Pickering emulsions: Preparation processes, key parameters governing their properties and potential for pharmaceutical applications

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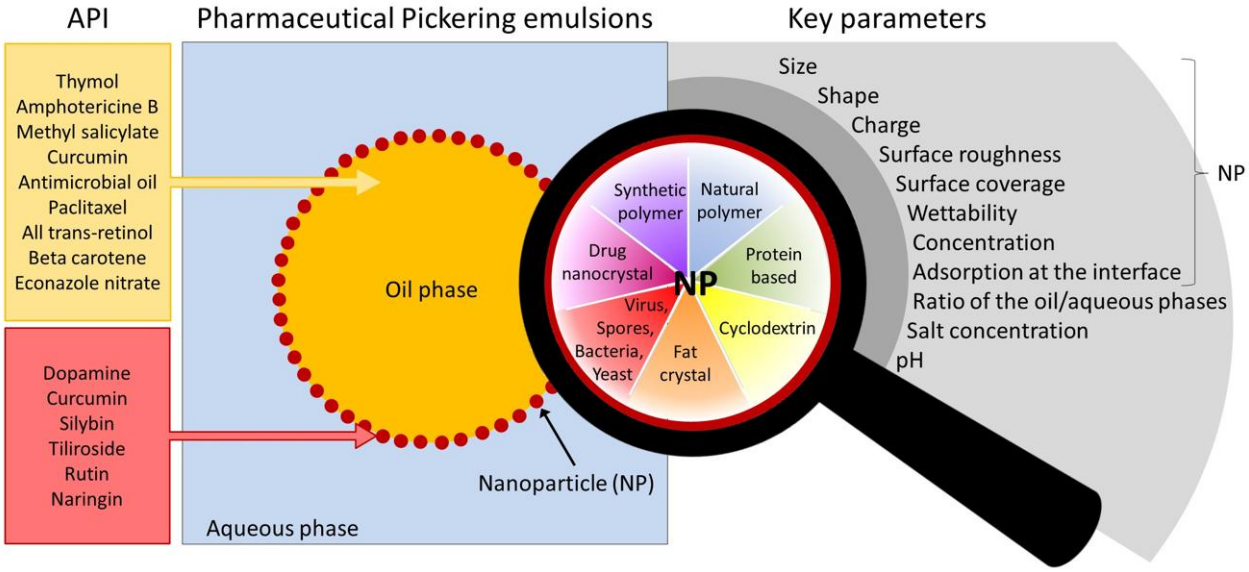
Abstract

An increased interest in Pickering emulsions has emerged over the last 15 years, mainly related to their very attractive properties compared to regular emulsions, namely their excellent stability and their numerous possible applications. In this review, after detailing the interest of Pickering emulsions, their main preparation processes are presented and their advantages and disadvantages discussed. In the third part, the key parameters that govern Pickering emulsions type, droplet size and stability are analyzed. Finally, the interest and the potential of Pickering emulsions for pharmaceutical applications are exposed and discussed, taking all the administration routes into consideration and focusing on organic particles.



Keywords: Pickering emulsion; pharmaceutical applications; organic particles; preparation processes; tuning parameters

List of abbreviations: AFM, atomic force microscopy; API, active pharmaceutical ingredient; CD, cyclodextrin; CNC, cellulose nanocrystals; DME, direct membrane emulsification; GTT, gel trapping technique; HIPE, high internal phase emulsion; LCST, lower critical solution temperature; MFC, microfibrillated cellulose; NP, nanoparticles; O/O, oil in oil; O/O/O, oil in oil in oil; O/W, oil in water; O/W/O, oil in water in oil; PME, premix membrane emulsification; RME, rotational membrane emulsification; SCME, stirred-cell membrane emulsification; SEM, scanning electron microscopy; SNC, starch nanocrystals; VME, vibrational membrane emulsification; W/O, water in oil; W/O/W, water in oil in water; W/W, water in water; W/W/W, water in water in water; XME, cross-flow membrane emulsification.

1. Introduction

Emulsions are widely used in pharmaceutical applications [1]. Creams, as well as some ointments, gels, pastes, transdermal patches and vaccines, are emulsions [2]. Pharmaceutical emulsions can be used as therapeutic vehicles by various routes of administration: injection (intravenously, intramuscularly) [3–5], oral administration [6], topical application (skin, transdermal and vaginal applications) [7], ocular application [8,9], pulmonary [10] and nasal administrations [11]. In simple emulsions, hydrophilic active pharmaceutical ingredients (API) are encapsulated in the aqueous droplets of a water-in-oil (W/O) emulsion, whereas hydrophobic API are incorporated in the oil droplets of an oil-in-water (O/W) emulsion. The main interest of pharmaceutical emulsions is that they protect the encapsulated API while increasing its solubility and bioavailability [12]. By the oral route, emulsions, in addition to improving API protection and absorption, also mask their possible unpleasant taste or texture, making them more palatable [13]. By topical route, they often improve the permeability of the API [12], and both O/W and W/O emulsions can be used. O/W emulsions have the advantage of being non-greasy and easily removable from the skin surface [14]. W/O emulsions possess an occlusive effect by hydrating the upper layer of the skin and avoiding evaporation. They are also greasy and not water washable [12]. By the intravenous route, the emulsion form may help to prevent the tendency of poorly water soluble API to crystallize [13] as the API is in the oil droplets of the O/W or W/O/W (water-in-oil-in-water) emulsions generally used in this case [12]. By the ophthalmic route, O/W emulsions are better tolerated than solutions and suspensions and avoid vision blurring effect observed with ointments [12]. Among emulsified systems, multiple emulsions are very attractive for pharmaceutical applications such as taste masking, vaccine adjuvants and so

on, thanks to their ability to encapsulate and protect simultaneously several API. They also allow a controlled and sustained release of the encapsulated API [14]. Despite their attractiveness, multiple emulsions can have limitations because of their complex structure and their thermodynamic instability due to an exchange of surfactants between the interfaces of the droplets and the inner droplets [15].

As emulsions are thermodynamically unstable systems, the use of stabilizers for the formulation of emulsions and for their long-term stability is required [16]. Until now, emulsions have mostly been stabilized by synthetic surfactants [17]. The list of surfactants usable for pharmaceutical applications is however reduced [12,18], and is even more limited for ocular and parenteral routes. Unfortunately, even with pharmaceutical authorized synthetic surfactants, irritations or allergic responses are often observed [19–22]. New and less toxic stabilization approaches have been developed such as the use of biopolymers [23] or solid particles [24–26]. They could be attractive for pharmaceutical applications.

This review is focused on emulsions stabilized by particles. Such emulsions are called Pickering emulsions according to the pioneering work of Pickering [27], even if they were first described by Ramsden [28]. Such stabilizers lower, or even avoid, the use of synthetic surfactants. Between 2000 and 2018, the proportion of publications on “Pickering emulsions” among all publications on “emulsions” increased from 0.05% to 8.0% (source: data from Web of Science). This increased interest is directly related to the very attractive properties of these emulsions. Indeed, Pickering emulsions display very good stability (sometimes up to several years), thanks to their high resistance to coalescence [25]. They also allow the fine-tuning of the emulsions towards their application, thanks to the very large number of possible combinations of the different types of particles, the aqueous and the oily phases used. Many types of particles (inorganic or organic) have been used to prepare Pickering emulsions, such as silica particles (widely studied because of the easy modification of their surface hydrophobicity with organosilanes) [29,30], metallic particles [31,32], natural clays [33,34], polymeric particles [35–38], proteins [39–41], cellulose [42,43], starch [44,45] and others. Besides allowing the stabilization of O/W and W/O simple emulsions [24,26], solid particles also allow the stabilization of W/W [46] and O/O [47] emulsions. Multiple W/O/W, O/W/O (oil-in-water-in-oil) and O/O/O (oil-in-oil-in-oil) Pickering emulsions can also be prepared in two steps using two types of particles [24,48] and, more surprisingly, in a single step using only one type of particle [38,49–56]. Multiple Pickering emulsions, in addition to providing the same benefits as multiple emulsions stabilized by surfactants (multiple encapsulation, protection, controlled and sustained release), are particularly

attractive as they exhibit a simple preparation process (the possibility to be prepared in a single step) and a long-term stability that are challenging to obtain when using surfactants [57]. More recently, high internal phase emulsions (HIPE, which is an emulsion with a volume fraction of dispersed phase above 0.74) stabilized by solid particles [58] and Pickering nanoemulsions [59] have also been prepared.

The increasing use of Pickering emulsions is also due to the numerous possibilities for applications in food [60], pharmaceuticals [61,62], material preparation [63–67], crude oil recuperation [68–70], colloidosomes formation [71–74], Pickering emulsion polymerization [75], catalysis [76–78], molecular imprinting [79] or solid dried emulsions [80,81]. The studies presented in this review deal with Pickering emulsions that can be potentially used for a pharmaceutical application and which are exclusively stabilized by particles without any additional surfactant. Numerous reviews have already been published on Pickering emulsions in general and on some of the key parameters governing their properties [24–26,62,82–86]. More recently, a few reviews have dealt with emulsions stabilized by natural emulsifiers [87], particles of biological origin [88], naturally-derived or biodegradable particles [89], or by particles intended for food applications [60]. However, very few reviews have focused on pharmaceutical aspects. Marto *et al*. [61] and Chevalier *et al*. [90] both proposed reviews devoted to topical delivery only and Wu & Ma [62] described biomedical applications of Pickering emulsions in the last part of their article.

Here, we propose to discuss the interest and the potential of Pickering emulsions for pharmaceutical applications, taking all possible administration routes into consideration. Regarding these pharmaceutical applications, even if biocompatible inorganic particles are interesting especially for theranostic [91], we will exclusively focus on organic particles as they are potentially more biocompatible and biodegradable than inorganic ones. Many definitions of the term biodegradable exist. We will consider biodegradable here to mean materials that are degradable in biological environments through enzymatic or non-enzymatic hydrolysis. In the first part, the main preparation processes of Pickering emulsions are presented and their advantages and disadvantages are discussed. Then, the key parameters governing Pickering emulsions type, droplet size and stability are analyzed. Finally, the potential of Pickering emulsions stabilized by various organic particles for pharmaceutical applications are discussed.

2. Emulsification processes for Pickering emulsions preparation

All emulsification processes used to prepare emulsions stabilized by surfactants can be applied to prepare Pickering emulsions. However, rotor-stator homogenization, high-pressure homogenization and sonication are the most commonly used to formulate Pickering emulsions. Recently, techniques such as membrane emulsification and microfluidic emulsification were also applied to Pickering emulsion preparation.

2.1. Rotor-stator homogenization

More than half of the Pickering emulsions presented in this review are prepared by rotor-stator homogenization (see part 4). A rotor-stator homogenizer simply consists of a rotor with blades and a stator with openings. As the rotor rotates, a depression is created, drawing the liquid in and out and resulting in liquid circulation (Figure 1). The droplet size of the dispersed phase is reduced because of the high liquid acceleration and of the shear force occurring between rotor and stator. The rotation speed and the homogenization time are the first parameters for the control of the emulsion droplet size with a rotor-stator homogenizer [92]. In most publications, the speed of the rotor-stator homogenizer is given in rpm (revolution per minute) which is not an indicator of power. Instead, the velocity of the rotor should be given but, as it cannot be calculated from most publications (because the diameter value is seldom provided), the rpm value will be presented here as well. Thus, in the case of Pickering emulsions, the rotation speeds are mostly in a range from 5 000 to 30 000 rpm (corresponding to a velocity of 5 to 20 m/s when calculation is possible), while the emulsification times range from 30 s to a few minutes. With such parameters, the droplet size distribution is broad (from a few microns to hundreds of microns).

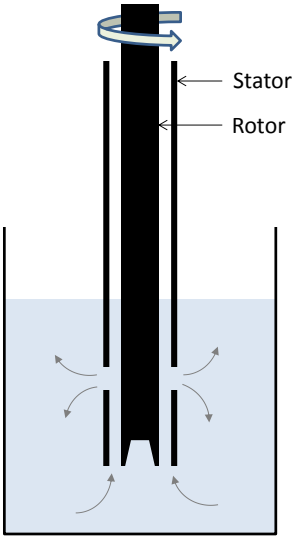


Figure 1: Schematic representation of a rotor-stator homogenizer

The advantages of rotor-stator homogenization are *i)* the low operating cost and the ease of setting-up which only requires to plunge the probe of the rotor-stator in the container of the three components of the emulsion [93]; *ii)* the rapidity of the process which typically takes a few minutes to obtain an emulsion [93]; *iii)* the small amount of liquid required, with the possibility to use only a few milliliters (for a preliminary test with expensive components for example) [93]; and *iv)* the existence of rotor-stator apparatus available for each step of an emulsion development, from the laboratory to industrial scales. The major drawbacks of the rotor-stator homogenization process are *i)* a possible lack of uniformity of the homogenized sample, especially when operating near the limit volume of the probe used, but which can be overcome by moving the probe around inside the sample during homogenization) [93]; *ii)* the risk of temperature increase that is mostly due to frictional forces during the process, which can induce the destabilization of temperature-sensitive particles and/or of the emulsion (to avoid this effect, the sample can be cooled during homogenization); *iii)* the limited energy input which limits the formation of small droplets (generally, the droplets formed with a rotor-stator are above 1 µm) [94]; *iv)* the broad droplet size distribution obtained [95]; and *v)* the high shear rate occurring between the rotor and the stator, which can destabilize or deform fragile particles or aggregates during the emulsification process [96,97]. In the case of microgels, Destribats *et al*. [96] showed that the morphology of the microgel changed with the emulsification energy. The microgels were flattened at the interface of emulsions prepared with high energy supply, while they remained spherical at the interface with low energy emulsification. Moreover, they noticed the occurrence of bridging between the droplets in the case of high energy emulsification.

2.2. High-pressure homogenization

Although high-pressure homogenization is the most frequently used continuous emulsifying process in the industry [98], this technique is not predominant to prepare Pickering emulsions. Only less than a fourth of the Pickering emulsions presented in this review was prepared by high-pressure homogenization (see part 4), probably because of the high running cost and the risk of NP degradation during the process (see the drawbacks of the technique discussed below). This technique consists of a high-pressure pump and a homogenizing nozzle. A step of pre-emulsification to obtain a primary coarse emulsion is recommended to obtain, afterward, a fine emulsion at the outlet of the homogenizer. This pre-emulsification step is often performed with a rotor-stator or with a vortex mixer (see part 4). The particles can be introduced at this step or at the inlet of the fine emulsion. Then, the pressure increases thanks to a high-pressure pump and the pre-emulsified mixture is injected in a homogenizing nozzle of small size which disrupts the drops, inducing emulsification (Figure 2). Various homogenizing nozzles exist and can be coupled with a high-pressure pump to form a high-pressure homogenizer [98]. For Pickering emulsions, the pressure values are commonly in the range from tens to hundreds of MPa (see part 4). Moreover, it is possible to pass the emulsion through the homogenizer repeatedly to reduce the droplet size even further down to the nanometer range [99]. The number of cycles through the homogenizer for Pickering emulsion formation is not always provided by authors. When information is given, it is often in the range from 1 to 10 (see part 4). With these parameters, the droplet sizes of the obtained Pickering emulsions range from hundreds of nanometers to hundreds of micrometers (see part 4). The emulsion droplet size can be controlled, during the emulsification process, by both the pressure value and the number of homogenizing cycles. Köhler *et al*. [94] noticed that, for emulsions stabilized with silica NP, a pressure increase from 10 to 100 MPa induces a droplet size decrease from 40 down to 9 µm. As a general rule, droplets formed with high-pressure homogenization are smaller than those formed with rotor-stator homogenization. The main difference between these two homogenization processes lies in the possibility to form Pickering nanoemulsions with high-pressure homogenization [99,100]. The formation of Pickering nanoemulsions may appear surprising as it is commonly admitted that the particles should be much smaller than the droplet they stabilize (see section 3.5). However, Gupta and Rousseau [99] successfully stabilized nanodroplets with an average diameter of 460 nm with solid lipid nanoparticles (SLN) of 150 nm. It appeared that the size of the SLN actually stabilizing the nanodroplets was between 20 and 120 nm. In this case, particles might have possibly been disrupted during the high energy emulsification process.

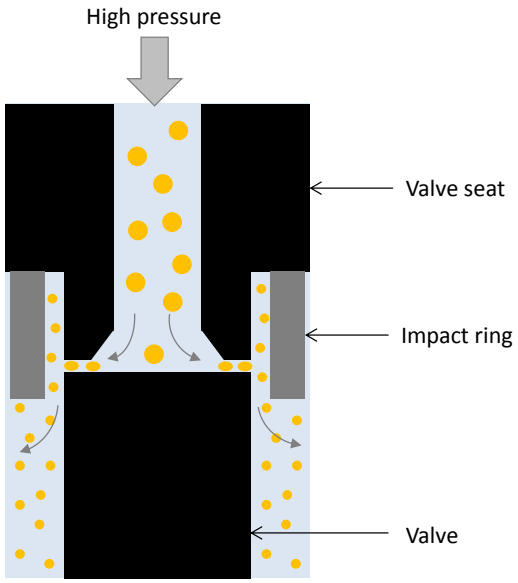


Figure 2: Schematic representation of a high-pressure homogenizer with a standard homogenizing nozzle

The advantages of high-pressure homogenization are *i)* the ability to process large volume samples in a continuous and reproducible manner [94]; *ii)* the possibility to obtain very small droplets, even down to hundreds of nanometers [94]; and *iii)* the possibility to tune the droplet size by increasing the pressure value [94] or the number of homogenizing cycles [101]. However, it also has some drawbacks such as *i)* the energy consumption inducing a high running cost [94]; *ii)* the minimum volume needed, which is of tens of milliliters (larger than with rotor-stator homogenizer), also inducing a high cost for emulsions with expensive components; *iii)* the difficult cleaning, which can induce cross-contamination; *iv)* the risk of damage to the high-pressure homogenizer that can be caused by highly abrasive particles. This last problem can be solved by the addition of the particles just after the nozzle with the mixing stream [94]. In this latter case, the droplet size is highly dependent on the adsorption kinetics of particles (see section 3.3); *v)* a temperature increase can require a cooling system to avoid particle and/or emulsion destabilization, as with rotor-stator homogenization [101]; *vi)* the high shear rate can deform or destabilize fragile particles or aggregates during the emulsification process [97] and *vii)* a broad droplet size distribution is obtained [95].

2.3. Ultrasonic (or sonic) emulsification

Ultrasounds are characterized by a frequency above 16 kHz. Only high power ultrasounds, with a frequency between 16 and 100 kHz (and to a lesser extent those between 100 kHz and 1 MHz), are able to interact with matter and can be used for emulsification [102]. As for high-pressure homogenization, only less than a fourth of the Pickering emulsions presented in this

review were prepared by ultrasonic emulsification (see part 4). Various types of ultrasonic devices exist, the most commonly used for Pickering emulsion preparation is the ultrasonic probe. A titanium probe vibrates due to a transducer that contains a piezoelectric crystal, which converts the electric energy to very high-frequency mechanical motion. The probe transmits the ultrasonic energy to the surrounding sample, inducing the emulsification mostly by cavitation [102] and ultrasonic forces. The ultrasound frequency and amplitude, as well as the emulsification time, are the major parameters influencing the droplet size [103]. As with the high-pressure homogenizer, a pre-emulsification step can help to form finer emulsion droplets [102]. Ultrasonic homogenization can be used with a large range of volumes, from hundreds of microliters to hundreds of milliliters. The most commonly used parameters to prepare Pickering emulsions are difficult to provide as, surprisingly, the frequency and the amplitude are often missing information in publications. Moreover, when the amplitude is provided, it is expressed in percentage, which is useless without the technical specification of the apparatus used. When provided, the amplitude ranges from tens to hundreds of watts and the frequency is often in the low range (20 - 40 kHz), which is known to be the range in which the smallest droplet sizes are obtained [102] (see part 4). The emulsification time is, generally, of a few minutes. With these parameters, the droplet sizes of the Pickering emulsions obtained are close to those obtained with high-pressure homogenization, from hundreds of nanometers to hundreds of micrometers (see part 4). With graphene oxide particles, He *et al*. [53] observed that an increased sonication time allowed to reduce droplet size and polydispersity. They explained this phenomenon by a decrease of the particle size (see section 3.5), since sonication can crush the particles. The authors also noticed that the influence of the emulsification time is less important than that of the particle concentration.

The main advantages of ultrasonic emulsification are, as with rotor-stator homogenization, *i)* the ease of setting up the process, which only requires lowering the ultrasonic probe in the vessel containing the three components of the emulsion; *ii)* the rapidity of the process which usually takes a few minutes to obtain an emulsion; *iii)* the small amount of liquid required to use the technique, with the possibility to use only a few milliliters (for preliminary tests with expensive components for example); and *iv)* the possibility to prepare Pickering emulsions with droplets of nanometer size [104–106].

However, the major drawbacks of this process are *i)* the risk of trace amounts of titanium deposition into the sample, which can be a problem in the case of pharmaceutical Pickering emulsions [107]; *ii)* the risk of fragile particle or particle aggregate disruption during

emulsification, as with the two previous processes presented above [53,97]; *iii)* the difficulties to use this technique for an industrial scale-up [104]; *iv)* the broad droplet size distribution obtained [95]; and *v)* the important temperature increase during the emulsification process [102], which can be a problem for thermo-sensitive particles or emulsion stability. However, this latter drawback can be overcome by using ultrasounds with a pulsed mode or, as seen in the two processes above, by using a cooling system.

2.4. Membrane emulsification

The membrane emulsification method is a drop-by-drop technology [108]. The two main types of membrane emulsification techniques are the direct membrane emulsification (DME) and the premix membrane emulsification (PME). In the DME, the dispersed phase is pressed or injected through a microporous membrane into the continuous phase (Figure 3a) [109]. The same principle is applied to the PME, except that it is the pre-emulsified mixture that is pressed through the membrane (Figure 3b).

Techniques derived from the DME principle using low shear forces acting on the surface of the membrane to detach the droplets are also used, such as the stirred-cell membrane emulsification (SCME) [95,110], the rotational membrane emulsification (RME) [97,111], the vibrational membrane emulsification (VME) [112] and the cross-flow membrane emulsification (XME) [97]. For the SCME (Figure 3d), an additional mechanical agitation is applied in the receptor chamber [95]. For the RME (Figure 3c) and VME, the dispersed phase is pressed through, respectively, a rotating or a vibrating membrane in the continuous phase [97]. For the XME (Figure 3d), the dispersed phase is pressed through a membrane tube in a flowing continuous phase. In all cases, the agitation causes the detachment of the droplets from the membrane, and thus induces a smaller droplet size [113].

In comparison with the three processes previously presented, the membrane emulsification processes have the advantages of *i)* being a well-suited technique for shear-sensitive products: as the shear is low, there is no risk of disruption for sensitive particles or particles aggregates [97]; *ii)* producing small, size-controlled and uniform emulsions with low polydispersity [97,110,113]; *iii)* consuming low energy, inducing a low running cost [95]; and *iv)* producing no heat during the emulsification process, and thus limiting the risk of destabilization for thermo-sensitive particles and emulsions.

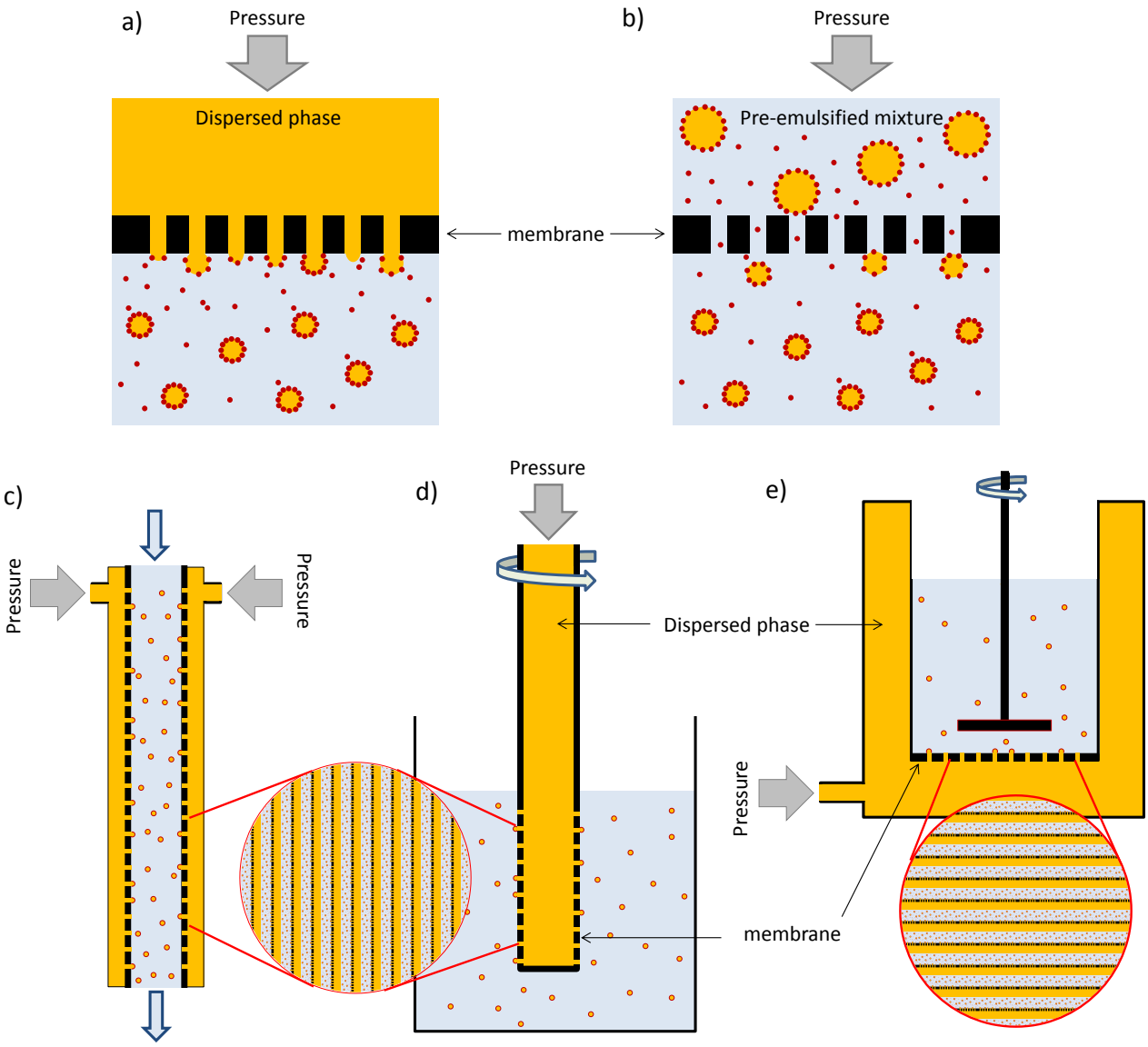


Figure 3: Schematic representation of the four main types of membrane emulsification techniques: a) direct membrane emulsification (DME), b) premix membrane emulsification, both adapted from Piacentini *et al*. [114], c) cross-flow membrane emulsification (XME), adapted from Yuan *et al*. [115], d) rotational membrane emulsification (RME), adapted from Manga *et al*. [111] and e) stirred-cell membrane emulsification (SCME).

Nevertheless, this technique also has some drawbacks: it is time-consuming (for example Sun *et al*. [110] used a flow rate of 2 mL/h). It is suitable for low viscosity systems only (the system should be able to be pushed through the membrane) [115] and this system is presently not suitable for industrial scale-up [116], even if parallelization is considered.

The droplet size is principally controlled by the membrane pore size, the injection rate and the agitation speed for SCME, RME, VME and XME. The membranes can exhibit a wide range of uniform pore size from tens of nanometers to tens of micrometers, with a tunable hydrophobicity

[113]. An increase of the membrane pore size logically induces an increase of the Pickering emulsion droplet size. The emulsion droplet size is usually 3 to 9 times larger than the membrane pore size [113]. A slower injection rate leads to smaller and more uniform droplets [95,97]. Yuan *et al*. [97] showed the existence of a critical flow rate value (0.1 $m^3.m^{-2}.h^{-1}$ with their parameters) below which the emulsions produced were very stable with constant droplet size, and above which the emulsion droplets were larger due to a coalescence phenomenon. Finally, an agitation/rotation speed increase leads to a droplet size decrease, because it induces an easier detachment of the droplets from the membrane [97,111]. At low rotation speed, the shear is very low. Thus, the droplets grow on the membrane before detachment occurs, leading to large droplet size. Manga *et al*. [111] also demonstrated that a minimum droplet size exists, even if the rotation speed still increases. This has been attributed to a competition between the particle adsorption rate at the oil/water interface and the droplet detachment rate from the membrane. If the particles have a slow rate of adsorption at the interface, the uncovered droplets have time to coalesce before being stabilized inducing a size increase [97,111]. This particle adsorption rate parameter will be further discussed in section 3.3.

2.5. Microfluidic devices

Microfluidic emulsification, as membrane emulsification, is a drop-by-drop technology that can be used to prepare Pickering emulsions [117–120]. Microfluidic devices consist of a micrometer size channel with a particular geometry in which fluids are circulating. They allow the formation of droplets of liquid in another liquid, and thus to produce emulsions. Indeed, in laminar flow, droplets are deformed and broken by simple shear flow or elongational flow. Droplet break-up results from extension, tip streaming or trailing. Several microfluidics devices are able to produce emulsions, such as T-junction devices [121–123] in which the dispersed phase is forced to flow through a small orifice into the perpendicular flowing continuous phase (Figure 4a), flow focusing devices [121–123] in which the flowing dispersed phase is focused by two perpendicular streams of the continuous phase from both sides, inducing the formation of a jet and then of droplets (Figure 4b), and terrace (or plateau) devices [116,123] in which the dispersed phase, surrounded by the continuous phase, circulates in a restricted microchannel with a step. Once arriving at the step, the Laplace pressure is reduced, inducing the formation of droplets. All these microfluidic devices can be used to prepare Pickering emulsions. However, to avoid coalescence in the system, sufficient time is needed for the droplets to be covered by particles before encountering other droplets [117]. The droplet size and the droplet coverage with particles can be tuned by changing the flow rate [118] or the microchannel geometry. An

increase in the flow rate induces an increase of droplet size [124]. Interestingly, this is also the only emulsification technique which allows the production of multiple emulsions with complete control on the number of encapsulated inner droplets and on their encapsulation rate [121].

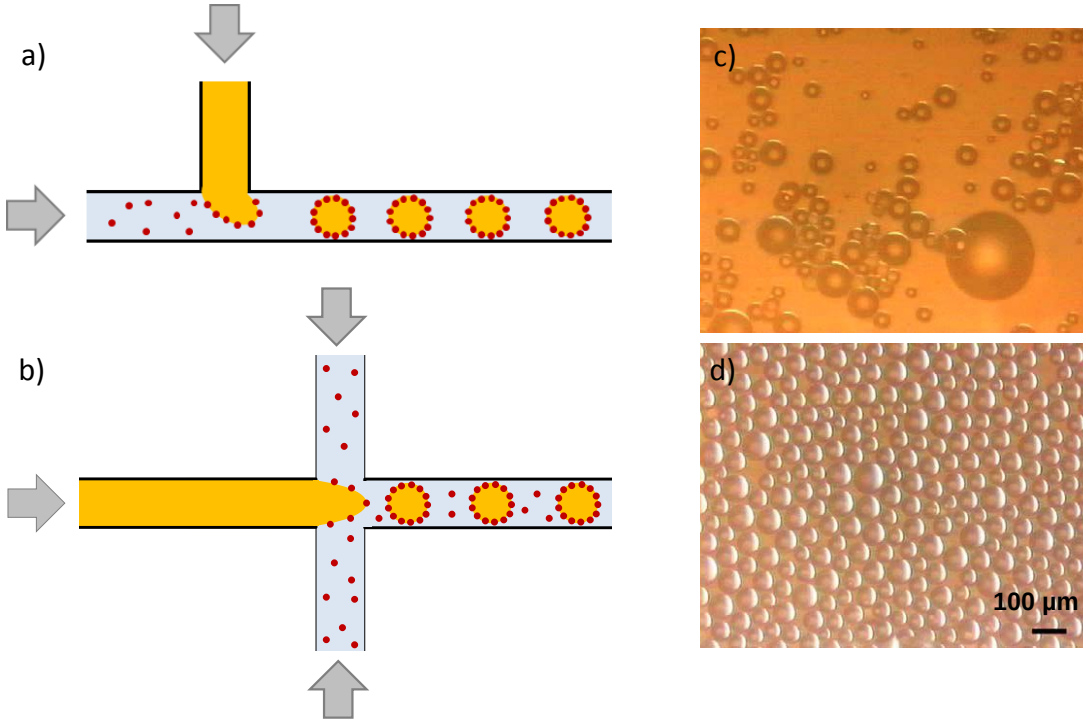


Figure 4: a) and b) examples of microfluidic devices for Pickering emulsions preparation: a) T-junction, b) flow-focusing. c) and d) light micrographs of silica-stabilized emulsions prepared by c) a homogenizer and d) a microchannel emulsification. Same scale bar on both. (c) and d) from Xu *et al*. [117]

As for the membrane emulsification methods, the microfluidic emulsification is interesting because of the following advantages: *i)* there is no extensive mechanical shear, and thus no significant disrupting effect on fragile particles or on particle aggregates during emulsification [97,117]; *ii)* an excellent control of droplet size is achieved [97] with an even better monodispersity (typically with coefficient of variation below 5%) than with membrane emulsification and, therefore, than with homogenization techniques (see Figure 4c and 4d) [95,110,117]; *iii)* the low energy consumption induces a low running cost; *iv)* a small amount of liquid is required; and *v)* there is no heat production during the emulsification process, and thus no risk of destabilization for thermo-sensitive particles and emulsions.

Nevertheless, this technique also presents some drawbacks such as *i)* the low preparation flux which leads to a low-throughput production, which can be a problem for a potential industrialization [116,124]; *ii)* the risk of interaction between the droplets and the channel

[121,125]; and *iii)* the limitation to liquids with low viscosities able to flow through the microchannel [118].

Table 1 summarizes the major advantages of each technique. Currently, no Pickering emulsion is produced at an industrial scale, but only rotor-stator homogenization and high-pressure homogenization could be used right away in case of industrialization. However, the other processes remain interesting. Indeed, if the scale-up issues were overcome, the low shear processes (membrane and microfluidic emulsification) would be particularly well suited for the formulation of pharmaceutical emulsions, as they allow the production of droplets with low polydispersity, they do not damage fragile particles and they present no risk of temperature increase, which is interesting for temperature-sensitive API. They also allow the formation of droplets with low energy consumption, which is a crucial criterion for future industrialization. Moreover, the low shear processes as well as the high-pressure homogenization allow the preparation of sub-micrometer droplets, which is interesting for parenteral administration, as the droplet should be smaller than 5 µm.

Table 1: Summary of the major advantages of the different emulsification techniques.

	Easy setting-up	Quick process	Absence of risk of particle disruption	Absence of risk of temperature rise	Possibility to obtain sub micrometric droplets	Low polydispersity	Low energy consumption	Current industrialization possibilities
Rotor-stator homogenization	+	+	-	-	-	-	+/-	+
High-pressure homogenization	-	+	-	-	+	-	-	+
Ultrasonic emulsification	+	+	-	-	+	-	+/-	-
Membrane emulsification	-	-	+	+	+	+	+	-
Microfluidic emulsification	-	-	+	+	+	+	+	-

+ = yes; - = no; +/- = intermediate

The emulsification process is the first leverage on which it is possible to act in order to control the emulsion properties such as emulsion type and droplet size, but there are numerous other key parameters which can be used in order to tune emulsion properties.

3. Key parameters governing Pickering emulsion type, droplet size and stability

3.1. Particle wettability: the three-phase contact angle

The particles used to formulate Pickering emulsions should be wetted by both the dispersed and the continuous phases. Thus, particle wettability is a crucial parameter [126,127]. In Pickering

emulsion studies, particle wettability is characterized by the three-phase contact angle (θ). The latter, measured in the aqueous phase, corresponds to the angle between the aqueous phase, the oil phase and the particles (Figure 5), and is commonly defined by the Young equation:

$$\cos\theta = \frac{\gamma_{po} - \gamma_{pw}}{\gamma_{ow}} \qquad \text{Equation 1}$$

where γ_{po}, γ_{pw}, γ_{ow} are, respectively the particle-oil, particle-water and oil-water interfacial tensions (Figure 5).

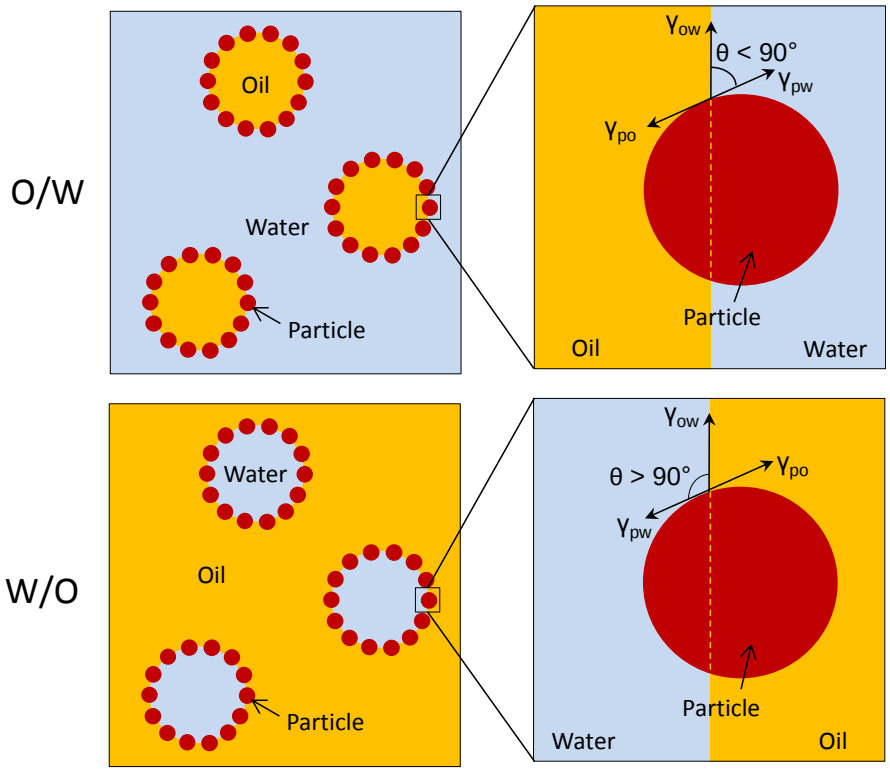


Figure 5: Schematic representation of an O/W and a W/O Pickering emulsion at microscopic, and nanoscopic scales. The three-phase contact angle (θ) as well as the particle-oil (γ_{po}), particle-water (γ_{pw}) and oil-water (γ_{ow}) interfacial tensions are materialized on nanoscopic scale pictures (right).

For particles stabilizing Pickering emulsions, θ is the equivalent of the HLB (hydrophilic-lipophilic balance) for surfactants [128]. They both denote the relative affinity of the particles or surfactants for oil and water. The emulsion type mainly follows the empirical Finkle rule, which is the equivalent for Pickering emulsions of the Bancroft rule used for emulsions stabilized by surfactants [126,129]. Indeed, it is commonly admitted that θ is directly linked to the type of the stabilized emulsion (O/W, W/O or multiple) [24]. When θ < 90 °, particles are mostly hydrophilic and can stabilize O/W emulsions as a larger part of the particles is immersed in the aqueous phase. Conversely, when θ > 90 °, particles are mostly hydrophilic and favor the stabilization of

W/O emulsion (Figure 5). To obtain a firm anchoring of the particles at the interface, θ should be close to 90° (this point will be further discussed in section 3.3.). However, this rule is not always verified. By changing other parameters that will be later described, particles with initially θ < 90° are able to stabilize O/W emulsions and, conversely, particles with θ > 90° are able to stabilize W/O emulsions [53]. It should also be noted that emulsion stabilization has been obtained with fully hydrophilic or hydrophobic particles [117]. In some recent studies, it was assumed that particles with θ = 90° (or very close) would enable the formation of double emulsions, thanks to their capacity to adsorb at both interfaces: O/W and W/O [51,52,130]. The stabilization mechanism with "droplets bridging" also depends on θ, as it is usually observed with particles whose θ is between 30° and 70° [131]. To control the emulsion type (O/W or W/O, simple or multiple) or the droplet size, the wettability of the particles can be tuned [132], as for example with silica NP silanization [50,130,133].

Numerous techniques were developed to measure θ at the oil/water interface. The review of Zanini & Isa [134] gives an excellent overview and description of these techniques. Briefly, they can be classified into two categories: the "ensemble methods" and the "single-particle methods". The "ensemble methods" are based on statistical measurements on a large range of particles. They include interfacial particle expulsion [135], monolayer compression [136], pendant drop tensiometer [137] or reflectivity methods [138]. The major advantages of this kind of techniques are that they can be applied to a large range of particles given statistical measurements and that they can be applied to very small particles. Nevertheless, they also present major drawbacks, namely they are insensitive to the particle heterogeneity due to an averaging effect, and they involve assumptions on the interface microstructure, on the particle shape at the interface and on specific adsorption/desorption mechanisms.

For their part, "single particle methods" are mostly based on direct observation of the particles or of their imprint, allowing the assessment of particles heterogeneity without requiring an assumption on particles and interface. The major drawbacks of these methods are that statistical measurements are a challenging task and that the measure of θ on very small particles is extremely complicated or even impossible, since techniques used for the observation are limited to tens of micrometers (in optical and bright field microscopies) or to few micrometers (in interferometry, scanning confocal, digital holographic and Bessel beam microscopies). To improve the sensitivity, some single-particle methods use an additional particle-immobilization technique thus allowing the use of more sensitive observation methods such as SEM (scanning electron microscopy) or AFM (atomic force microscopy). One of them is GTT (gel trapping

technique). In this technique, one of the phases is gelified to entrap the particles at the interface. It is combined with SEM [139], which requires a further metalization of the sample or with AFM [140]. The size resolution is then pushed down to hundreds of nanometers [141], but the addition of a gelation agent (such as gellan gum) in the aqueous phase and an additional heating step are required, which can induce particle or interface deformation. More recently, the freeze-fracture and shadow-casting cryo-SEM (FreSCa cryo-SEM), another single-particle method using a particle-immobilization technique, was developed [142]. Even if a complex machinery is required for this technique, the resolution is pushed down to tens of nanometers. This is the best resolution obtained with “single-particle methods” so far. However, the choice of the oil is primordial in cryo-SEM techniques in order to avoid oil crystallization, which can induce artifacts or interface deformation during freezing. A self-adsorption of the particles at the interface is also essential, as particles are deposed on a planar liquid-liquid interface without further energy input, which may be a limitation to the adsorption of some particles.

3.2. The oil phase and the oil phase/aqueous phase ratio

According to the Young equation (equation 1), the three-phase contact angle is directly linked to the oil used through the interfacial tensions (γ_{po} and γ_{ow}). Consequently, the choice of the oil is crucial, as the nature of the oil directly affects the value of θ. Even if every other parameter such as the particle type, the particle concentration, the aqueous phase/oil phase ratio and the emulsification process are kept constant, a change in oil can be dramatic for the emulsion stabilization [53,56,143–146].

The oil polarity can induce a change in the type or in the stability of the emulsions obtained. Binks and Lumsdon [143] showed that silica NP with intermediate wettability allow the stabilization of O/W emulsion with non-polar oils (such as hydrocarbons) and W/O emulsions with polar oils (such as esters and alcohols). Silica NP were found to be more hydrophilic in the presence of non-polar oils and more hydrophobic in the presence of polar oils. Read *et al*. [56] made the same observation with polystyrene latex. Thickett and Zetterlund [144] found that the stabilization energy associated with the adsorption of graphene oxide particles was higher for non-polar oil compared to polar oils, leading to more stable emulsions in the first case. For their part, He *et al*. [53] highlighted that the stabilizing ability of graphene oxide is improved with aromatic solvents such as aromatic benzyl chloride than with non-aromatic ones such as n-hexane. They explained this phenomenon by preferential π-π interactions between graphene oxide particles and aromatic oil molecules.

The oil phase viscosity can also influence the droplet size and the stability of the emulsion [145,147]. Fournier *et al*. [145] noticed that, at constant emulsification time and for a fixed amount of iron particles, the volume of emulsified oil increased when the oil viscosity decreased. The oil viscosity is a damping factor for particles anchoring at the oil/water interface as it slows down the particles diffusion and adsorption rate. Tsabet and Fradette [147] obtained a constant emulsion droplet size distribution with silicone oils with a viscosity lower than 486 mPa.s. Above this value, they observed a dramatic size increase. They explained this behavior as a result of a combination between a decrease of the droplets breakage efficacy, the increase of droplets coalescence and the slowdown of the glass particle adsorption rate at the interface.

The oil phase/aqueous phase ratio also affects the droplet size and the type of emulsions. He *et al*. [53] also noticed that the emulsion droplet size increased as the dispersed phase ratio increased with constant graphene oxide particle concentration. Indeed, at a constant droplet size, an increase of the dispersed phase ratio leads to an increase of the interfacial area. However, if the quantity of particles remains constant, it is not possible to stabilize a larger interfacial area, inducing the formation of larger droplets. Some authors have observed, upon an increase of the dispersed phase ratio, a critical phase inversion (from O/W to W/O or conversely) [143] or a change in the emulsion type (from simple to multiple or conversely) [53,54]. He *et al*. [53] and Tang *et al*. [54] both noticed, without providing any explanation, the formation of multiple emulsions for an oil/water ratio of 50/50 or higher. Binks & Lumsdon [143] also showed that, in a water/toluene emulsion stabilized by silica particles containing 67 % of silanol groups on their surface, the critical phase inversion occurred at different ratios depending on the phase in which the particles were firstly dispersed: at a ratio of 60/40 for particles initially dispersed in oil, of 40/60 for particles initially dispersed equally in oil and water, and of 35/65 for particles initially dispersed in water. Below these ratios, these emulsions were W/O, and above, they were O/W.

Moreover, the phase in which the particles are dispersed before emulsification also plays a significant role in the type of emulsion obtained. Particles previously dispersed in the aqueous phase will often lead to O/W emulsions. Conversely, when particles are previously dispersed in the oil phase, W/O emulsions will often be preferentially formed [30,143]. The interactions between the particles and the liquids could induce a variation of particle hydrophobicity [50,55]: particles with initially the same wettability could then display different wettabilities according to the liquid with which they first established contact.

3.3. Particle adsorption at the interface

The stabilization mechanism of Pickering emulsion is based on the adsorption of the particles at the oil/water interface. Thus, the adsorption of particles at the interface is a key parameter for Pickering emulsion stabilization.

The free energy of adsorption ΔG_d represents the energy required to remove a spherical particle of radius r and of three-phase contact angle θ from an oil/water interface with an interfacial tension γ_{ow}. It is defined by equation 2 [148]:

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

As shown in Figure 6a, the energy required to desorb the particles from the interface is the highest for θ = 90 °. This is consistent with the observation exposed in section 3.1 on the three-phase contact angle influence on Pickering emulsion stabilization. For particles of same θ but of different size, the energy of adsorption is the highest for the larger ones (Figure 6b). For particles of same radius r and same contact angle θ, the O/W interfacial tension also affects the energy of adsorption, but the influence is less important than the one of the radius (Figure 6c). In all three cases, the energy of adsorption is higher than the thermal energy (k_BT) at 293 K. Thus, from an energetic standpoint, the particles can be considered as irreversibly anchored at the interface. This principle of irreversibility of adsorption is commonly admitted in Pickering emulsion studies [29,149].

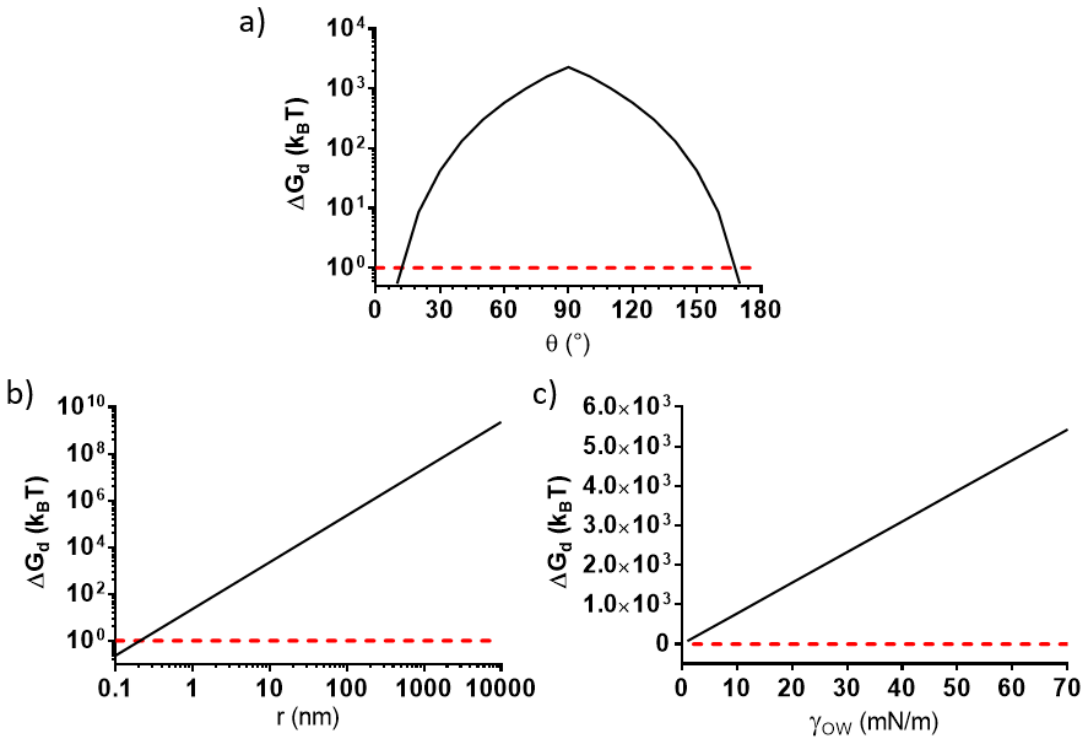


Figure 6: Variation of the energy required to remove a particle from an oil/water interface as a function of a) the three-phase contact angle (with γ_{ow} = 30 mN/m and r = 10 nm), b) the radius of the particles (with θ = 90 ° and γ_{ow} = 30 mN/m) and c) the interfacial tension at the oil/water interface (with θ = 90 ° and r = 10 nm). In Fig. 6a, the y-axis is on a logarithmic scale. In Fig. 6b, x- and y-axes are on a logarithmic scale. On the three graphs, the red horizontal dashed line corresponds to the k_BT value at 293 K.

The adsorption rate of the particles at the interface is also an important parameter. If the adsorption rate is slower than the coalescence rate of the droplets, droplets can coalesce before being stabilized by particles. This is particularly important in the emulsification techniques without shear, such as membrane and microfluidic emulsifications. With the homogenization techniques, shear facilitates the contact between particles and interface, which reduces the importance of the adsorption rate. An increase of the particle concentration can also favor the formation of smaller droplets, as the interaction between particles and interface is facilitated due to a reduced particle-interface distance.

3.4. Particles concentration and surface coverage

Several studies have highlighted a correlation between particle concentration and droplet size. Three regimes have been identified at low, intermediate and high particle concentration, and related to the interfacial area created during the emulsification process [150]. At intermediate concentration, the interfacial area created during the emulsification is slightly larger than the one the quantity of particles is able to stabilize. Thus, the droplets coalesce until the entire droplets are sufficiently covered. An emulsion with droplet size controlled by the particle content is often

obtained: the size of the droplets decreases when the particle concentration increases. This phenomenon has been called “limited coalescence” [151]. The resulting emulsions present a homogeneous droplet size distribution directly linked to the particle mass and to the droplet coverage by the following equation [26]:

$$\frac{1}{D} = \frac{m_p}{6 \times C \times \rho_p \times V_d} \frac{a_p}{\vartheta_p} \qquad \text{Equation 3}$$

where D is the final drop diameter, m_p is the mass of particles, ρ_p is the particle density, V_d is the volume of the dispersed phase, C is the surface coverage (the fraction of the droplet interfacial area covered by the particles), a_p is the particle area projected on the interface and ϑ_p is the particle volume.

This equation can be applied only if the particles are completely and irreversibly adsorbed at the interface and if the emulsification process produced more O/W interface than what the particles can cover. Then, the coalescence process stops as soon as the O/W interface is sufficiently covered by the particles (Figure 7).

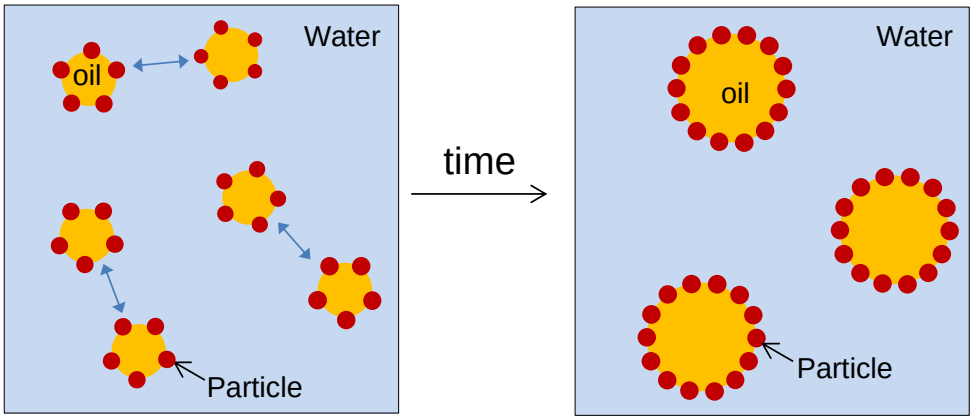


Figure 7: Schematic representation of the limited coalescence theory. The double arrows schematize the droplets coming closer together.

At low particle content, instability is often observed due to a lack of particles to stabilize the droplets: the droplets coalesce before the particles have time to stabilize them [152]. At high particle concentration, there are too many particles compared to the oil/water interfacial area created during the emulsification process. Thus, two possibilities are encountered: the droplets formed during the emulsification process are stabilized right away no matter their size, which induces size heterogeneity, or constant droplet size are obtained but particles are in excess in

the continuous phase, possibly leading to a network in the continuous phase. This network can possibly improve emulsion stability [24].

However, for most Pickering emulsion systems, even if the increase in particle concentration improves surface coverage, high concentration of particles does not always result in a dense coverage (*i.e.* densely packed particles layer on the surface) of the droplets [29,148]. Levine *et al*. [148] also noticed that, rather than having a random distribution, the weakly covered (*i.e*. not densely packed particles on the surface) droplets exhibited areas with close-packed particles and areas without particles. Conversely, weak coverage does not necessarily induce poor emulsion stability [153–155]. Stable Pickering emulsions were obtained by Vignati *et al*. [155] using silica particles with coverage of only 5%. They also observed that at low surface coverage, the particles adsorbed at the droplet surface were able to redistribute themselves in the contact region between droplets and to inhibit droplet coalescence.

The particle concentration can also induce a phase inversion [156] or tune the emulsion type (simple or multiple) [53, 54]. For example, by only increasing the concentration of silica particles of intermediate wettability (57% and 71% of silanol on the surface), an O/W emulsion is inverted into a W/O emulsion [156]. The particle concentration of inversion is lower for the most hydrophobic particles (approximately 1% (w/w) with the 57% SiOH and 2% (w/w) with the 71% SiOH). This inversion only occurred if the particles were first dispersed in oil. Binks *et al.* [156] suggested that the effective hydrophobicity of silica particles in the oil dispersion increased with particle concentration because, at high concentration, particles aggregates were formed by hydrogen bonds between silanol groups of different particles. This led to fewer free (hydrophilic) silanol groups available among all particles. Consequently, the particle aggregates, rendered more hydrophobic, stabilized preferentially W/O emulsions. In addition, the formation of multiple emulsions was observed near the inversion point [130,156]. He *et al*. [53] and Tang *et al*. [54] observed this change from simple to multiple emulsion by reducing particle concentration. They obtained multiple W/O/W emulsions for particle concentrations below 1 mg/mL and simple O/W emulsion above.

3.5. Particle size

It is currently admitted that the particles used to stabilize emulsions should be substantially smaller than the targeted emulsion droplet size [35,157]. Levine *et al*. [148] claimed that the stabilizing particles should be, at least, one order of magnitude smaller in diameter than the smallest droplets. However, in some studies [53,99,100], the particle diameter seems too large

compared to the diameter of the resulting stabilized droplets (for example, 150 nm particles stabilizing 450 nm droplets [99]). He *et al*. [53] linked this to a loss of particle integrity during the emulsification process: the particles effectively stabilizing the emulsion were much smaller than those initially introduced.

The particle size influences the emulsion stability and the droplet size. The diameter of the emulsion droplets increases with increasing the particle diameter [94,158]. Indeed, the larger the particle size, the longer the adsorption time at the interface, resulting in an increase of the final droplet size [147]. This is consistent with equation 2 in which, through the energy of adsorption, the size influences the ability of the particles to adsorb at the interface. For their part, Binks & Lumdson [35] showed that the stability of the emulsion towards sedimentation increased upon size decrease.

3.6. Particle shape

The first Pickering emulsion studies were conducted with spherical particles. Then, Pickering emulsions stabilized with non-spherical particles were also obtained with rods [42,159–161] (Figure 8a and 8b), ellipsoidal particles [162] (Figure 8c and 8d), fibers [161], cubes [163,164] (Figure 8 g), peanuts [163] (Figure 8h), Janus [165], microbowls [55] (Figure 8i) and even with deformable nanogels [166–168] (Figure 8e and 8f).

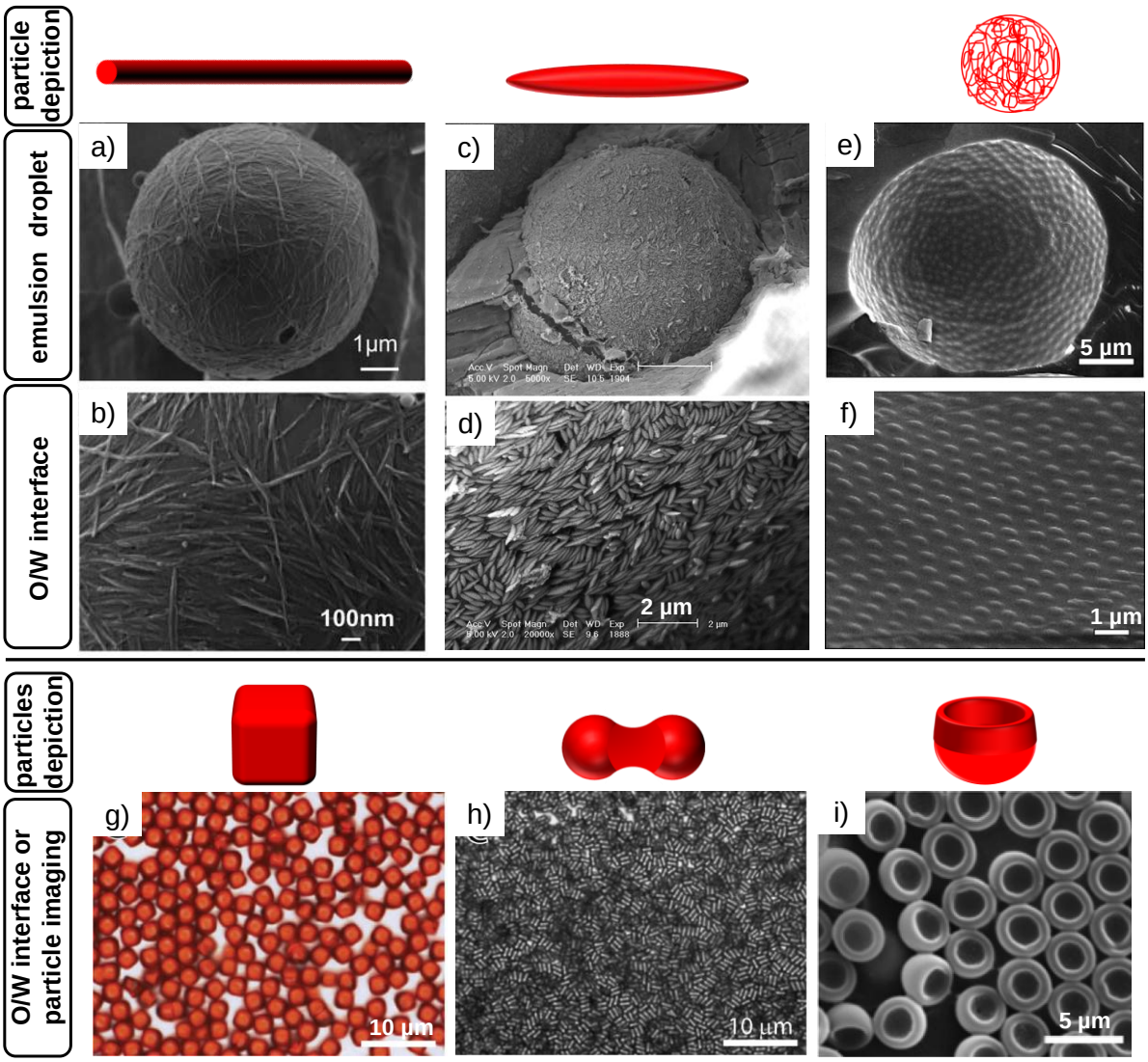


Figure 8: a) and b) SEM images of polymerized styrene–water emulsions stabilized by bacterial cellulose nanocrystals (images from Kalashnikova *et al*. [159]), c) and d) Cryo-SEM images of a water droplet covered with polystyrene ellipsoids (images from Madivala *et al*. [162]), e) and f) Cryo-SEM images of dodecane drops covered by microgels; during sample fracture the frozen oil has been removed, allowing direct visualization of microgels residing at the interface (images from Destribats *et al*. [166]), g) arrangement of cubic particles at the oil−water interface (image from de Folter *et al*. [163]), h) peanuts assembled at the oil−water interface in interdigitating stacks (image from de Folter *et al*. [163]) and i) SEM image of microbowls but not at the O/W interface (image from Nonomura *et al*. [55])

Stable O/W [159,161] and W/O [162], as well as stable multiple emulsions [55], were obtained with non-spherical particles. The mechanisms of stabilization with such particles are not exactly the same as with spherical particles and are not yet fully elucidated. With non-spherical particles, the detachment energy is trickier to determine as equation 2 is not applicable anymore. The particle orientation and at least two characteristic sizes should be taken into account. Equation 3, too, is not valid anymore with non-spherical particles. However, de Folter *et al*. [163] showed that the limited coalescence principle was applicable to emulsions stabilized with cubic

or peanut-like particles using an equation derived from equation 3. Other authors noticed a higher droplet size polydispersity with non-spherical particles than with spherical particles [161,162]. Madivala *et al*. [162] prepared particles of the same composition but with different aspect ratios (from 1 to 9). They observed that emulsions stabilized with low aspect ratio particles were less stable than those stabilized with high aspect ratio particles. They also noticed that the amount of the emulsified phase increased with the aspect ratio. This could be explained by the fact that anisotropic particles were able to cover a larger area of the interface, inducing higher interfacial packing, viscoelastic moduli and stability [84,162,163,169].

The coverage can also be enhanced if the particles are deformable like rod-shaped cellulose nanocrystals [42] or microgels [166,168]. Indeed, if they are flexible enough, they can bend at the droplet surface, resulting in an efficient interfacial anchoring [42]. Moreover, microgels that are spherical before adsorption may undergo substantial flattening upon adsorption at the oil-water interface. They can adopt fried-egg or core-corona morphologies (Figure 9) upon adsorption at an oil-water interface [166,168]. The softness of particles induces a change of particle-particle interactions and of the adsorption mechanism compared to rigid particles [85]. The way particles adsorb and arrange at the interface directly impacts the emulsion stability. Li *et al*. [37] noticed that by varying the poly(N-isopropyl acrylamide)-styrene microgels softness, the softer ones allowed better emulsification and better stability than the rigid ones. Moreover, these microgel-stabilized emulsions can be produced using the limited coalescence principle, in the same way as rigid particle-stabilized emulsions [167].

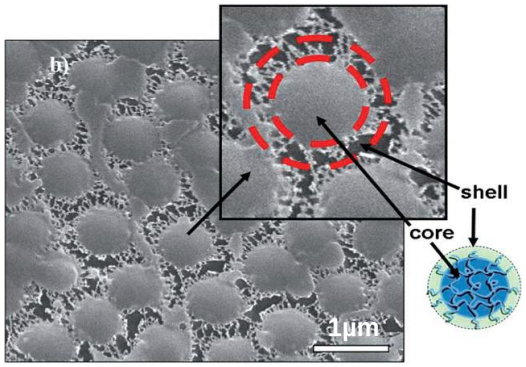


Figure 9: Cryo-SEM image of the interface of a heptane-in-water emulsion drop covered by 2.5 mol% N,N'-Methylenebisacrylamide cross-linked microgels after sublimation (front view). From Destribat *et al*. [166].

The three-phase contact angle determination is also more complex with non-spherical particles. However, Coertjens *et al*. [170] demonstrated that the three-phase contact angle of an ellipsoidal particle can be assessed with the freeze-fracture shadow-casting cryo-SEM technique.

Moreover, characterizing soft particles such as microgels with their three-phase contact angle in their spherical state is also questionable as they will not remain in their original spherical state at the interface after the emulsification step [96].

3.7. Particle surface roughness

The wettability of particles can be significantly influenced by their surface roughness. Yet, as previously mentioned, the particle wettability influences the formation and the stability properties of Pickering emulsions. Vignati *et al*. [155] noticed that the particle roughness reduced their contact surface and negatively affected the emulsion stability. However, the opposite phenomenon was also observed by San-Miguel & Behrens [171]. In this latter study, the zeta potential was also slightly modified in addition to roughness modification. More studies should be conducted in order to make a general claim on the influence of particle roughness in Pickering emulsions.

3.8. Particle charge, salt concentration and pH

Particle surface charge is a parameter influencing the stability of Pickering emulsions [172,173]. Indeed, in case of poor adsorption of particles at the interface, the electrostatic repulsion can play an important role in emulsions stability. Ridel *et al*. [172] decreased the surface charge of bare silica particles using pH modification. They observed a stability improvement with the surface charge decrease. They also noticed that this improvement was more effective when the surface charge was modified by a surface charge density decrease than when it was modified by an ionic strength increase. Moreover, electrostatic repulsions between particles and droplets induce a slow adsorption rate of particles, and subsequently poor stability of the emulsions [172].

With a pH or a salt concentration modification, significant variations in the zeta potential of the particles as well as in their three-phase contact angle are often noticed [51,53,54,174]. So, it is not surprising that, in numerous studies, pH or salt concentration variations were used to control the stability of Pickering emulsions. Aveyard *et al*. [24] observed that the stability of their emulsions was very dependent on salt concentration. He *et al*. [53] noticed an improvement of the emulsification efficiency with salt (NaCl or $MgCl_2$) concentration increase. Yang *et al*. [174] even observed that emulsions could not be formed without salt (NaCl) and that the droplet size of the emulsion could be tuned by varying the salt concentration. For their part, Binks & Lumsdon [35] showed that an increase of salt (NaCl) concentration could induce a phase inversion of the emulsion and that the salt concentration required for the phase inversion depended on the droplet size. Moreover, the interparticle interactions can be varied from

repulsive to attractive by modifying the salt concentration or pH [53,82,175]. This can induce the aggregation of the particles and affect their adsorption at the interface, which in turns influences emulsions properties and stability.

A change in pH can also stimulate pH-responsive particles inducing significant changes in the emulsion properties and stability. The reader can refer to the review of Tang *et al.* [176] on stimuli-responsive Pickering emulsions for further information on these kinds of systems.

All these key parameters reviewed in section 3 are interlinked and may influence the nanoparticle wetting properties, and consequently, the obtained emulsion and its stability. Though these parameters allow the tuning of emulsion properties and characteristics in order to meet the requirements of specific applications, it is very complicated to study their contribution independently. It would indeed be interesting to know what kind of emulsions would be formed with particles of same charge, size, shape and surface roughness, but with different materials. All other parameters being identical, different surface chemical composition could lead to different surface physicochemical properties, and consequently to different wetting properties and emulsions. Nevertheless, to our knowledge, no systematic studies on this question have been conducted yet.

4. Promising Pickering emulsions for pharmaceutical applications

In the pharmaceutical field, oral delivery accounts for 50% of the dosage forms, parenteral for 25% and topical for 10%. For emulsions, this repartition is completely changed as 55% of dosage forms are parenteral (mostly for parenteral nutrition), 30% are topical and only 5% are oral [2]. Among topical emulsions, creams are the most popular and commonly used.

Until now, studies performed on Pickering emulsions are mostly fundamental works aiming to better understand the stabilization mechanisms or the parameters influencing the emulsion properties. Studies devoted to pharmaceutical applications are scarce. Unlike conventional emulsions in which 55% of dosage forms are parenteral, pharmaceutical Pickering emulsion studies are mostly devoted to topical and oral drug delivery systems and to a lesser extent to the injection route. This can be explained by the size of the droplets of Pickering emulsions and sometimes by the nature of the stabilizing particles. Indeed, objects with a size above 5 µm are usually not suitable for injections [1] as the diameter of the smallest vessel is approximately 6 µm [5]. Moreover, all injected formulations should also be at pH 7.4 and isotonic with blood [12]. Yet, we have seen in section 3.8 that the salt concentration and the pH value of Pickering

emulsions were key parameters of the emulsions properties and could induce emulsion destabilization.

A wide range of inorganic and organic biocompatible particles was studied to stabilize either O/W or W/O emulsions. Both, organic and inorganic particles can be biocompatible but only organic particles can be biodegradable. Moreover, inorganic particles might be able to cross biological barriers and accumulate, over time, in the human body inducing adverse effects [177]. For this reason, in this part devoted to Pickering emulsions with potential interest for pharmaceutical applications, we only focused on emulsions stabilized with biocompatible and/or biodegradable organic particles.

The oils used to formulate pharmaceutical emulsions also have to be biocompatible. They must be non-toxic and be readily excreted or metabolized after administration [178]. There is an extensive list of approved and regulated natural and synthetic oils among which castor oil, soybean oil, arachis oil, sunflower oil, olive oil, tri/di/mono glycerides, cocoa butter, coconut oil, vaseline, paraffin, dimethicone… As much as possible, we present in this review emulsions formulated with biocompatible oils. However, some emulsions using a non-biocompatible oil but stabilized with particles which could be of interest for pharmaceutical applications were also described in the literature. Regarding their potential interest for future pharmaceutical applications, we decided to also present these systems. However, replacement of a non-biocompatible oil by a biocompatible one could completely modify the properties of the systems.

4.1. Natural polymer-based particles

4.1.1. Polysaccharide-based particles

Polysaccharides are natural polymers. Some of them are insoluble in water and in oil, which makes their particles valuable candidates for Pickering emulsion stabilization [179]. The most represented polysaccharides in Pickering emulsion stabilization are starch, cellulose and chitosan.

4.1.1.1. Starch-based particles

Starch is extracted from plants such as corn, potato, wheat or rice. It is composed of linear amylose and branched amylopectin. Native starch contains crystalline and amorphous regions [180]. Its molecular weight (from 50 000 to 500 000 kDa) depends on its origin. Starch is an odorless, tasteless, non-toxic and non-irritant material, widely used as a food ingredient and as a pharmaceutical excipient in both oral and topical pharmaceutical applications [18]. In capsules

and tablets, it is used as a binder, a diluent or a disintegrant. In pharmaceutical preparation, the particle size generally ranges from 5 to 50 µm. It is insoluble in cold water but it is able to swell in hot water [181]. The swelling temperature depends on the starch origin (for example 64 °C for corn starch).

Studies intended or not for pharmaceutical applications have been conducted on Pickering emulsions stabilized with starch particles using biocompatible oils. In these works, small starch particles of micron size (few micrometers) [182–184] and nano size (tens to hundreds of nanometers) [100,185,186] were used (see Table 2). The micron size starch granules are commercially available; consequently, their preparation is often not described in publications.

Table 2: Examples of Pickering emulsions stabilized by natural polymer-based particles (starch- and cellulose-based particles)

particles				emulsion					drug / localization	route	references
	composition	shape	size	aqueous phase	oil phase	type	droplet size	emulsification method			
starch	modified cassava starch	discs	≈ 5 nm x 100 nm	water *	olive oil	O/W	≈ 300 nm	rotor-stator (2 min, 24 000 rpm)	thymol amphotericin B / oil	oral	Cossu et al, 2015 [100]
	modified quinoa starch granules	granules	≈ 1–2 µm	phosphate buffer pH=7, NaCl *	Miglyol paraffin shea nut oil	O/W	≈ 30 to 75 µm	high-shear mixer (1 min, 22 000 rpm) *pre-emulsion vortex mixer*	methyl salicylate / oil	topical	Marku et al., 2012 [182]
		granules	≈ 2–4 µm	phosphate buffer pH = 6.5 *	Miglyol 812 N	O/W	≈ 30 µm	high-shear mixer (30 s, 22 000 rpm)	curcumin / oil	oral	Marefati et al., 2017 [183]
	OSA-modified starch granules	granules	≈ 0.85 µm	water *	Miglyol Orange oil	O/W	≈ 50 µm	high-shear homogenization	Resveratrol	-	Matos et al., 2018 [187]
	corn starch nanocrystals	polygonal	≈ 40 to 100 nm	water, 0.002%(w) NaN_3*	short, medium and long chain triacylglycerols	O/W	≈ 25 to 50 µm	rotor-stator (2.5 min, 22 000 rpm)	-	oral	Liang et al., 2016 [185]
	OSA corn starch nanoparticles	spherical	≈ 10 nm to 1 µm	phosphate buffer pH=7, NaCl *	MCT oil	O/W	≈ 10 to 30 µm	high-shear mixer (1 min, 22 000 rpm) *pre-emulsion vortex mixer*	-	-	Saari et al., 2017 [186]
	esterified starch nanospheres	nanosphere	≈ 360-3000 nm	water *	Tricaprylin	O/W and W/O	≈ 35 to 60 µm	rotor-stator (30 s, 13 500 rpm)	-	-	Tan et al., 2014 [188]
	corn and OSA (2%) corn starch spherulites	spherulite	≈ 4 µm	water *	orange oil	O/W	≈ 1 to 50 µm	high-pressure homogenizer (300 bar = 30 MPa) *pre-mixing rotor-stator (3 min, 150 000 rpm)*	-	-	Wang et al., 2017 [184]
cellulose	cellulose nanocrystal (CNC) microfibrillated cellulose (MFC)	fiber	CNC ≈ 230 x 30 nm MFC > 1 µm x 30 nm	water, calcium chloride 3mM *	cinnamaldehyde eugenol limonene	O/W	≈ 10 to 35 µm (CNC) ≈ 30 to 50 µm (MFC)	rotor-stator (5 min, 24 000 rpm)	antimicrobial oil	-	Mikulcova et al., 2016 [189]
	Nanofibrillated mangosteen cellulose (NFC)	fiber	> 1 µm x 60 nm	phosphate buffer pH=7 (Nanofiber)	Soybean oil	O/W	≈ 9-24 µm	high-shear mixer (2 min)	vitamin D_3	oral	Winuprasith et al., 2018 [190]
	cellulose microgels cellulose microgels-Fe_3O_4	spherical	≈ 30 to 600 nm	water *	paraffin	O/W	≈ 4 µm	sonication probe (5 min)	-	-	Zhang et al., 2016 [191]
	Aminated nanocellulose NP (ANC) at 0.2 wt%	spherical	-	water *	MCT oil	O/W	≈ 89 nm	high-shear mixer (2 min, 10 000 rpm)	Coumarin Curcumin	-	Asabuwa et al., 2018 [192]
	butylamino fonctionalized cellulose nanocrystals	rod like	≈ 3.5 x 130 nm	water *	soybean oil	O/W	≈ 10–15 µm	rotor-stator (1 h, 10 000 rpm)	-	-	Visanko et al., 2014 [193]
	Cellulose nanocrystals (CNC)	rod like	-	water *	Oregano essential oil	O/W	≈ 1.2 - 2.9 µm	sonication at 0.4 kW for 3s with 2 s stand by for 3 min	antimicrobial oil	-	Zhou et al., 2018 [194]
	bacterial cellulose nanocrystals	fiber	≈ 10 x 200 nm	water *	palm oil	O/W	≈ 1 to 10 µm	ultrasonic bath (power level 45%, 3 min) cycles of 3 s sonication 3 s pause	-	-	Wang et al., 2016 [195]
	bacterial microfibrillated cellulose	-	-	water *	soy bean oil	O/W	≈ 2 to 50 µm	rotor-stator (1 min, 11000 rpm + 4 min, 15000 rpm)	-	-	Winuprasith et al., 2015 [196]
	nanofibrillated cellulose + cellulose nanocrystal (native and C12 modified)	needle like	≈ 8 x 1000 nm (NFC) ≈ 10 x 150 nm (CNC)	water *	hexadecane	W/O O/W/O	≈ 3 µm to 80 µm	rotor-stator 30s, 5 000 rpm (hand premixing)	-	-	Cunha et al., 2014 [197]
	PNIPAM grafted on cellulose nanocrystals	rod-like	≈ 3–15 x 50–250 nm	water *	heptane	O/W	≈ 30 to 300 µm	rotor-stator (1 min, 6 000 rpm)	-	-	Zoppe et al., 2012 [198]
	PDMAEMA grafted on cellulose nanocrystals	rod-like	≈ 60 to 350 nm length	water *	heptane toluene	O/W	≈ 8 to 20 µm	rotor-stator (2 min, 6 000 rpm)	-	-	Tang et al., 2014 [199]
	POEGMA-PMAA grafted cellulose nanocrystals	rod-like	-	water *	heptane	O/W	≈ 10 to 50 µm	rotor-stator (2 min, 6 000 rpm)	-	-	Tang et al., 2016 [200]
	Fe_3O_4-cellulose nanocrystal nanocomposite	rod-like	≈ 150–200 nm	water *	palm olein	O/W	≈ 10 to 110 µm	ultrasonic horn (3 min)	-	-	Low et al., 2017 [201]

OSA = octenyl succinate, MCT = medium chain triglycerides, PNIPAM = poly(N-isopropylacrylamide), PDMAEMA = poly[2-(dimethylamino)ethyl methacrylate], POEGMA-PMAA = poly(oligoethylene glycol) methacrylate - poly(methacrylic acid), * = phase containing the particles

Table 3: Examples of Pickering emulsions stabilized by natural polymer-based particles (chitosan-, chitin-, lignin-based particles and others)

particles				emulsion					drug / localization	route	references
composition		shape	size	aqueous phase	oil phase	type	droplet size	emulsification method			
chitosan - chitin	chitosan NP-tripolyphosphate	spherical	≈ 200 to 500 nm	water (NP)	MCT	O/W	≈ 40 to 250 µm	rotor-stator (3 min, 10 000 rpm)	curcumin / oil	-	Shah et al., 2016 [202]
	Chitosan NP	spherical	≈ 550 nm or 1 µm	water pH = 6.9 *	palm oil	O/W	≈ 50 to 150 µm	rotor-stator (5 min, 5 000 rpm)	-	-	Ho et al., 2016 [203]
			≈ 180 to 830 nm	water *	liquid paraffin	O/W	≈ 50 to 500 µm	hand-shaking (5 min)	-	-	Liu et al., 2012 [204]
			≈ 4 to 850 nm	water *	corn oil	O/W	≈ 2 µm	ultrasonic probe (1 000 W, 20 kHz) (8 min, 90% amplitude = 900 W))	-	-	Wang et al., 2016 [205]
			≈ 38 nm	soybean lecithin in water (NP)	Soybean oil	O/W	≈ 2.5 µm	rotor-stator (5-15 min, 10 000 rpm)	Hesperidin	-	Dammak et al., 2017 [206]
	chitin nanocrystals	rod like	≈ 20 x 250 nm	water, HCl pH= 3 *	corn oil	O/W	≈ 10 to 100 µm	ultra-sonic probe (50/60 Hz) (2 min with 20 s intervals)	-	-	Tzoumaki et al., 2011 [207]
			-	water, HCl pH= 3 *	sunflower oil	O/W	≈ 5 to 10 µm	ultrasonic probe (24 kHz) (2 min, 20 s intervals)	-	oral	Tzoumaki et al., 2013 [208]
	Zein - chitosan complex particles	spherical	≈ 2 to 6 µm	water *	corn oil	O/W	≈ 10 - 20 µm	rotor-stator (5 min, 6 000 rpm)	curcumin / NP		Wang et al., 2015 [209]
	chitosan-gelatin complex	spherical	≈ 15 to 450 nm	water *	corn oil	O/W	≈ 4 to 10 µm	high intensity ultrasonic processor (20 kHz, 1 000 W) (8 min, 90% amplitude = 900 W)	-	-	Wang & Heuzey, 2016 [210]
Dopamine-hyaluronan nanoparticles (HA-DOPA)		spherical	≈ 150 - 220 nm	water *	white oil, toluene silicone oil isooctyl palmitate dicaprylyl carbonate propylheptylcaprylate	O/W	≈ 20–100 µm	XHF-D H-speed dispersator homogenizer (2 min, 8 000 rpm)	dopamine / NP	-	Zhu et al., 2015 [211]
hydrophobic modified calcium alginate NP (MCA) at 4 %wt			≈ 316-412 nm	water pH=6,5 *	corn oil	O/W	≈ 3-6 µm	homogenizer (5 min, 10 000 rpm)	curcumin	oral	Zhang et al., 2018 [212]
lignin	Lignin particles	spherical	≈ 350 nm to 2 µm	water *	kerosene	O/W	≈ 5 to 20 µm	sonication probe (400 W) (10% amplitude, 1 min) cycles of 10 s sonication and 5 s pause	-	-	Ago et al., 2016 [213]
	Lignin supracolloids	spherical	≈ 90 to 600 nm	water *	hexadecane	O/W	≈ 7 to 35 µm	sonication probe (400 W) (10% amplitude, 1 min) cycles of 3 s sonication 3 s pause	-	-	Nypelo et al, 2015 [214]
	Lignin NP - polyacrylamide	spherical	≈ 7 to 100 nm	water, NaCl *	cyclohexane	O/W	≈ 5 to 200 µm	ultrasonication probe (70% amplitude, 10 min) cycles of 85 W pulses 1 s pause	-	-	Silmore et al., 2016 [215]
	lignin-DEAEMA NP		≈ 240 - 400 nm	water *	decane	O/W	≈ 20–60 µm	homogenizer (1 min, 20 000 rpm)	-	-	Qian et al., 2014 [216]

MCT = medium chain triglycerides, DEAEMA = 2-(diethylamino)ethyl methacrylate

* = phase containing the particles

Table 4: Examples of Pickering emulsions stabilized by biocompatible synthetic polymer-based particles

particles				emulsion					drug / localization	route	references
composition		shape	size	aqueous phase	oil phase	type	droplet size	emulsification method			
synthetic polymer	PNIPAM-co-AA nanogels	nanogels	≈ 70–200 nm	water *	isopropyl myristate	O/W	≈ 2 µm	rotor-stator (10 min, 13 000 rpm)	paclitaxel / oil	IV	Chen et al., 2011 [217]
	PNIPAM-co-MAA microgels	microgels	-	water *	sunflower oil	O/W	≈ 10–50 µm	membrane emulsification (2 mL/h, 400 rpm, 2.5 to 9.2 µm)	-	-	Sun et al., 2014 [110]
	PLA-PEG NP	spherical	≈ 40–50 nm	PB pH=7.4*	Miglyol 812 N (MCT)	O/W	≈ 2–3 µm	spontaneous emulsification	all-trans retinol / oil	topical	Laredj-Bourezg et al., 2013 [218]
	PCL-b-PEO NP	spherical	≈ 35–50 nm	water *	triglyceride oil	O/W	≈ 2–15 µm	rotor-stator (5 min, 22 000 rpm)	-	-	Laredj-Bourezg et al., 2012 [36]
	Cashew gum - poly-L-lactide copolymer NP (CGPLAP)	spherical	≈ 10 nm	water *	Miglyol 812 (MCT)	O/W	≈ 450 nm	spontaneous emulsification, centrifugation (1h, 15 000 G, 25 °C)	amphotericin B	oral	Richter et al., 2018 [219]
	PLGA NP PLGA-PVA NP	spherical	≈ 200 nm	water *	Miglyol 812 N	W/O/W O/W	≈ 30–50 µm	rotor-stator (2 min, 20 000 rpm)	-	-	Albert et al., 2018 [38]
	PLGA-PVA NP	spherical	≈ 200 nm	water *	Lipiodol	W/O	≈ 30–50 µm	Syringe mixing	Oxaliplatine / water Doxorubicin	IV	Deschamps et al, 2018, 2019 [220,221]
			≈ 200 nm	water *	Dodecan, PDMS, Toluene,Isopropyl myristate	O/W	≈ 4 to 30 µm	rotor-stator (10 min, 1300 rpm)	-	-	Whitby et al., 2012 [222]
			≈ 300 nm to 1 µm	water *	hexadecane, octanol, sunflower oil	O/W	≈ 30 to 200 µm	rotor-stator (30 s, 7200 rpm)	-	-	Qi et al., 2014 [223]
	PEO	brushed	≈ 24 nm	water, NaCl*	cyclohexane xylene	O/W	≈ 5–40µm	rotor-stator (60 s, 1.65 W)	-	-	Saigal et al., 2013 [224]

MCT = medium chain triglycerides, PNIPAM = poly(N-isopropyl acrylamide), AA = coallylamine, IV = intravenous, MAA = methacrylic acid, PLA = poly(lactic acid), PEG = poly(ethylene glycol), PCL = poly(caprolactone), PEO = poly(ethylene oxide), PLGA = poly(acid lactic-co-glycolic) acid, PVA = poly(vinyl alcool)

* = phase containing the particles

The starch spherulites of micron size particles are prepared by heating a starch suspension followed by recrystallization upon cooling [184]. Nano size starch particles can be starch nanoparticles (starch NP) or starch nanocrystals (SNC) (also called starch crystallite, microcrystalline starch and hydrolyzed starch). Their techniques of preparation are well described in the review of Le Corre *et al*. [180]. Briefly, SCN can be obtained by disruption of amorphous regions by acid hydrolysis of native starch and starch NP can be prepared by regeneration techniques (such as precipitation [186,188]) or mechanical techniques (such as high-pressure homogenization). For both types of nanosize starch particles, the process parameters as well as the resulting composition, size (from few nanometers to hundreds of nanometers) and shape (spherical [186,188], oval, discs [100]…) vary as a function of the starch origin. Often, the particle surface is tuned for example with octenyl succinic anhydride to modify its hydrophobic properties.

It was shown by Saari *et al*. [225] that small starch particles obtained by starch granules hydrolysis stabilized smaller droplets than the original granules. However, surprisingly, the resulting Pickering emulsion droplet sizes, in the studies presented in Table 2, were similar (≈ tens of micrometers) independently of the biocompatible oil as well as of the size or of the origin of the particles used. The only exception is the emulsions of Cossu *et al*. [100], using olive oil and stabilized with modified cassava starch discs of ≈ 5 nm x 100 nm, for which the droplet size was of approximately 300 nm.

Liang *et al*. [185] tested the *in vitro* digestion of Pickering emulsions stabilized with SNC from corn starch. They demonstrated that, when the chain length of the triglyceride oil used increased, the rate of lipid digestion decreased whereas the percentage of SNC digested increased. This is most likely caused by the different properties of the triglyceride oils and it could lead to Pickering emulsions with tunable digestion rates.

The interest of such emulsions stabilized by starch particles for pharmaceutical application has been further explored by Cossu *et al.* [100], Marefati *et al.* [183], Marku *et al.* [182], Matos *et al*. [187] and Marto *et al.* [226]. They formulated O/W emulsions with an encapsulated API in the oil droplets intended for oral [100,183] or topical [182,187,226] applications. Marefati *et al.* [183] successfully encapsulated curcumin in Miglyol 812 oil droplets with high encapsulation efficiency (≈ 80%). This API has numerous biological and pharmacological activities (antioxidant, anti-inflammatory…), but is very challenging to formulate due to its low solubility and its easy

degradation [227]. The starch-based Pickering emulsion efficiently retained and protected curcumin from degradation during storage and simulated *in vitro* oral, gastric and intestinal digestions [183]. Another study by Cossu *et al.* [100] showed the potential of starch Pickering emulsions, alone or incorporated in an alginate film, as antifungal preparations against *candida albicans* in the oral cavity. Thymol and amphotericin B were encapsulated and released in a controlled manner from the Pickering emulsion during *in vitro* digestion with α-amylase. Marku *et al*. [182] performed simple sensory tests on starch Pickering emulsion without API on a panel of nine volunteers. They evaluated the visual appearance and the skin feel. They also evaluated the *in vitro* skin penetration for these emulsions with encapsulated methyl salicylate. They found a nearly twice higher API penetration rate with Pickering emulsions than with the API solution. This result is in agreement with previous observations performed with Pickering emulsions stabilized by silica particles and encapsulating caffeine [228]. Marto *et al.* [226] performed *in vitro* and *in vivo* (with mice) experiments with starch-based W/O emulsions loaded with minocycline hydrochloride, an effective drug for the eradication of topical pathogens in superficial infections. The emulsions provided a sustained release of the drug (which did not permeate through the entire skin layer) and led to an efficient topical treatment.

Pickering emulsions stabilized by starch particles seem very promising for pharmaceutical applications. However, further *in vitro* and *in vivo* studies should be conducted to confirm their potential.

4.1.1.2. Cellulose-based particles

Cellulose is mostly extracted as fibers from fibrous plants but is also synthesized by algae and some bacteria [229]. Cellulose fibers are constituted of amorphous and crystalline domains. Crystallinity and molecular weight depend on the cellulose origin [230]. Like starch, cellulose is an odorless, tasteless, relatively non-toxic and non-irritant material [18], widely used as a food ingredient and a pharmaceutical excipient. Cellulose has interesting properties such as biodegradability, low density, high aspect ratio, high strength and stiffness. As a pharmaceutical excipient, cellulose is used for oral or topical formulations and to a lesser extent for ophthalmic, injectable or inhalable formulations [18]. Since the cellulose surface contains many reactive hydroxyl groups, it can be easily chemically modified [231]. It is then used in pharmaceutical formulations under several forms, such as cellulose powder, microcrystalline cellulose, cellulose acetate, methyl or ethylcellulose, hydroxyethyl or propyl cellulose. It acts as an absorbent, glidant, coating, emulsifying, viscosity increasing, anti-adherent, binder, diluent, disintegrant,

thickening or suspending agent depending on its chemical composition [18]. In pharmaceutical preparations, the size of the particles usually ranges between 20 and 200 µm.

As cellulose is insoluble in water, it is a valuable candidate for pharmaceutical Pickering emulsions stabilization. It has been extensively studied, using sometimes biocompatible oils for pharmaceutical applications. For Pickering emulsion stabilization, nano-scale cellulose is used with various aspect ratios (from few nanometers to tens of nanometers in width and from tens of nanometers to few micrometers in length) (Table 2). The nano-scale cellulose used can be cellulose nanocrystals (CNC) (also called cellulose microcrystals, nanoparticles whiskers, nanorods, rod-like or needle-like particles) [193,195,198–200], microfibrillated cellulose (MFC) (also called cellulose nanofibers or nanofibrils) [196,197] or cellulose microgels [191]. In their review, Siro & Plackett [229] and Habibi *et al*. [232] described the preparation methods of respectively MFC and CNC. Briefly, MFC can be prepared from native cellulose by mechanical treatments, such as high-pressure homogenization, cryocrushing or grinding. An alkaline, oxidative or enzymatic pretreatment can also be applied to increase cellulose purity or to reduce the energy input [229]. For their part, CNC can be prepared by acid disruption of the amorphous regions of native cellulose. Specific protocols have been developed depending on native cellulose origin [232]. The resulting nanoscaled cellulose is usually obtained as whiskers, needle-like, rod-like or ribbon-like particles. However, spherical nanocrystals can be obtained by a combination of acidic and ultrasonic treatments [232]. The source of the cellulose as well as the parameters under which the hydrolysis is performed drive the length and width of the CNC obtained. Cellulose microgels can be prepared by mechanical treatment of a cellulose hydrogel formed by the cross-linking of a cellulose suspension [191].

The properties of cellulose particles can be tuned by modification of their surface with oxidation, cationization, esterification, silylation or polymer grafting. These modifications can induce a change in the surface charge, in the surface charge density or in the hydrophobicity of the particles [232], resulting in a change of the Pickering emulsion properties [160].

Zoppe *et al*. [198] have grafted thermo-responsive poly(N-isopropyl acrylamide) (PNIPAM) on the surface of CNC, inducing an emulsion destabilization at a temperature above the lower critical solution temperature (LCST) of PNIPAM (around 30–35 °C). This could be used for pharmaceutical applications: an encapsulated API could be retained and protected during storage at a temperature under the LCST of the polymer and be immediately released from the emulsion once in the body at 37 °C (temperature higher than the polymer LCST). Tang *et al*. [199,200] prepared pH-responsive CNC by grafting PDMAEMA (poly[2-dimethylamino)ethyl

methacrylate]) or POEGMA (poly(oligoethylene glycol) methacrylate) and PMAA (poly(methacrylic acid)). The resulting Pickering emulsions are pH-responsive inducing destabilization below a critical pH value. If the polymer used is biocompatible, the resulting emulsions could be used for pharmaceutical applications as the pH is not the same in all the regions of the body: an encapsulated API could be retained and protected in some region in which the pH is above the critical pH value and be immediately released from the emulsion once in a region of the body in which the pH is under the critical pH value. In these three cases, the oil used was non-biocompatible (heptane) and should be replaced by a biocompatible one for further investigation of pharmaceutical applications. Magneto-responsive Pickering emulsions based on biocompatible but not biodegradable Fe_3O_4-CNC complexes have also been formulated by Low *et al*. [201].

Pickering emulsions stabilized by nano-scale cellulose particles and using a biocompatible oil were mostly O/W emulsions with a droplet size ranging from few to hundreds of micrometers (Table 2). However, Cunha *et al*. [197] were able to produce W/O Pickering emulsions using MFC or CNC hydrophobized by surface esterification inducing more hydrophobic particles. They also obtained O/W/O emulsions by combining native and modified MFC and/or CNC. However, in both cases, they used a non-biocompatible oil (hexadecane) that should be replaced for a pharmaceutical application.

The interest of emulsions stabilized by cellulose particles for pharmaceutical application has been further explored by Mikulcova *et al*. [189] and Zhou *et al.* [194] to investigate the antimicrobial activity of some essential oils. For example, Mikulcova and co-workers used CNC and MFC to stabilize droplets of antimicrobial essential oils. These Pickering emulsions exhibited better antimicrobial activities compared to the non-emulsified essential oils. In this study, no significant difference of antimicrobial activities was observed between emulsions stabilized with cellulose microcrystals or with microfibrillated cellulose. More recently, new structure-modified celluloses such as NFC (nanofibrilated mangosteen cellulose) and ANC (aminated nanocellulose) have been investigated for the stabilization of green Pickering emulsions as novel oral delivery systems for curcumin [192] and vitamins [190].

4.1.1.3. Chitin/chitosan-based particles

Chitin is an odorless and insoluble in water polysaccharide. It is extracted from crustacean shells such as shrimps and crabs. Chitin polymer can be deacetylated and, when the degree of deacetylation is sufficient to obtain a soluble product in acidic conditions, the resulting polymer is

called chitosan. Chitosan is already used in cosmetic applications and under investigation for numerous pharmaceutical applications such as drug delivery for oral, nasal, parenteral, transdermal, ophthalmic and implant administration [233]. It is considered as a non-toxic and non-irritant material and it has intrinsic antibacterial properties [18,234]. Moreover, like cellulose, chitin surface contains many reactive hydroxyl groups which can easily be modified [233]. It is also pH-sensitive. Indeed, it is water soluble at low pH (under 6.5, its pKa value) thanks to its amine groups which are protonated and positively charged and it is insoluble in water at pH above 6.5, as its amine groups become deprotonated and uncharged [204]. Its solubility also depends on its degree of deacetylation. For all these reasons, chitin and chitosan under their insoluble form are very attractive candidates for pharmaceutical Pickering emulsion stabilization.

Pickering emulsions can be stabilized for example by self-aggregated chitosan particles [203,204,235], chitin nanocrystals (also called chitin whiskers, nanowhiskers or rod-like chitin) [207,208] or chitosan complex with proteins such as zein or gelatin [209,210] (Table 3).

Chitosan nanoparticles can be prepared by various techniques such as ionic gelation, or by emulsion-diffusion-evaporation [233,236]. The size of the self-aggregated chitosan particles can be reduced by lowering the molecular weight of chitosan using enzymatic hydrolysis, chemical hydrolysis or ultrasonication pretreatments [203,205,235]. However, Ho *et al*. [203] have shown that an ultrasonication pretreatment of chitosan reduced the hydrophobicity of self-aggregated particles, inducing larger Pickering emulsion droplets (from ≈ 80 to 150 µm *vs* from ≈ 50 to 70 µm), even if the particles were twice smaller (≈ 500 nm *vs* ≈ 1 µm). They explained the hydrophobicity decrease by a reduction of the number of acetyl units per polymer chain due to the shortening of the polymer chain by ultrasonication. The resulting smaller particles contained fewer acetyl units in their surface, inducing a lower hydrophobicity. The size of the self-aggregated particle can also be tuned with pH and salt concentration [204,205]. Liu *et al*. [204] showed that, by changing the pH from 6.4 to 6.7, the particle size increased from ≈ 85 up to 180 nm, and their zeta potential decreased from ≈ 12 down to 7.5 mV. An increase of salt concentration (from 0 to 200 mmol/L of NaCl) induced a particle size increase (from ≈ 180 up to 830 nm). The authors also demonstrated the possibility to prepare pH-responsive Pickering emulsions with such particles: the emulsions stabilized by self-aggregated chitosan particles at pH > pKa were destabilized at pH < pKa when chitosan become water soluble. This type of pH-responsive emulsions is easy to prepare, as the particle preparation is much simpler than the grafting of cellulose particles with pH-responsive polymers.

Chitin nanocrystals are usually prepared by disruption of the amorphous region of chitin by acid hydrolysis which generally leads to rod-like nanocrystals [237]. Tzoumaki *et al*. [207,208] prepared Pickering emulsions using chitin nanocrystals (≈ 20 x 250 nm) with two different biocompatible vegetable oils (sunflower and corn oils). They obtained a significantly smaller emulsion droplet size with sunflower oil (≈ 5 to 10 µm) than with corn oil (≈ 10 to 100 µm), which confirmed the importance of the oil used as discussed in section 3.2. Moreover, they demonstrated the potential of Pickering emulsions stabilized with chitin nanocrystals, to slow down the lipid digestion during *in vitro* enzymatic protocol [208]. The authors proposed to use these systems to treat obesity by reducing appetite and promoting satiety. It could also increase API bioavailability and promote its gastrointestinal delivery.

Chitosan-protein complexes such as chitosan-gelatin or chitosan-zein are also used to stabilize Pickering emulsions. These complexations are mostly driven by electrostatic interactions between chitosan and a protein [210]. Wang & Heuzey [210] successfully stabilized Pickering emulsions with chitosan-gelatin complex (size ≈15-450 nm). This complex was insoluble in water at pH from 5.5 to 6.5. Thus, it is conceivable to produce pH-responsive Pickering emulsions with a destabilization induced once the pH is in the range in which the complex becomes water soluble. Wang *et al*. [209] have, for their part, demonstrated the potential of Pickering emulsions stabilized by chitosan-protein complex to protect lipid droplets from peroxidation. This protection was further improved by introducing curcumin, known for its antioxidant properties, in the particles. This property could be useful to protect fragile encapsulated API.

Shah *et al*. [202] successfully encapsulated curcumin in the oil droplets of emulsions stabilized by chitosan nanoparticles crosslinked with tripolyphosphate. Better protection of curcumin against degradation during storage and slower release rate were obtained with such Pickering emulsions than with classical emulsions. A sustained release depending on the pH was also obtained with such systems: after 24 h, ≈ 40% of curcumin was released at pH 7.4, whereas ≈ 50–55 % were released at pH 2 (corresponding to a gastric environment). Dammak *et al*. [206] also described an O/W Pickering emulsion stabilized by chitosan NP for the encapsulation of hesperidin, a flavonoid commonly used for its antioxidant and anti-inflammatory properties. They obtained very stable Pickering emulsions with a small droplet size (≈ 2 µm), a polydisperse droplet size distribution (PDI=0.33) and a sustained release of hesperidin.

These emulsions stabilized by chitosan- or chitin-based particles seem to be very promising for a potential pharmaceutical application with the advantage to allow the easy preparation of pH-responsive emulsions.

4.1.1.4. Other polysaccharides-based particles

Polysaccharides other than starch, cellulose and chitin/chitosan were also used as insoluble particles to stabilized O/W Pickering emulsions. For example, Zhu *et al*. [211] used particles of hyaluronan-dopamine as Pickering emulsions stabilizers. Hyaluronan is a well-known polysaccharide involved in many biological processes and widely studied for tissue engineering and drug delivery [238]. Dopamine is a biocompatible and natural compound which exhibits strong bonds with organic and inorganic surfaces, and which could consequently improve the interfacial stabilization of the emulsions according to the authors. The dopamine modified hyaluronan was prepared by self-assembly of dopamine grafted hyaluronan co-polymers. The co-polymer grafting degree could be tuned, which influences the size of the resulting spherical NP (from ≈ 150 - 220 nm) as well as the emulsion properties (droplet size from ≈ 20–100 µm) (Table 3). Interestingly, some of the oils used in this study were biocompatible.

Another promising pH-responsive Pickering emulsion was described by Zhang *et al*. [212]. They used hydrophobically-modified calcium alginate (MCA) NP as pH-sensitive emulsifiers. Alginate particles are obtained from the crosslinks between sodium alginate and Ca^{2+}, and exhibited several properties such as pH-responsibility, biodegradability, bioadhesion and non-toxicity. pH-responsive O/W Pickering emulsions were prepared using corn oil as an oily phase, in which curcumin was solubilized. The release behavior of curcumin *in vitro* was then investigated. Authors demonstrated that these Pickering emulsions released more specifically curcumin in the simulated intestinal fluid (37% at pH=6.8) compared to the simulated gastric fluid (3% at pH=1.5) after 4h, proving that MCA stabilizing pH-sensitivity Pickering emulsions appears as a promising candidate for the controlled oral delivery of drug substances.

4.1.2. Lignin-based particles

Natural polymers that do not belong to the polysaccharide family can be used as particles to stabilize Pickering emulsions. Lignins belong to this category. They are complex, non-toxic, aromatic natural polymers with variability in composition and structure depending on their origin and isolation procedure [239,240].

For Pickering emulsion stabilization, lignins were used as nanoparticles [213–216] (see Table 3). Lignin nanoparticles can be prepared by numerous preparation methods such as precipitation, emulsification-polymerization [214] and aerosol flow [213]. Lignin can also be modified chemically by, for example, alkylation, acetylation, esterification or polymer grafting. Qian *et al*. [216] and Silmore *et al*. [215] used polymer modified lignin nanoparticles with respectively

diethylaminoethyl and polyacrylamide to stabilized Pickering emulsions. This modification allowed to tune NP hydrophobicity and thus, the emulsion properties, depending on the grafting degree.

Pickering emulsions stabilized by lignin NP are valuable candidates for a pharmaceutical application as they are non-toxic, but, on the downside, they are complex and depend a lot on their bulk materials. Moreover, to the best of our knowledge, none of the studies using lignin NP as Pickering emulsion stabilizers were performed with a biocompatible oil.

4.2. Biocompatible synthetic polymer-based particles

Only a few synthetic polymers are largely recognized for their biocompatibility and their biodegradability. The best-known are poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their co-polymers, poly(lactide-co-glycolide) (PLGA) and poly(caprolactone) (PCL) [241]. Poly(N-isopropyl acrylamide) (PNIPAM) and poly(ethylene oxide) (PEO), which are also widely used in the biomedical field, are considered biocompatible, but not biodegradable [242–244]. Biocompatible synthetic polymers have been extensively studied, particularly for the formation of nanoparticles, intended for pharmaceutical applications such as drug delivery [245]. Thus, they are valuable candidates for the stabilization of pharmaceutical Pickering emulsions.

Numerous synthetic polymer-based particles have been proposed as emulsion stabilizers, but their biocompatibility remains to be proved and a biocompatible oil is not always used in these studies. For Pickering emulsion stabilization, biocompatible synthetic polymers have been used as nanoparticles [36,218,224], nanogels [217] and microgels [110] (Table 4) prepared with numerous techniques. These techniques are well described in the reviews of Rao & Geckeler [246] and of Chacko *et al*. [247] for NP and nanogels, respectively. Briefly, NP can be prepared either from the polymer by nanoprecipitation, emulsion evaporation, salting-out, dialysis or supercritical fluid technology, or directly from monomer polymerization, by emulsion polymerization or interfacial polymerization. Nanogels can also be prepared either from the polymer (by cross-linking) or directly from monomers (by heterogeneous polymerization).

Usually, the biocompatible synthetic polymer-based particles used to stabilize Pickering emulsions are spherical with a size ranging from tens to hundreds of nanometers (see Table 4). The resulting droplets are relatively small, ranging from a few to tens of micrometers. For example, Laredj-Bourezg *et al*. [36] used PCL-b-PEO (poly (caprolactone)-block-poly(ethylene oxide)) NP (≈ 35–50 nm) as stabilizers using a biocompatible oil (triglyceride oil). The resulting

emulsion is an O/W emulsion with a droplet size of ≈ 2 to 15 µm. In previous works [38,220,221], our team used PLGA-PVA (poly(vinyl alcohol)) NP and PLGA NP (≈ 200 nm) to stabilize emulsions prepared with biocompatible oils (Miglyol 812N and Lipiodol). Albert *et al.* [38] formulated emulsions with bare PLGA NP on the one hand (*i.e.* without stabilizing polymers during NP preparation), and PLGA-PVA NP (*i.e.* PLGA NP covered with PVA) on the other hand. With bare PLGA NP, a co-existence between multiple W/O/W droplets and simple oil droplets was observed, whereas a simple O/W emulsion was obtained with PLGA-PVA NP. The existence of multiple droplets with bare PLGA NP could be explained by a contact angle close to 90°, an intrinsic variation of the NP hydrophobicity and/or the proximity of the phase inversion. The resulting emulsion droplet size, for either simple or multiple (W/O/W) droplets, were ≈ 30–50 µm. Multiple emulsions are interesting for pharmaceutical use as they could allow a multiple co-encapsulation (see section 5).

Laredj-Bourezg *et al*. [218] encapsulated a model API (all-trans retinol) in the oil droplets of an emulsion stabilized with PLA-PEG (polylactic acid-polyethyleneglycol) NP. They studied the *in vitro* skin distribution and penetration with pig skin. They observed a greater accumulation of the API in the *stratum corneum* with such formulation compared to the emulsion stabilized with surfactants. The authors suggested that this effect was probably due to the hydrophobicity and surface charge properties of the NP. This accumulation is promising for topical drug delivery. Interestingly, Chen *et al*. [217] encapsulated an anti-cancer drug, paclitaxel, in the oil droplets of an emulsion intended for intravenous injection stabilized with PNIPAM-co-AA (poly(N-isopropylacrylamide-co-allylamine)) nanogels. This is one of the rare Pickering emulsions studied for intravenous injection. The tissue distribution and antitumor efficacy studies proved that this Pickering emulsion, loaded with an anti-cancer drug, was promising as a drug delivery system for cancer therapy. Richter *et al*. [219] provided proof-of-concept of the formation of O/W Pickering emulsion stabilized by nanoprecipitated NP of hydrophobic derivatives of cashew tree gum grafted with polylactide (CGPLAP) (size ≈ 10 nm). These CGPLAP nanoparticles were also loaded with Amphotericin B (AmB), an antifungal drug characterized by a low oral bioavailability, generally used for the treatment of neglected diseases such as leishmaniasis. The AmB-loaded Pickering emulsions were obtained by spontaneous emulsification, by mixing CGPLAP nanoparticles suspension as aqueous phase, and Miglyol 812 as oil phase. The resulted emulsions exhibited a small droplet size of ≈ 450 nm with narrow size distribution and good stability. Furthermore, AmB was incorporated with 21-47 % of encapsulation efficiency in these nano-sized emulsions, with less aggregated state than observed in commercial AmB formulations. Deschamps *et al.* formulated W/O Pickering emulsions for the treatment of

hepatocellular carcinoma, stabilized by PLGA [220,221]. Doxorubicin, a chemotherapy drug, was encapsulated in the aqueous emulsion droplets (physiological saline). The external phase was composed of Lipiodol, an iodized oil used for its embolic effect and its radiopacity. For an emulsion with a 1/3 water/oil ratio (as recommended by the medical community for this kind of treatment), the doxorubicin release was very progressive and stretched out over more than 10 days. With a conventional emulsion, the release was complete in 24 h. *In vitro* experiments on two different cell lines showed no significant toxicity of the emulsion (without API) and of its components. Droplet sizes were controlled by NP concentration *via* the limited coalescence phenomenon, and droplets of 40 µm were obtained with a 25 mg/mL NP concentration. Such droplet size was adapted to the diameter of the vessels close to the tumor (40-60 µm) [221]. Oxaliplatin, another chemotherapy drug, could also be encapsulated in these water/Lipiodol emulsions. Compared to conventional emulsions, the *in vivo* drug release in an animal liver tumor model was sustained, avoiding a burst effect [220].

Table 5: Examples of Pickering emulsions stabilized by protein-based particles

particles				emulsion					drug / localization	route	references
	composition	shape	size	aqueous phase	oil phase	type	droplet size	emulsification method			
protein	soy glycine protein particles	-	-	water, sodium azide *	soybean oil	O/W	≈ 2–10 µm	microfluidizer (40 MPa, 1 x) *pre-emulsion rotor-stator (2 min, 10 000 rpm)*	beta-carotene / oil	oral	Liu & Tang, 2016 [248]
	soybean protein isolate	gel particles	≈ 0,2–160 µm	water *	corn oil	O/W	-	high-pressure homogenizer (240 bar = 24 MPa) *pre-mixing Rosso hand blender, 2 min*	-	-	Matsumiya et al, 2016 [249]
	pea protein isolate	-	-	water pH = 3, sodium azide*	soybean oil	O/W	≈ 3–20 µm	microfluidizer (40 MPa, 1 x) *pre-emulsion rotor-stator (2 min, 8 000 rpm)*	beta-carotene / oil	oral	Shao et al., 2016 [250]
	whey protein microgels	spherical	≈ 250–300 nm	water *	sunflower oil	O/W	≈ 40 µm	2 stage high-pressure homogenizer (25/5 MPa, 2x) *pre-emulsion rotor-stator (5 min, 5 000 rpm)*	-	oral	Sarkar et al., 2016 [251]
	gelatin NP	spherical	≈ 250 nm	water *	sunflower oil	O/W	≈ 10–30 µm	rotor-stator (30 s, 12 000 rpm)	beta-carotene / oil	oral	Tan et al., 2017 [252]
	kafirin NP	-	-	water *	vegetable oil	O/W	≈ 50 µm	rotor-stator (3 min, 13 000 rpm)	curcumin / oil	oral	Xiao et al., 2015 [253]
	ovalbumin	fibrous or granular	≈ 80 nm	Water pH = 3–4 *	sunflower oil	O/W	≈ 10–20 µm	rotor-stator (2 min, 13 000 rpm)	-	-	Chang et al., 2016 [254]
	zein	colloidal particles	≈ 70–85 nm	water pH = 4 *	soybean oil	O/W	≈ 10–200 µm	rotor-stator (13 500 rpm)	-	-	Folter et al., 2012 [255]
	ferritin	NP	≈ 12 nm	water *	n-dodecane, toluene, castor oil, olive oil, vegetable oil	O/W	≈ 20 - 200 µm	rotor-stator (2 min, 30 000 rpm)	-	-	Fujii et al, 2009 [256]
	lactoferrin lactoferrin NP-alginate lactoferrin NP-carrageenan	NP	-	water *	olive oil	O/W	≈ 0.45-10 µm	high-pressure homogenizer, 103 MPa, 4x *pre-emulsion rotor-stator (1 min, 35 000 rpm)*	-	-	Meshulam et al., 2014 [257]
	Lactoferrin nanogel particles Composite layer of lactoferrin-inulin NP	spherical	≈ 100 -116 nm	water *	sunflower oil	O/W	≈ 25 µm	rotor-stator type mixer (2 min, 10 000 rpm)	-	-	Sarkar et al., 2018 [258]
	E2 protein	dodecahedron nanocage	≈ 25 nm	tris buffer pH = 8.7, EDTA, sodium azide *	rosemary oil	O/W	≈ 300 nm	ultrasonication probe (500 W, 20 kHz) 2 min, 40% amplitude *pre-emulsion mechanical stirring*	-	-	Sarker et al., 2017 [105]
	casein	nanoemulsion droplets	≈ 150 nm	phosphate buffer pH = 7 *	n-hexane	O/W	≈ 1–70 µm	rotor-stator (2 min, 30 000 rpm)	-	-	Ye et al., 2013 [259]
	βlactoglobulin fibrils-dipalmitoyl phosphatidylcholine	fiber like	≈ 100–400 nm length	phosphate buffer pH = 7 sodium azide*	soybean oil	O/W	≈ 10–100 µm	rotor-stator (3 min, 20 000 rpm)	-	-	Gao et al., 2017 b [260]
	βlactoglobuline - pectin	microgel	≈ 55–300 nm	sodium acetate buffer pH = 6* acetate buffer pH = 4.8*	corn oil	O/W	≈ 1 µm	high-pressure microfluidic homogenizer (5 000 psi ≈35 MPa, 5x) *pre-emulsion rotor-stator (20s, 22000 rpm)*	-	-	Zimmerer et al., 2014 [261]
	Lupin protein aggregate particles (LP22-APs)	aggregates	-	water pH = 7 *	sunflower oil	O/W	≈ 1.9 - 6.26 µm	high-speed homogenization (2 min, 10 000 rpm)	-	-	Diaz et al., 2019 [262]
	Soluble flaxseed protein and mucilage nano-assemblies	-	≈ 369 nm	water pH=3 *	tricaprylin oil	O/W	≈ 4.75 - 9.76 µm	high shear blender (5 min, 24 000 rpm)	-	-	Nasrabadi et al., 2019 [263]

EDTA = Ethylenediaminetetraacetic acid, IV = intravenous, * = phase containing the particles

4.3. Protein-based particles

Proteins are biocompatible biopolymers already largely used in food formulations. Protein particles can be prepared from the native protein by various techniques such as anti-solvent precipitation [252,253,255], heat treatment [40,248,257,258] or mechanical treatment (with for example high-pressure homogenization) [254]. Protein microgels can also be obtained by heat treatment of the globular protein [261], cross-linking of the protein isolate [251] or top-down approach by breaking a protein macrogel [249]. Many protein-based particles impart proper hydrophobicity and hydrophilicity balance allowing them to stabilize Pickering emulsions.

Various protein particles have already been studied as Pickering emulsions stabilizers such as soy [248,249], pea [250], whey [251], gelatin [252], kafirin [253], ovalbumin [254], zein [255], beta-lactoglobulin-pectin [261], beta-lactoglobulin [40,264,265], ferritin [256], lactoferrin [257,258], lupin [262], flaxseed protein [263] (Table 5). These particles have different shapes and softness as some of them are spherical NP [255–257,266], microgels [251,261], fibers [40,254], granules [254], dodecahedron nanocages [105] or gel particles [249]. Those particles can have very different size range (from tens of nanometer to hundreds of micrometers) and can stabilize emulsion droplets from hundreds of nanometers to hundreds of micrometers (Table 5). For instance, Sarker *et al*. [105] formulated O/W Pickering nanoemulsions (≈ 300 nm) with dodecahedron hollow protein nanocages using a biocompatible oil (rosemary oil).

Liu & Tang [248], Shao & Tang [250] and Tan *et al*. [252] encapsulated β-carotene in the oil droplets of Pickering emulsions respectively stabilized by soy protein particles, pea protein particles and gelatin particles. In these three cases, the emulsion droplets had the same size range (from a few to tens of micrometers). They studied the release of β-carotene during *in vitro* digestion and found a sustained release and additional stability of the API. Tan *et al*. [252] showed that the API bioaccessibility was improved by a factor of 5 after the *in vitro* digestion of the Pickering emulsion encapsulating API compared to the *in vitro* digestion of the API solubilized in oil. Xiao *et al*. [253] encapsulated curcumin in oil droplets of Pickering emulsions stabilized by kafirin particles and demonstrated the protection of curcumin from photo-oxidation and the protection of oil from lipid oxidation.

Even if these emulsions were intended for a food application and not for a pharmaceutical one, they all used biocompatible oil making these systems potential pharmaceutical Pickering emulsions, especially for oral administration.

4.4. Fat crystals

Fat crystals (also called solid lipid nanoparticles) are colloidal systems with a size below 1 µm and with a weak polydispersity [267,268]. To the best of our knowledge, no fat crystal stabilized Pickering emulsions have been studied for pharmaceutical application even if they are valuable candidates. Indeed, fat crystals are non-toxic, cost-effective, easy to prepare and they offer scale-up possibilities. They were intensively studied for drug delivery by various routes [267,269]. Moreover, they are already used as emulsion stabilizers in food products such as margarine or ice cream [99]. Thus, they might also be used in pharmaceutical applications, at least for oral administration.

Such Pickering emulsions can be prepared at a temperature above or below the fat melting point. If the emulsification process is performed at a temperature above the melting point, the crystals are formed directly at the droplet surface during a cooling phase, decreasing the temperature below the fat melting point. If the emulsification process is performed below the fat melting point, the fat crystals are prepared upstream. Numerous techniques that can be used to prepare fat crystals are well described in the review of Mehnert & Mäder [268]. The most common emulsification processes are high shear homogenization, ultrasound, high-pressure homogenization, membrane and microfluidic emulsifications. These techniques sometimes require the use of surfactants, which can modify the surface properties of the fat crystals such as their hydrophobicity, and thus their ability to stabilize Pickering emulsions [270].

Table 6: Examples of Pickering emulsions stabilized by fat crystals, cyclodextrin particles, drug nanocrystals, viruses, spores, bacteria and yeasts

particles				emulsion					drug / localization	route	reference
	composition	shape	size	aqueous phase	oil phase	type	droplet size	emulsification method			
fat crystals	glyceryl stearyl citrate crystals	spherical ellipsoidal	≈ 10–20 x 20–140 nm	water *	canola oil	O/W	≈ 460 nm	high-pressure homogenizer (7 000 psi ≈ 48 MPa, 5x) *pre-mixing rotor-stator 30 s, 27 000 rpm*	-	-	Gupta et al., 2012 [99]
	tripalmitin crystals	spherical	≈ 130 nm	water *	sunflower oil	W/O	≈ 5–15 µm	high-shear mixer (2 min, 10 000 rpm)	-	-	Pawlik et al., 2016 [270]
	mono/tri glyceride crystals	-	-	water	sunflower oil	W/O/W	≈ 2–50 µm	rotor-stator (3 min, 8 000 rpm)	-	-	Spyropoulos et al, 2011 [271]
cyclodextrins	β-cyclodextrin emulsifier (βCD)	-	-	water *	isopropyl myristate	O/W	< 100 µm	homogenizer (5 min, 10 000 rpm)	captopril / water	transdermal	Taguchi et al., 2019 [272]
	α-, β- and γ-CD/oil complexes and complexes NP	spherical	≈ 30–250 nm ≈ 1–4 µm	Water	paraffin oil isopropyl myristate	O/W	≈ 10–20 µm	rotor-stator (1 min, 11 500 rpm)	econazole nitrate / oil	topical	Leclercq et al., 2016 [273]
	β-, tripropanoyl-β- and tributanoyl-β-CD/oil complexes	-	-	water *	squalene soybean oil liquid paraffin	O/W and W/O	≈ few to hundreds µm	high shear homogenizer (5 min, 10 000 rpm)	-	-	Inoue et al., 2010 [274]
	soft heptakis(2,6-di-*O*-methyl)-β-CD	nanogels	≈ 30–120 nm	water *	n-dodecane toluene	O/W and W/O	≈ 20–200 µm	rotor-stator (1 min, 8 000 rpm)	-	-	Kawano et al., 2015 [275]
	α- and β- CD/oil complexes	microrods	≈ 5–100 µm	water *	n-tetradecane silicone tricaprylin sunflower oil	O/W	≈ 10–40 µm	rotor-stator (20 s, 11 000 rpm)	-	-	Mathapa et al., 2013 b [276]
drug nanocrystals drug nanoparticles		spherical	≈ 220 nm	Water (NP)	sunflower oil	O/W	≈ 1 µm	sonication probe (20 s, 95% amplitude) *pre-mixing high shear mixer, 3 min, 6 000 rpm*	curcumin / NP	-	Aditya et al., 2017 [277]
			≈ 300 nm	Water (NP)	glyceryl monocaprylate	O/W	≈ 30–70 µm	high-pressure homogenizer (100 MPa, 10x) *pre-mixing*	silybin / NP	oral	Yi et al., 2017 [278]
		-	-	water	n-tetradecane	O/W	≈ 5–16 µm	high-pressure jet homogenizer (300 bar =30 MPa) *pre-emulsification vortex full speed, 2.5 min*	Tiliroside, rutin, naringin / NP	-	Luo et al., 2011 and 2012 [279,280]
spores	spore coated with divinyl benzene-methacrylic acid or hydroxyethyl methacrylate polymer	spherical with polygon like patterned surface	≈ 20 µm	water	hexadecane *	O/W	-	mechanical or hand shaking (10 min)	-	-	Ballard et al., 2011 [281]
	spore of lycopodium clavatum	spherical with polygon like patterned surface	≈ 30 µm	water, NaCl	octane, isopropyl, myristate, methyl myristate, toluene, cyclohexane, tricaprylin, PDMS, undecanol *	O/W	≈ 0.2-6 mm	hand shaking (50 s) or rotor-stator (2 min, 13 000 rpm)	-	-	Binks et al., 2005 [282]
virus	turnip yellow mosaic virus	hexagonal arrays	≈ 30 nm	water, NaCl *	perfluorodecalin	O/W	≈ 50–200 µm	hand shaking	-	-	Kaur et al., 2009 [283]
	cowpea mosaic virus	hexagonal arrays	≈ 30 nm	potassium phosphate buffer pH=7 *	perfluorodecalin	O/W	≈ 20–70 µm	hand shaking	-	-	Russel et al., 2005 [284]
Bacteria and yeasts	bacterial cells	-	-	phosphate buffer pH=7 *	n-hexadecane	O/W and W/O	-	vortex mixer (5 min)	-	-	Dorobantu et al., 2004 [285]
	bacterial cells-chitosan	rod-like	≈ 2–3 µm	water, acetic acid*	tetradecane	O/W	≈ 100–250 µm	hand shaking	-	-	Wongkongkatep et al., 2012 [286]
	baker's yeast lactic acid bacteria	-	-	water *	olive oil	O/W	≈ 1- 5 µm (yeast) ≈ 10 µm (bacteria)	magnetic stirring (500 rpm) or for 50/50 (w/w) vortexing (3 000 rpm)	-	-	Firoozmand et al., 2015 [287]
	yeast	-	≈ 5 µm	water *	hexadecane	O/W	≈ 60 µm	high shear homogenizer (30 min, 900 rpm)	-	-	Furtado et al., 2015 [288]

* = phase containing the particles

The fat crystals used to stabilize Pickering emulsions have a size of hundreds of nanometers and the resulting emulsion droplets are relatively small (from hundreds of nanometers to tens of micrometers) (Table 6). All types of emulsions, O/W, W/O and multiple, can be obtained with fat crystals. Gupta & Rousseau [99] formulated O/W emulsions stabilized with glyceryl stearyl citrate crystals of spherical or ellipsoidal form (≈ 10–20 x 20–140 nm) using a biocompatible oil (canola oil). The resulting emulsions exhibited small droplets (≈ 460 nm). Pawlik *et al*. [270] formulated W/O emulsions stabilized with tripalmitin spherical crystals using a biocompatible oil (sunflower). They varied the surfactants used to prepare the tripalmitin crystals and obtained emulsion droplets of ≈ 5–15 µm. Spyropoulos *et al*. [271] formulated W/O/W emulsion using sunflower oil. Only the inner droplets of the emulsion were stabilized by mono and triglyceride crystals. But, in principle, it should be possible to stabilize multiple emulsions with fat crystals only as they allow the stabilization of O/W and W/O emulsions. However, studies of these kinds of systems in the pharmaceutical field are still lacking.

4.5. Cyclodextrin particles

Cyclodextrins (CD) are cyclic oligosaccharides derived from starch hydrolysis by cyclodextrin glycosyl transferase bacterial enzyme (CG-Tase). There are three major types of native CD: α-CD, β-CD and γ-CD corresponding to six, seven and eight glucose units, respectively, bridged through glycosidic bonds. CD possess a cone-shaped chemical structure with a hydrophobic subnanometer-sized cavity allowing encapsulating molecules through non-covalent interactions forming inclusion complexes. The cavity volume changes with the type of CD: 174 Å for α-CD, 262 Å for β-CD and 427 Å for γ-CD [289]. CD are non-toxic depending on the dosage and the administration route. They are used as pharmaceutical excipients to increase the aqueous solubility, stability and bioavailability of complexed API, but also to reduce gastrointestinal or ocular irritation or to mask an unpleasant taste or smell [290]. Though CD molecules in water have no surface activity, they can form amphiphilic complexes with oil. Inoue *et al*. [291] showed the ability of precipitated α-, β- and γ- CD/oil complexes to stabilize emulsions with an influence of the complex on the interfacial tension. They found that the most stable emulsions were obtained using β-CD/oil complexes which, among the three types of CD, had its three-phase contact angle the closest to 90 °. A non-biocompatible oil (n-alkane) was, however, used in this study. Inoue *et al*. [274] demonstrated the emulsification ability of β-CD complex with biocompatible oils (squalene, soybean oil and liquid paraffin) (Table 6). They formulated O/W Pickering emulsions stabilized with β-CD/oil complexes and W/O Pickering emulsions stabilized with complexes between the oil and β-CD modified with tripropanoyl or tributanoyl. Mathapa &

Paunov [276] demonstrated the ability of molecularly dissolved α- and β-CD to assemble into microrod particles directly at the emulsion droplet surface, and thus to effectively allow the formation of Pickering emulsions. They also showed that these microrod particles were longer with α-CD (≈ 100 µm) than with β-CD (<10 µm). Taguchi *et al.* [272] formulated O/W emulsions stabilized with β-CD/oil complexes, with isopropyl myristate as the oil phase. Captopril, an angiotensin converting enzyme inhibitor used as a model drug in this study, was located in the aqueous phase. *In vitro* skin permeation studies on excised skin of hairless mice showed that these Pickering emulsions could improve skin permeability of captopril compared to aqueous solutions, oil suspensions or surfactant-stabilized emulsions. Above a given drug concentration, β-CD/captopril complexes were formed, which inhibited the formation of β-CD/oil complexes. This led to more unstable emulsions, since it was expected that the contact angle of β-CD/captopril complexes was smaller than that of β-CD/oil complexes.

CD/oil complexes are not the only form of CD capable of stabilizing Pickering emulsions (Table 6). Kawano *et al*. [275] showed the ability of a soft CD nanogel to stabilize emulsions using non-biocompatible oils. CD nanogels were prepared by the cross-linking of heptakis(2,6-di-*O*-methyl)-β-CD. The CD nanogel hydrophobicity could be tuned by their cross-linking degree. Leclerq & Nardello-Rataj [273] demonstrated the potentiality of Pickering emulsions stabilized by CD/oil complexes and CD/oil complexes particles for pharmaceutical applications. CD/oil complexes acted as a surfactant with the CD as the polar head and the uncomplexed apolar part of the oil as the hydrophobic tail. The CD/oil complexes were then able to self-assemble, forming NP when their concentration increased. Thus, the authors were able to formulate Pickering emulsions stabilized either by CD/oil complexes (at low CD concentration) or by CD/oil complexes NP (at high concentration) and to encapsulate econazole nitrate, an antifungal API, in the oil droplets of these emulsions. The antifungal and antimicrobial activities of such Pickering emulsions were evaluated *in vitro*, showing an efficiency at least as important as a commercially available form and without the risk associated with the synthetic surfactants.

4.6. Drug nanocrystals/nanoparticles

Pickering emulsions were also directly stabilized by active molecule or drug nanoparticles or nanocrystals [277–280] (Table 6). Aditya *et al*. [277] stabilized sunflower oil Pickering emulsions with nanosized amorphous curcumin. Curcumin nanoparticles (≈ 220 nm) were obtained by antisolvent precipitation technique. The resulting Pickering emulsions were stable with relatively small droplets (≈ 1 µm). For their part, Luo *et al*. [279,280] prepared particles from various

flavonoids (a family of molecules known for their potential health impact that are insoluble in water and in oil) to stabilize emulsions using a non-biocompatible oil (n-tetradecane). They obtained stable emulsions with tiliroside, rutin and naringin with droplet size of ≈ 16 µm, 6 µm and 5 µm, respectively. These flavonoids were pH-responsive due to their change of solubility with pH. Yi *et al*. [278] used silybin nanocrystals to stabilize an O/W emulsion using a biocompatible oil (glyceryl monocaprylate). This flavonoid has a poor solubility in water and a poor oral bioavailability. It was already used for the treatment of acute and chronic liver diseases and it showed efficacy against tumor growth, angiogenesis, inflammation and metastasis [292]. The silybin nanocrystals (≈ 300 nm) were prepared by high-pressure homogenization treatment of silybin coarse powder suspension in water. An *in vitro* dissolution study of the silybin and a pharmacokinetic study in rats were also conducted. The authors noticed a faster *in vitro* dissolution and released of the silybin from the Pickering emulsion than from the nanocrystal suspension, which was itself faster than with the coarse suspension. These differences were explained by *i)* the silybin state (the size of nanocrystals was smaller with a larger surface, inducing more contact with the medium), and by *ii)* the dissolution of part of the sibylin in the oil phase of the emulsion, leading to a faster dissolution than when sibylin was only present in water. They also noticed an increase in the blood concentration of sibylin in rats in the case of the Pickering emulsion compared to the nanocrystal suspension. Such systems could thus enhance the bioavailability of a poorly soluble drug due to its accelerated and partial dissolution in the oil phase of the emulsion. These emulsions are undoubtedly promising for pharmaceutical applications.

4.7. Virus, spores, bacteria and yeasts

Nature is also able to produce directly particles of micro-nanometer size such as viruses, spores, bacteria and yeasts. They present the advantage of being very monodisperse in size and possibly functionalized [284]. Moreover, they are already used for pharmaceutical applications. For example, probiotics are human-friendly bacteria for the treatment and prevention of diseases [293]. Various viruses (human, plant or animal viruses) can be used as vaccines or as vectors/carriers for drugs or genes to target cells; the bacteriophage viruses can even be used as an alternative to antibiotic treatments [294,295].

Some works have demonstrated the ability of such natural particles to stabilize Pickering emulsions. Binks *et al*. [282] have shown that *lycopodium clavatum* spores (already used in homeopathic treatments) could stabilize Pickering emulsions using various oils, including some

biocompatible ones. These spores are valuable candidates to stabilize pharmaceutical Pickering emulsions as they have been used for centuries in the treatment of diarrhea, eczema and gout. Ballard & Bon [281] have modified the hydrophobicity of spores by coating their surface with polymers. The polymer was adsorbed onto the polygon-like surface of the spore, modifying it according to the polymerization degree. They also showed that these polymer coated spores were able to stabilize Pickering emulsions. However, the non-biocompatible oil used (hexadecane) should be changed for a further possible pharmaceutical application.

For their part, Russel *et al*. [284] and Kaur *et al*. [283] used, respectively, cowpea and turnip yellow mosaic virus as a model virus to stabilize O/W Pickering emulsions using perfluorodecalin as the oil. They demonstrated that the droplets were fully covered by a monolayer of viruses. They also showed that viruses maintained their structure and integrity during emulsification.

Bacterial cells can also be used as Pickering emulsions stabilizers. Dorobantu *et al*. [285] and Firoozmand & Rousseau [287] used various bacterial cells to stabilize O/W and W/O Pickering emulsions (*Acinetobacter venetianus*, *Rhodococcus erythropolis*, *Rhizomonas suberifaciens, Pseudomonas fluorescens, Lactobacillus acidophilus* and *Streptococcus thermophilus*). They noticed that the bacteria were able to attach and form a film with particle interactions at the interface, inducing the Pickering emulsion stabilization. The ability of bacteria to adsorb at the interface is linked to their surface properties and composition (in proteins, polysaccharides and polypeptides) and their ability to induce hydrophobic interactions [285]. Wongkongkatep *et al*. [286] have coated bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli* and *Lactobacillus sakei*) with chitosan in order to enhance their hydrophobic properties. Such particles were able to stabilize Pickering emulsions by the formation of a self-assembled bacterial-chitosan network at the droplet interface. However, among the studies performed with bacteria, only Firoozmand & Rousseau [287] used a biocompatible oil (olive oil).

Firoozmand & Rousseau [287] and Furtado *et al*. [288] also demonstrated the ability of yeast cells to stabilize Pickering emulsions using a biocompatible oil (olive oil) for the first ones and a non-biocompatible oil (hexadecane) for the second. Like bacteria, yeast cells have proteins and polysaccharides on their surface allowing them to anchor at the interface of the droplets.

4.8. Other particles

Ye *et al*. [259] firstly prepared a nanoemulsion stabilized by native protein micelles (casein). This nanoemulsion is not a Pickering emulsion. Then, they used these oil nanodroplets stabilized by

casein micelles (≈ 150 nm) to stabilize an O/W emulsion with droplet size around 1 to 70 µm. The same non-biocompatible oil (n-hexadecane) was used for the nanoemulsion droplets and for the Pickering emulsion droplets. The nanodroplets are deformed at the interface and the authors noted the influence of the nanoemulsion droplets on the size of the emulsion droplets and on their surface coverage. They compared the resulting emulsion to a Pickering emulsion. This concept could be used for pharmaceutical applications. Two different API could also be encapsulated: one in the oil of the nanoemulsion droplets and one in the oil of the Pickering emulsion droplets. It is even conceivable to encapsulate two API with the highest possible encapsulation rate as possible by using two different biocompatible oils, the ones leading to the best solubility for each API.

5. Discussion

5.1. Main interests of Pickering emulsions for pharmaceutical applications

The use of NP in Pickering emulsions can be seen as an issue since possible health concerns are raised by NP [296–298]. The impact of NP on the body and the environment is still relatively unknown [297–300]. In this context, biodegradable Pickering emulsions obtained from biodegradable and biocompatible particles and oils appear particularly attractive. This includes, among others, particles of cellulose, chitosan, chitin, starch, PLGA and PCL which are already used to prepared Pickering emulsions intended or not for pharmaceutical applications [301].

5.1.1. API encapsulation and co-encapsulation

As with classical emulsions stabilized by synthetic surfactants, an API can be encapsulated in the droplets of Pickering emulsions. Many examples have been provided in section 4. They exhibit the same advantages, such as API protection, API solubility and bioavailability increase, bad taste or texture masking. Moreover, Pickering emulsions could help to lower or even to avoid the toxicity risk linked to synthetic surfactants. They also display very good physical stability, sometimes up to several years. Compared to conventional emulsions, Pickering emulsions improve the protection of the API from degradation due to the solid barrier of particles around the droplets [209,248,250,252,253]. Thanks to this protection during oral and gastric digestion they allow an intestinal release [183]. They could also enhance API skin absorption and accumulation [182,217,218,228] as well as API efficacy [189,273] and bioaccessibility [252]. To the best of our knowledge, no clear mechanisms were provided for these observations.

In Pickering emulsions, the API can be encapsulated not only in the oil but also within the particles or grafted onto their surface. For instance, Wang *et al*. [209] have encapsulated an active molecule (curcumin) in particles (zein-chitosan complex particles). However, API could be encapsulated or grafted at the surface of all the particles presented in section 4. The API particles can also be by themselves the emulsion stabilizer like with drug nanocrystals or nanoparticles [277–280].

The major advantage of Pickering emulsions, compared to classical simple emulsions stabilized with synthetic surfactants, is the possibility to co-encapsulate several API in a single emulsion: one in the droplets and one in the particles. Various sustained release profiles could be obtained between the API encapsulated in the droplets and the one encapsulated in the particles, allowing to reduce the number of administrations needed, and thus to improve the patient compliance. A synergistic effect between the co-encapsulated API might also be obtained, allowing to decrease the doses.

It is interesting to note that the potential pharmaceutical Pickering emulsions presented in section 4 are almost exclusively simple and mostly O/W ones. However, multiple W/O/W [271] and O/W/O [197] Pickering emulsions were also formulated. Multiple emulsions are interesting for pharmaceutical applications as they should allow the co-encapsulation of three API: one in the internal droplets, the second one in the larger droplets and the last one in the particles. When stabilized by surfactants, multiple emulsions are highly unstable due to the use of two types of surfactants, one hydrophilic and the other hydrophobic, being both able to desorb from the interface [302]. With multiple Pickering emulsions, the particles are strongly adsorbed at the interface, creating much more stable multiple emulsions than with synthetic surfactants. To the best of our knowledge, no study has been conducted to confirm the potential of multiple Pickering emulsions for pharmaceutical applications yet.

5.1.2. Tuning the Pickering emulsion characteristics for pharmaceutical applications

The targeted droplet size depends on the desired pharmaceutical application. For example, as previously mentioned in section 4, for the injection route, the droplet size should usually be smaller than 5 µm. The opportunity to tune the droplet size towards the application is, thus, particularly attractive for the pharmaceutical field. As shown in sections 2 and 3, particles composition, wettability, adsorption, concentration, size, shape, surface charge as well as the emulsification process, oil phase type, salt concentration and pH, are many ways to modulate the droplet size of Pickering emulsions.

Particles are available with various size ranges, rigidities, shapes and surfaces. Thus, according to the particles chosen to stabilize the emulsion, the pharmaceutical benefit can be tuned. For example, when the particles reach the bloodstream, these parameters significantly influenced their long-term circulation. Particles with a size lower than 5 nm are recognized for having a fast clearance from the circulation, whereas the larger particles (up to 5 µm) are accumulated in the body and can be uptaken by the cells [303]. The characteristics of the particles can also influence their biodistribution, their cellular uptake in a specific cell type, their internalization rate or their ability to cross biological barriers [303]. If the particles do not contain an API, it might be appropriate to choose particles which exhibit a fast clearance if they reach the bloodstream, or which are not able to penetrate the skin if the emulsions are applied topically.

Most of the studies on Pickering emulsions were performed with non-biocompatible model oils such as n-dodecane, toluene, n-tetradecane or hexadecane. This is because these oils are well-defined model oils, and thus are easier to use for numerous characterization techniques than most of the biocompatible oils which are complex mixtures of triglycerides. The change for a biocompatible oil is required for a pharmaceutical application. This could induce dramatic modifications in the emulsion properties as already explained in part 3.2.

5.1.3. Stimuli-responsive emulsions

The possibility to obtain stimuli-responsive emulsions using particles sensitive [176] to pH [304–307], ionic strength [308], temperature [309] magnetic field [31,310,311] or electric field [312–314] is also very promising. Indeed, an emulsion disruption with external stimuli can induce *i)* enhanced stability during storage if the emulsion is only destabilized with an external stimulus which can be controlled during storage; and *ii)* a targeted release of the API in the human body. For example, an emulsion stabilized with temperature-responsive particles can be stored with good stability at a given temperature and be disrupted once in the human body, allowing the release of the API. With an emulsion stabilized with pH-responsive particles, it is possible to target a body region for the API release as the physiological pH varies (≈ 6.7-7.4 for the lungs, ≈ 4.5-5.5 for the skin, ≈ 7.35-7.45 for the blood, ≈ 1-3 for the stomach, ≈ 8 for the rectum or the gut, ≈ 3.8-4.5 for the vagina) [2]. For example, an emulsion that is stable at pH = 1-3 and disrupted at pH = 8 will release the API in the gut when administered by the oral route. Emulsions stabilized with electric or magnetic field responsive particles, for their part, could be used for theranostic applications, with an API release induced by an external electric or a magnetic field, even if such particles are often only biocompatible and not biodegradable [176].

Those potential pharmaceutical applications of Pickering emulsions represent exciting opportunities.

5.2. Challenges to overcome for an industrial application of Pickering emulsions

No product based on Pickering emulsions is commercialized yet, but a lot of systems were patented. Some obstacles to the Pickering emulsions industrialization remained to be overcome. The particles preparation will need to be scaled up, which is not obvious for all the particle types. The storage stability should be improved, in particular when API are encapsulated in biodegradable particles. The particles should be degraded only once administered and not during storage. The use of stimuli-sensitive particles can be helpful in this aspect. Interestingly, some Pickering emulsions can be dried. Indeed, in certain cases, the particles at the interface are able to maintain the droplet integrity even after the external phase removal. Such systems can be compared to liquid marbles [81]. For example, Marefati *et al*. [315] freeze-dried Pickering emulsions stabilized with starch granules forming an oil powder. This oil powder can then be rehydrated to reconstitute the Pickering emulsion. This technique can be a valuable strategy for Pickering emulsion storage. Indeed, if the particles degradation mechanisms imply hydrolysis, removing the aqueous phase could protect the NP from degradation, and thus allow long-term stability. Moreover, the API contained in the oil phase or in the particles would be protected against oxidation during storage.

The sterilization of the formulations is already an issue for emulsions stabilized by surfactants [316] and is again more likely to be problematic for Pickering emulsions. The sterilization process by filtration is performed with a membrane with 0.2 µm pores. This cut off is sometimes smaller than the particles used for Pickering emulsions [317]. The sterilization by heating is not appropriate for high temperature-sensitive particles. The best strategy would be to produce aseptically the emulsions from sterilized components [316], but the sterilization of particles could be difficult to achieve. A lot of work remains to be done on this issue.

6. Conclusion

Pickering emulsions are mostly prepared by high shear techniques (rotor-stator, high-pressure homogenization and sonication) and low shear techniques (membrane and microfluidic emulsifications). High shear techniques are quicker and easier to set up than low shear techniques, but the latter have the advantages not to modify the particles and to produce droplets in a controlled manner and with a lower polydispersity. The emulsification parameters

as well as the particle wettability, the nature of the oil phase, the aqueous phase/oil phase ratio, the particle adsorption rate, concentration, size, shape, roughness, surface charge, the salt concentration and the pH can be modified to tune the emulsions type (simple or multiple, O/W or O/W), the droplet sizes and their stability. All these parameters are interlinked and, often, changing one parameter induces changes for the others.

Pickering emulsions stabilized with organic particles exhibit a real potential for pharmaceutical applications. This includes Pickering emulsions stabilized with particles based on natural polymers (such as starch, cellulose, chitin/chitosan or lignin-based particles), biocompatible synthetic polymers (such as PNIPAM, PLA, PLGA, PCL or PEO), proteins (from soy, pea, whey, egg white, zein, ferritin, gelatin or β-lactoglobulin) and cyclodextrin complexes. This also encompasses emulsions stabilized by fat crystals, drug nanocrystals or nanoparticles, viruses, spores, bacteria and yeast. A part of the studies on the subject was already performed for specific pharmaceutical applications and others could be adapted for the pharmaceutical field by changing the oil nature. Numerous combinations of particles and oils are possible for as many possible pharmaceutical emulsion preparations. These emulsions could be used for multiple API encapsulations as well as for theranostic applications with stimuli-responsive particles. A growing scientific community focuses its interest on Pickering emulsions and their application, especially in the pharmaceutical field. Some work remains to be done to gain a better knowledge of their stability during storage, to successfully sterilize these emulsions or to clearly demonstrate the benefit to co-encapsulate API in such systems.

Conflict of interest

The authors have no conflicts of interest to declare.

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