behavior -Decrease in transparency -Acceleration in disintegration -Higher stiffness with PLLA grafting	[122–125,127]
Starch NPs	•PLA	•Acid hydrolysis	•Crosslinking with ECH •PLA grafting	Solution casting	+Lower water vapor permeability ±Similar thermal behavior with PLA grafted SNPs -Lower glass transition temperature with epichlorohydrin crosslinked SNPs	[130,131]
Chitin NPs	•PLA •PLA and plasticizer •PLA, PEG and plasticizer	•Acid hydrolysis	•L-lactide grafting	Solution casting or melt mixing	+Higher tensile strength and Young's modulus +Lower water vapor permeability +The use of PEG reduced the aggregation of NPs ±Increase in biodegradability of chitin NPs reinforced PLA film ±Similar thermal behavior -Lower elongation at break (%) values	[126,132–134]
Chitosan NPs	•PLA	•Radical polymerization •SCASA •Unknown	•SMA grafting	Melt mixing	+Better miscibility between SMA-grafted CsNPs and PLA +Slight increase in elongation of PLA until 3% CsNPs content ±Similar thermal behavior	[10–12]

PHB: Polyhydroxy butyrate, PEG: Polyethylene glycol, ECH: Epichlorohydrin, SMA: Stearyl methacrylate.

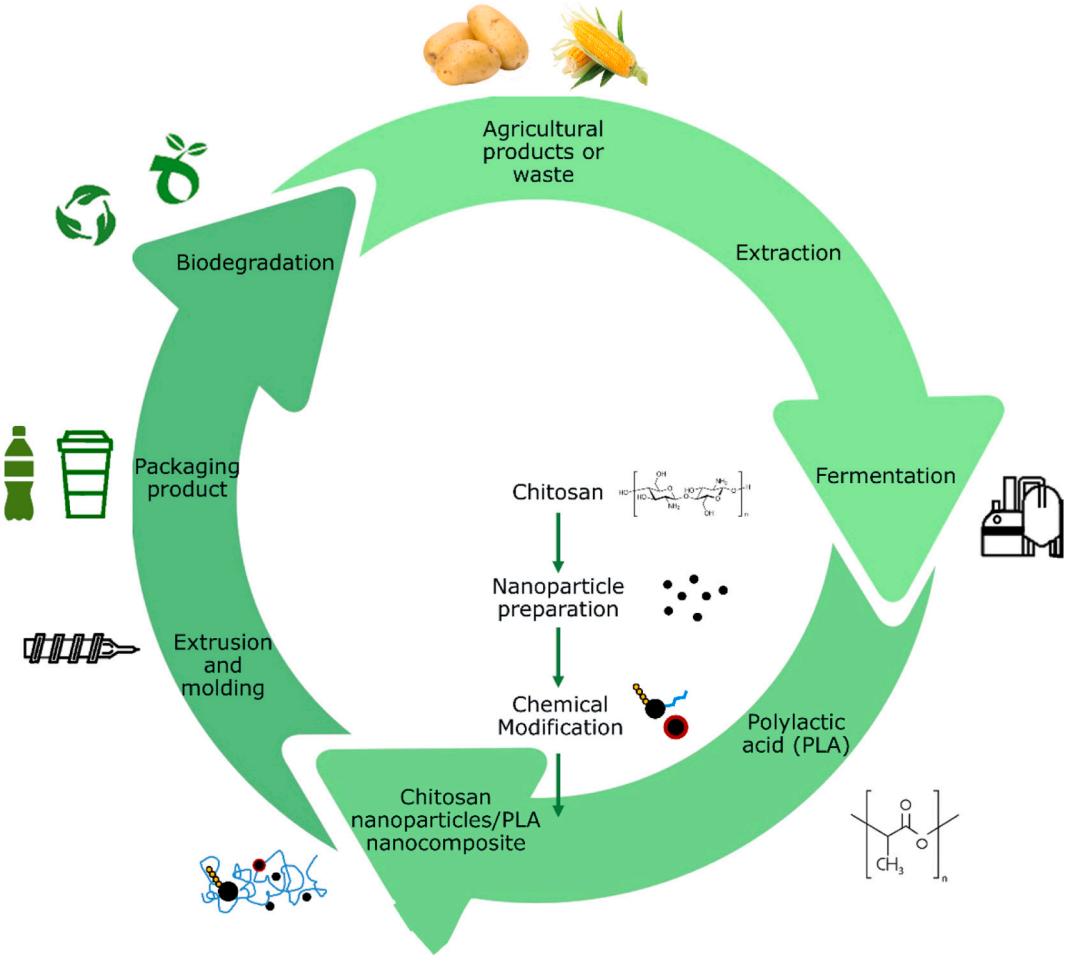

Fig. 6. The envisioned life cycle of chitosan NPs reinforced polylactic acid nanocomposites.

observed in wines processed with the chitosan-based film [148] or after the use of chitosan bandages [149]. The use of fungi-based chitosan could be an alternative to that obtained from crustaceans, although possible residue of mycotoxins and spores may then be a drawback that should be considered carefully [150,151]. On the other hand, different origin and preparation routes can lead to variable properties in bio-based molecules like chitosan, e.g. degree of deacetylation or molecular weight, which, as explained earlier is a promising route to further functionalization. Therefore, chitosan characterization for standard and reproducible material production is a critical point for industrial applications. Furthermore, determining the biodegradation and composting properties of NPs and packaging material will be needed.

5. Conclusions

Chitosan NPs have established an important place in different industries and scientific fields after their first description approximately two decades ago. Numerous preparation and modification methods have developed, including greener preparation methods that do not include harmful or toxic chemicals, for example, spray drying and supercritical-CO_2 assisted methods. The application of chitosan NPs is mostly to realize sustained release and high loading capacity of drugs or active ingredients in various fields such as pharma and agriculture.

Despite the relative ease of preparation, only a few studies are geared toward the application of chitosan NPs in biodegradable plastics. Preliminary studies show the great potential of chitosan NPs to upgrade PLA film properties (oxygen and water transfer) bringing them close to what is needed for food application. Further, NPs can be used to, directly or indirectly after surface modification, create additional features such as antioxidant and antimicrobial effects, which form a lead toward future active packaging options.

The authors anticipate that chitosan NP enriched PLA nanocomposites will play a significant role in biodegradable food packaging. These plastics have properties comparable to petrol-based polymers and may be given additional functionality, e.g. antimicrobial and antioxidant. Furthermore, they comply with societal aspects such as increased awareness of plastic waste and its' effects on nature and human life, and the demand for sustainable development of materials. So both from technical and societal points of view, this nanoparticle reinforced biodegradable food packaging will be in high demand.

Author statements

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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