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Review Article

# Octenyl succinic anhydride starch and its polyelectrolyte complexes as stabilizers in Pickering emulsions

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## ABSTRACT

Pickering emulsions, also known as emulsions stabilized by solid particles, have been increasingly applied in pharmaceutical products due to their high stability and non-toxicity. Due to unwanted toxicity from low molecular weight surfactants used as emulsifiers in classical emulsions, solid particles of biopolymers have been used as stabilizers in Pickering emulsions. This review summarizes the recent research on using octenyl succinic anhydride (OSA) starch and its polyelectrolyte complexes as stabilizers in Pickering emulsions. OSA starch-based Pickering emulsion has been reported to prepare various dosage forms such as emulsion, nanoemulsion, microcapsules, nanocapsules, and redispersible dry emulsion. The information obtained indicates the increasing trend in the application and practical uses of Pickering emulsions in the pharmaceutical industry.

**Keywords:**
Pickering emulsions, octenyl succinic anhydride starch, chitosan, polyelectrolyte complex, emulsifier, stabilizer

## 1. INTRODUCTION

Pickering emulsions have gained increasing interest in pharmaceutical product development because of their high stability and environmental friendliness. Various organic and inorganic solid particles are used as stabilizers in Pickering emulsions. However, some disadvantages exist, such as complicated synthetic steps, high cost, low biocompatibility, and unwanted toxicity. Therefore, the practical uses of synthetic organic particles and inorganic particles in Pickering emulsions are highly limited, especially in pharmaceutical products. The biopolymer solid particles which are generally regarded as safe are gained more interest to be used as stabilizers in Pickering emulsions. These solid particles do not decrease surface tension as low-molecular-weight surfactant used in the classical emulsion; therefore, most articles classified Pickering emulsions as surfactant-free emulsions. As the unwanted toxicity from low molecular weight surfactants used in classical emulsions are reported, the Pickering emulsions seem to be promising dosage forms to overcome the unwanted toxicity of low molecular weight surfactants in the classical emulsions. Generally, the solid particles are used to stabilized o/w emulsions. The active ingredients or drugs which are dissolved in the oil phase of emulsion could be encapsulated in drug delivery system; for example, fenofibrate, co enzyme Q-10, curcumin.

Biopolymers have received much attention as carriers and excipients in pharmaceutical dosage forms and drug delivery systems. Many scientists have recently focused on the fabrication of polysaccharides-based micro/nanoparticles, especially cellulose, chitin, chitosan, and starch-based micro/nanoparticles, as well as investigating their applications in stabilizing Pickering emulsions, due to their various advantages, such as high biocompatibility, biodegradability, and non-toxicity. Polyelectrolytes are macromolecules or polymers that consist of many functional charged groups such as chitosan, alginate, and pectin. The polyelectrolytes can become charged under suitable aqueous conditions (i.e., pH and ionic strength)[1].

Moreover, the ionized polyelectrolytes in the solution can interact with the oppositely charged polyelectrolytes to form polyelectrolyte complexes (PECs) or interpolyelectrolyte complexes. The PECs possess the proper characteristics, such as biocompatibility and biodegradeability, thus gaining much attraction in pharmaceutical and related products. In addition, the PECs can be prepared by a simple, uncomplicated, and solvent-free method[2-3],

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which is possible for industrial applications. Moreover, PECs could form nanoparticles that are used as stabilizers in Pickering emulsions.

Starch is commonly used as excipients in solid dosage forms such as powders, granules, capsules, and tablets. Physical and chemical treatments could modify and improve the functional properties of starch, thus enabling its use for different purposes[4]. In classical solid dosage forms, starch and modified starch are used as the diluent, binder, and disintegrant. In advanced drug delivery systems, modified starch is used as a carrier and encapsulating agent for preparing nanoparticles. Starch-based Pickering emulsion has been used in the delivery and encapsulation of bioactive ingredients[5]. However, the information related to the pharmaceutical application of starch and modified starch in Pickering emulsions is not summarized systematically. Starch granules are modified with octenyl succinic anhydride (OSA) for emulsion formulations[6]. Since the OSA group is hydrophobic, starch becomes amphiphilic and thus making it suitable for Pickering emulsion applications[7]. Furthermore, OSA starch could form PECs with chitosan and be used as solid emulsifiers in Pickering emulsions. This review summarizes the application of OSA starch and its PECs as stabilizers in Pickering emulsions.

## 2. PICKERING EMULSIONS

Pickering emulsions are emulsions stabilized by solid particles, namely particle-stabilized emulsions[8]. Figure 1 depicts the emulsion droplets of Pickering emulsions compared with classical emulsions. Pickering emulsion is stabilized by solid particles in place of low molecular weight or polymeric surfactants. Some solid particles are generally recognized as safe (GRAS), thus it has gained much attention to use in food, cosmetics, and pharmaceutical fields. Unlike the classical emulsions, the advantages of Pickering emulsions are strong stabilization against coalescence, nontoxicity, and high reproducibility[9].

The adsorption mechanism at the oil/water interface differs from any surfactant because the solid particles do not need to be amphiphilic. The interfacial tension is not dramatically changed after the adsorption of solid particles at the oil/water interface[10]. The important characteristic of solid particles for stabilizing emulsion is partial wettability, characterized by contact angle (θ). In contrast, highly hydrophilic or hydrophobic solid particles do not adsorb at oil/water interfaces because they are not wetted enough by both phases. The particles with high water-wettability (θ<90°) are suitable for forming o/w emulsions, whereas the low water-wettability particles (θ>90°) can be used to form w/o emulsions[11-12]. As shown in equation 1, the energy required to remove a particle from the interface (desorption energy or ΔE) depends on the particle size, the interfacial tension between oil and water, and the contact angle of the particle.

$$\Delta E=\pi r^2\gamma(1-|\cos\theta|)^2 \qquad \text{(Equation 1)}$$

Where r is the particle's radius, γ is the interfacial tension between oil and water, and θ is the contact angle of the particle at the interface. In addition to the high desorption energy, the particles at the interface prevent the droplets from coalescence and act as a mechanical barrier. The emulsifier particles above 10 nm are irreversibly adsorbed at the oil/water interface. On the other hand, the very small particle (<1 nm) will detach very easily and cannot be a good emulsifier[13]. The emulsifier particle size should be substantially smaller than the emulsion droplet size[9].

## 3. OCTENYL SUCCINIC ANHYDRIDE (OSA) STARCH

### 3.1. Chemistry and properties of OSA starch

Octenyl succinic anhydride starch (OSA starch) is one type of starches modified by an esterification reaction between hydroxyl groups of native starch and OSA starch under alkaline conditions (Figure 2)[32]. OSA starch can be synthesized from various starches such as waxy maize starch, maize starch, and tapioca starch[7]. The average number of OSA derivative per glucose unit is called the

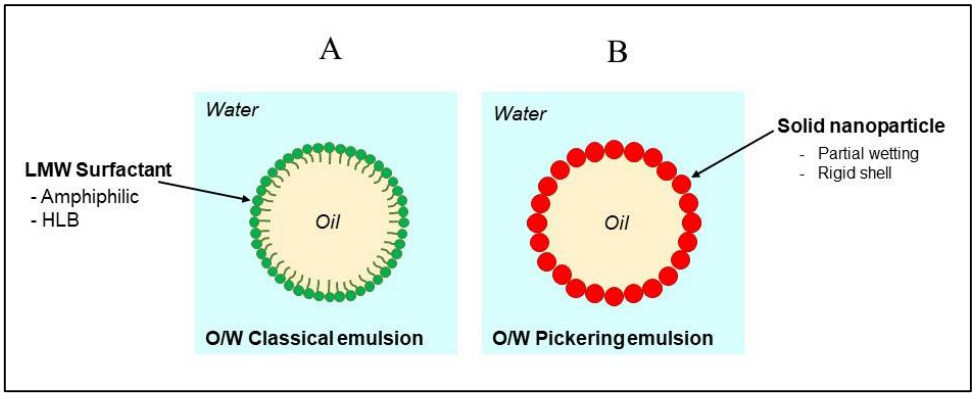


**Figure 1.** Microstructure of o/w classical emulsion (A), and o/w Pickering emulsion (B).

**Table 1.** Examples of Pickering emulsions stabilized by solid particles.

| Solid particles | | | | Emulsions | | | | Ref. |
|---|---|---|---|---|---|---|---|---|
| **Name** | **Particle preparation** | **Particle size (µm)** | **Zeta potential (mV)** | **Type** | **Oil phase** | **Droplet size (µm)** | **Zeta potential (mV)** | |
| Native starch granules | - | 4.5 - 47 | n/a | o/w | Paraffin liquid | 188 - 3131 | n/a | (24) |
| OSA starch nanoparticle | Non-solvent precipitaion | 0.1 - 0.2 | n/a | o/w | Miglyol 812 (MCT) | 0.5 - 100 | n/a | (20) |
| OSA Rice Starch | Microfluidization | 0.045± 0.009 | -27.0 ±6.30 | | Olive oil | 0.345 ±0.002 | -13.07±0.06 | (25) |
| Alumina or silica colloids | PEC formation | 0.016 | -50 to 0.0 | o/w | Dodecan or diethylothalate | 1-10 | n/a | (26) |
| Chitosan particles | pH adjustment | Few nm - ~1.8 µm | +18 to +55 | o/w | MCT | 40 - 82 | ~ 24 | (27) |
| Chitosan nanoparticles | pH adjustment and ultrasonic process | 0.04 - 0.85 | +10 to +55 | o/w | Corn oil | 2-14 | n/a | (22) |
| Quinoa starch | OSA modification | 1.65 - 1.74 | n/a | o/w | Miglyol 812 (MCT) | 12 - 81 | n/a | (6) |
| Silybin nanocrystal | High pressure homogenization | 0.3 - 0.4 | n/a | o/w | Capmul MCM C8 | 30 - 64 | n/a | (28) |
| Chitosan and alginate | PEC formation | 0.3 - 1.3 | -50 to +50 | o/w | Ethyl acetate | 20 - 120 | n/a | (16) |
| Biodegradable block copolymer | Polymer synthesis | 0.03 - 0.05 | n/a | o/w | Miglyol 812 (MCT) | 2 - 3 | n/a | (29) |
| Hydrophobic silica HDK H20 | - | n/a | n/a | w/o | Cyclomethi-cones | 9.7 | n/a | (30) |
| Chitosan-zein complex | Antisolvent method | 0.06 - 0.1 | 52 - 68 | o/w | n-tetradecane | 43 - 77 | n/a | (18) |
| Chitosan-OSA starch | PEC formation | n/a | n/a | o/w | Tuna oil | 0.36 - 0.43 | 48 - 53 | (31) |

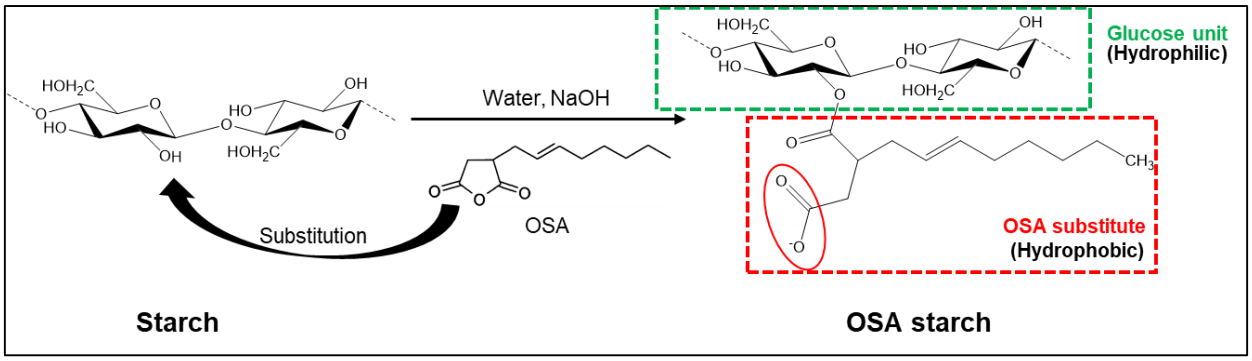


**Figure 2.** Synthesis of OSA starch.

"degree of substitution (DS)." According to the United States Food and Drug Administration (US FDA) regulation for the food-use purpose of starch, the maximum level of OSA substitution with native starch is limited to 3% based on dry weight (DS ≈ 0.02)[33]. Due to the OSA substitution, OSA starch becomes surface-active molecules (amphiphilic) that contain a starch region (hydrophilic part) and OSA region (hydrophobic part)[34], but it cannot reduce surface tension as well as small molecule surfactants[35]. Moreover, OSA starch is a polyelectrolyte containing charged carboxyl groups (-COO-), which are present in the OSA chain[36]. Hence OSA starch can be a negative charge in suitable pH solutions[37] and interact with oppositely charged molecules[38-40]. Negative charge densities of OSA starch also depend on the degree of substitution[41]. However, due to the low degree of substitution, it is a weakly charged polyelectrolyte[39]. Thus, the main stabilizing mechanism of OSA starch is a steric hindrance due to its high molecular weight and branched structure[36-37]. Moreover, the esterification of starch results in an increased hydrophobicity, a reduced swelling ability, and enhanced resistance to enzymatic hydrolysis[41-42]. Therefore, OSA starch has beneficial characteristics for developing drug delivery systems. OSA starch is used to prepare dispersion[34,43], emulsions[44-45], micellar encapsulation[46], microencapsulation[47-48], microparticles[38] and nanoencapsulation[49].

### 3.2 Application of OSA starch as stabilizers in Pickering emulsions

Tesch et al.[44] investigated the emulsion stabilization by OSA starch. Interfacial tension measurements could verify that OSA starch was a surface-active material. Moreover, the main emulsion stabilizing mechanism of OSA starch was a steric hindrance because the emulsification results are independent of pH value and ion valence. Qian et al.[50] compared the emulsifier performance in forming and stabilizing OSA starch with other biopolymers (β-lactoglobulin, gum arabic). The droplet size of the emulsion progressively decreases with increasing emulsifier concentration. For β-lactoglobulin, gum arabic, and OSA starch: the minimum droplet size achievable were 171, 497, and 254 nm, and emulsifier-to-oil ratios were 1:10, 1:1, and 1:5, respectively. Moreover, the droplet size of the emulsion stabilized by OSA starch did not change with the pH, indicating good pH stability. Liang et al.[51] developed nanoemulsion stabilized by OSA starch to improve the stability and bioaccessibility of β-carotene. During 30 days of storage under different conditions, the emulsion droplet size was increased by 30-85%. The retention of β-carotene in nanoemulsions was significantly higher but bioaccessibility was lower when compared with bulk oil.

Yu et al.[46] prepared OSA starch micelle to encapsulate curcumin for improving the *in vitro* anticancer activity. They demonstrated that OSA starch was able to form micelles, and the solubility of curcumin was enhanced by about 1670-folds. The curcumin was encapsulated in OSA starch micelles and did not alter the micelle structure. In addition, the curcumin-loaded micelles revealed enhanced *in vitro* anticancer activity compared to free curcumin. Furthermore, Pongsamart et al.[52] reported the use of OSA starch as an emulsifier and solid carrier in fenofibrate dry emulsion. The spray-dried emulsions with a small droplet size of 1-2 μm and enhanced dissolution rate were successfully prepared. In addition, the dissolution of drug from the dry emulsion was unchanged after storage at 40°C for 2 months.

## 4. OCTENYL SUCCINIC ANHYDRIDE (OSA) STARCH-CHITOSAN POLYELECTROLYTE COMPLEXES (PECs)

### 4.1. Formation of OSA starch-chitosan PECs

Polyelectrolyte complex (PEC) is simultaneously formed by electrostatic interaction between two polymers with opposite charges (Figure 3) (i.e., positively charged and negatively charged polymers) in suitable aqueous solutions without any chemical cross-linking agent[53]. The intermolecular interactions, including electrostatic interaction, hydrophobic bonds, van der Waals forces, and hydrogen bonding forces, involve the PEC formation[54-55]. The entropy gain associated with the release of counter-ions is one of the major driving forces for PEC

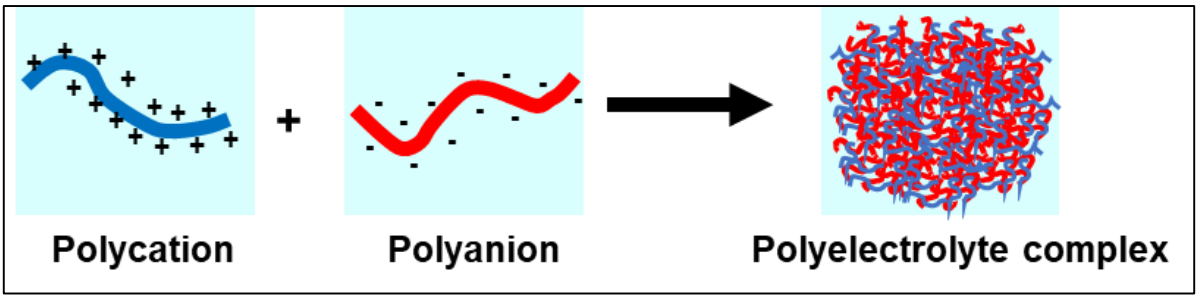


**Figure 3.** Polyelectrolyte complex formation between polycation and polyanion.

formation[56-57]. The first step of PEC formation is the formation of primary PEC through the electrostatic interaction, with the simultaneous release of the counterions. The second step is a rearrangement of these primary complexes and involves the formation of new bonds[58]. In particular, the formation and physicochemical properties of PEC depend on various parameters such as molecular structures, preparation processes, and media[59]. The parameters related to the molecular structure include molecular weight, charge density, pKa, percentage of the ionic group, and chain flexibility. The preparation process parameters are molar-charge ratio, mass ratio, PEC concentration, order of addition, reaction time, and mixing machine. Finally, ionic strength and pH of media are also important parameters.

The most important factor affecting PEC formation is the molar-charge ratio[60]. It is the ratio of charge densities between positive and negative charges of polymers at a given pH[61-62]. The charge density (mol-charge/g) of each polyelectrolyte is defined as the number of ionic groups (per weight) that can be ionized at specific pH, and the pH also determines the degree of ionization of these ionic groups[61,63]. Therefore, the mixing of two oppositely charged polyelectrolytes cause two types of PECs that are mainly controlled by the molar-charge ratio: (i) soluble PEC (non-stoichiometric charge ratio) and (ii) insoluble PEC (stoichiometric charge ratio)[54,61]. The drawings of non-stoichiometric charge ratio and stoichiometric charge ratio PECs are presented in Figure 4.

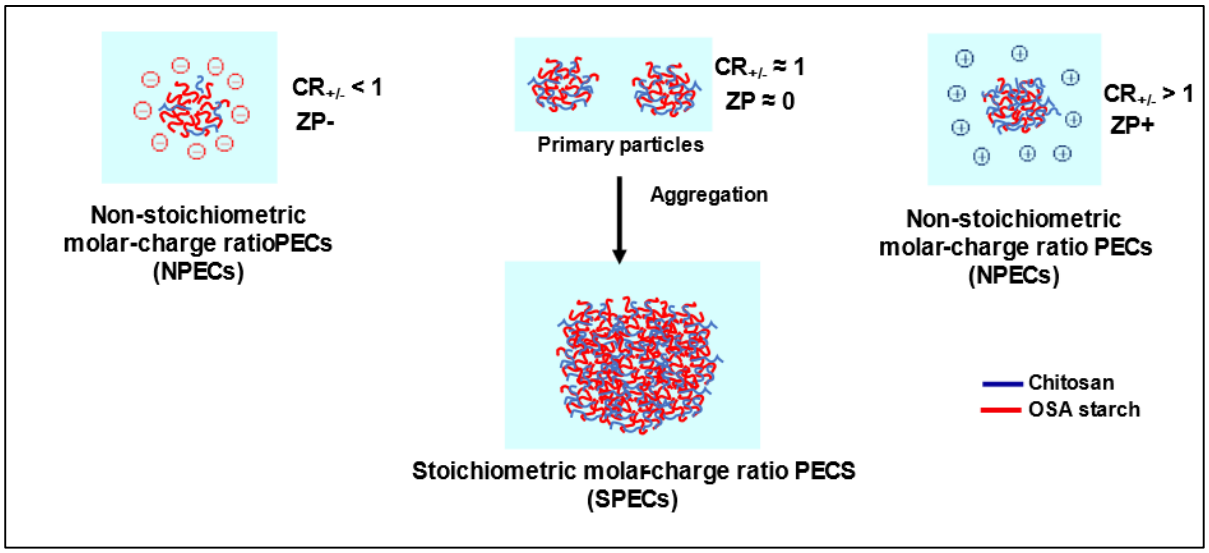


**Figure 4.** Formation of non-stoichiometric charge ratio and stoichiometric charge ratio PECs.

The soluble PEC is obtained with an excess of either positively charged polymer or negatively charged polymer (charge ratio ≠ 1). The soluble PEC is preferred to prepare the micro/nanoparticles stabilized by surface charge because they have good colloidal stability and are favorable for cellular uptake[55]. In contrast, the insoluble PEC is obtained when the charge densities of two polymers are equal (charge ratio=1) and the total charge of PEC is zero leading to macroscopic phase separation upon formation[56,61]. The insoluble PEC is used for controlled drug releases[64] and complex coacervation for microencapsulation[65-66]. The comparison between stoichiometric charge ratio and non-stoichiometric charge ratio PECs are summarized and shown in Table 2.

Chitosan, a natural polysaccharide polymer, is obtained from the partial deacetylation of chitin under alkaline conditions[67]. As shown in Figure 5, the natural sources of chitin are the main component of the exoskeleton of crustaceans such as shrimp, lobsters, prawns, crabs, or in the cell walls of fungi and yeast[68]. Chitosan is a copolymer of β-(1→4)-linked 2-acetamido-2-deoxy-D-glucopyranose (acetylated unit) and 2-amino-2-deoxy-

D-glucopyranose (deacetylated unit). The mole fraction of deacetylated unit in the chitosan polymer chain is called the "degree of deacetylation," which is higher than 50%[67]. Chitosan has the pKa of 6.2-7.0[69]. Moreover, the degree of deacetylation affects positive charge density because only deacetylated units carry amino groups[40,70-71]. Chitosan is insoluble in water, alkali, and organic solvent but soluble and forms salts in solution of inorganic acids, and organic acids[72-73] such as hydrochloric acid, and acetic acid (74), respectively. Chitosan is soluble in acidic media (pH<pKa) by protonation of the amine groups of deacetylated repeating units[68,74]. Afterward, chitosan becomes the positive polyelectrolyte in an acidic solution and can interact with oppositely charged substances such as anionic polysaccharides, synthetic polymers, proteins, and nucleic acids[75-76].

### 4.2 Application of OSA starch-chitosan PECs as stabilizers in Pickering emulsions

It was reported that OSA starch could form a PEC with chitosan through electrostatic interaction between carboxylate moieties (COO-) of OSA substituted groups of OSA starch and protonated amines (NH3+) of deacetylated units of chitosan[31]. Recently, OSA starch combined with chitosan was used for microencapsulation of food and pharmaceutical ingredients[31,40,86,87].

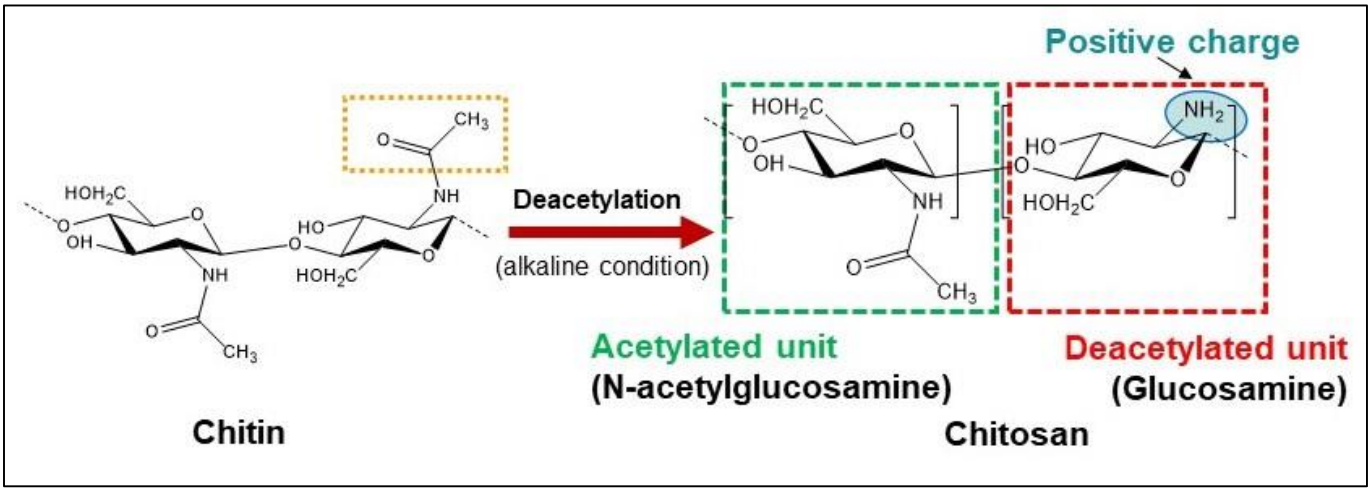


**Figure 5.** Sources, deacetylation process, and chemical structure of chitosan.

**Table 2.** Characteristics of stoichiometric and non-stoichiometric charge ratio PECs.

| Characteristics | Stoichiometric charge ratio PECs | Non-stoichiometric charge ratio PECs |
|---|---|---|
| Molar-charge ratio | Charge ratio ≈ 1 (Equal charge density) | Either positively or negatively charged polyelectrolyte is excess. |
| Zeta potential | Nearly zero (neutral) | Positive or negative zeta potential |
| Colloidal stability | Low | Stable at zeta potential > \| ± 30 mV \| |
| Water-soluble | Insoluble | Soluble |
| Phase | Separate phase or homogenous turbid | Homogenous solution |
| Particle structure | Aggregate structure (Secondary structure) | Non-aggregate structure |
| Particle size | Larger | Smaller |
| Turbidity | Turbid | Clear |
| Viscosity | Low | High |
| Phase behavior | Interphase | Bulk solution |
| Applications | Controlled drug release, complex coacervation | Drug delivery systems, micro/nanoparticles |

There are two methods for using OSA starch-chitosan PECs as stabilizers in Pickering emulsions. The first method is called the PEC method. In this method, the OSA starch-chitosan PECs were firstly formed, then mixed with the oil phase for preparing the emulsions[31]. The second method is called layer-by-layer (LBL) method. The primary emulsions were prepared using one emulsifier (either OSA starch or chitosan), and then oppositely charged polyelectrolytes were added to the primary emulsions[40,86,88].

The OSA starch-chitosan PECs are applied for preparing emulsions, and nano/microcapsules. Shen et al.[31] had developed microcapsule powders of fish oil by using OSA starch-chitosan PECs as wall materials. OSA starch was mixed with chitosan in solution at pH 4.9 and 6.0 before adding the oil phase. After that, the dispersions were high-pressure homogenized and then spray-dried to obtain the powder. They suggested that the pH affected the electrostatic interaction between OSA starch and chitosan, which influenced the stability of the microcapsule powder. Preetz et al.[40] prepared a three-layer polyelectrolyte nanocapsules, in which the emulsion stabilized with OSA starch was prepared by high-pressure homogenization, followed by the stepwise addition of the additional layer components of chitosan and carrageenan. The obtained nanocapsules showed improved stability and protecting capability of labile substances. Carvalho et al.[86] prepared LBL microcapsules to improve the stability of green coffee oil. Emulsions of green coffee oil were prepared and stabilized by lecithin and chitosan. Incorporating OSA starch in the wall materials could improve the stability and encapsulation efficiency of green coffee oil spray-dried powder. Abbas et al.[17] prepared the multilayer shell nanocapsules by sequential adsorption of chitosan and sodium carboxymethyl cellulose on the curcumin-loaded nanoemulsions stabilized by OSA starch. The obtained nanocapsules exhibited improved physical stability of lipophilic bioactive compounds.

Recently, OSA starch-chitosan PECs were used as stabilizers for preparing the redispersible dry nanoemulsions by spray drying[89]. The formulation consisted of fenofibrate nanoemulsions stabilized with chitosan-OSA starch PECs as stabilizers and lactose as a solid carrier. The droplet size of nanoemulsions remarkably decreased as the OSA starch to oil ratio increased. The spray-dried nanoemulsions with improved redispersibility and smaller droplet sizes were obtained at higher lactose levels.

## 5. CONCLUSION REMARKS AND FUTURE TREND

Both OSA starch and chitosan are biopolymers that possess proper properties such as biocompatibility, biodegradability, and non-toxicity. The PECs between chitosan and OSA starch show unique characteristics and could be prepared using a simple solvent-free method. Both OSA starch and OSA starch-chitosan PECs can be used as solid emulsifiers or stabilizers in Pickering emulsion. The application of OSA starch and OSA starch-chitosan PECs in preparing various dosage forms such as nanoemulsion, nano/microcapsules, and dry emulsion have been reported. These studies demonstrate the potential uses of OSA starch and OSA starch-chitosan PECs as stabilizers in Pickering emulsions for the pharmaceutical industry, and more applications in the pharmaceutical field are expected in the future.

**Conflict of interest**

There is no conflict of interest.

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