# Pickering Emulsions for Controlled Drug Delivery to the Skin

19

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## 19.1 Introduction

Pickering emulsions are emulsions of any type, either oil-in-water (o/w), water-in-oil (w/o), or even multiple, stabilized by solid particles in place of surfactants (Aveyard et al. 2003; Binks 2002; Binks and Horozov 2006). Although such emulsions did not receive much development towards their application, their properties are quite attractive and deserve special attention. The interest lays in the fact that Pickering emulsions essentially remain emulsions, i.e., they share most properties of emulsions with their conventional surfactant-based homologues. Additionally, they have also few specific properties that are advantageous in the field of drug delivery to the skin. The solid stabilizing particles behave in quite a similar way as surfactant molecules: one part is adsorbed at the oil-water interface and the residual part is remaining in the continuous phase according to the adsorption equilibrium. Solid particles form a dense coating that can be seen by optical microscopy when the particles are large enough (Fig. 19.1).

The name "Pickering emulsion" was given after their early disclosure by S.U. Pickering (1907). Actually, the adsorption of solid particles at the air-water interface has been reported earlier (Ramsden 1903). However, the merit has been given to S.U. Pickering, because his paper specifically dealt with emulsions stabilized by solid particles; he reported improved stability for these

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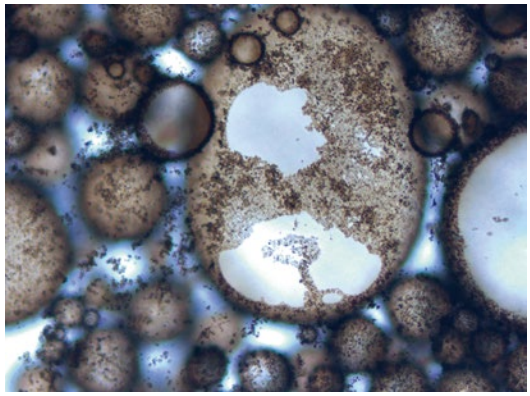

**Fig. 19.1** Optical microscopy picture of an o/w Pickering emulsion of silicone oil stabilized by zinc oxide (ZnO) particles. Addition of a large concentration of sodium chloride (NaCl, 1 mol·L$^{-1}$) caused the partial flocculation of ZnO particles into large aggregates that could be observed at the surface of oil droplets by optical microscopy. The oil droplets are covered by a dense coating of ZnO particles over the brown areas where large aggregates are also visible. The white areas are bare. The picture also shows free ZnO particles dispersed in the aqueous phase which are seen as aggregates in between the oil droplets

emulsions with respect to surfactant-based emulsions and provided a definite proof for the adsorption of solid particles, being the origin for such stabilization.

Pickering emulsions are essentially emulsions, so that their main properties are common with classical emulsions stabilized by surfactants (emulsifiers). Pickering emulsions are prepared using the same manufacturing processes as for classical emulsions. There might be a specific process for Pickering emulsification; however, the most often used preparation methods are the same as for classical emulsions. As a consequence, the application domains of Pickering emulsions are the same as for classical emulsions, and an application based on classical emulsions can easily be switched to Pickering emulsion. Pickering emulsions show some improved properties compared to classical emulsions. Adsorbed solid particles act as a more effective barrier against coalescence than surfactants. Such important benefit opens the possible stabilization of coarse emulsions and multiple emulsions. The "surfactant-free" character makes them attractive to applications to life sciences where surfactants often cause either irritancy or hemolysis.

Applications of Pickering emulsions in pharmaceutical and cosmetic fields rely on either their specific properties manifested in vivo (low irritancy related the surfactant-free character, specific interactions with biological interfaces) or the development of new dosage forms having improved ex vivo properties (emulsion stability, thickening with no polymeric thickener) over surfactant-based emulsions. The present chapter is dealing with percutaneous penetration-enhancing properties of Pickering emulsions and covers the former aspect where drug-loaded Pickering emulsions modify the transport of drug molecules into/through skin. This includes the classical "penetration enhancer" action similar to that of "penetration enhancer" chemicals and also any modification of the drug transport induced by the formulation in a Pickering emulsion. The behavior of Pickering emulsions is discussed with respect to a reference surfactant-based emulsion.

The physicochemical properties of Pickering emulsions are shortly reviewed in the first part of the chapter. The second part reports on the skin absorption behavior of drugs followed by a discussion of the mechanism of the effects induced by Pickering emulsions compared to surfactant-based emulsions.

## 19.2 Physical Chemistry of Pickering Emulsions

The origin of emulsion stabilization is the adsorption of solid particles at the surface of emulsion droplets. The mechanism of adsorption is partial wetting of the particles by oil and water, which is very different of surfactants; the solid particles are not amphiphilic. Stabilization takes place by preventing destabilization events: coagulation, coalescence, and Ostwald ripening. There are strong similarities with classical surfactant-based emulsions; and there are few differences that provide specificities to Pickering emulsions. The manufacturing processes of Pickering emulsions used so far are the same as those of classical emulsions.

### 19.2.1 Adsorption of Solid Particles at Interfaces and Stabilization of Emulsions

Particles adsorbed at the oil-water interface are wet both by oil and water. Wetting conditions depend on interfacial tensions of the solid-water, solid-oil, and oil-water interfaces, $\gamma_{s\text{-}w}$, $\gamma_{s\text{-}o}$, and $\gamma_{o\text{-}w}$. Under partial wetting conditions, the contact angle in water, $\theta_w$, is given by the Young's law:

$$\cos\left(\theta_w\right) = \frac{\gamma_{s\text{-}o} - \gamma_{s\text{-}w}}{\gamma_{w\text{-}o}} \qquad (19.1)$$

Partial wetting is quite common. Complete wetting by water occurs for very hydrophilic surfaces; such particles remain dispersed in the aqueous phase. This is the case of silica that cannot be used as stabilizing particle for most common oils (Frelichowska et al. 2009a). Silica is very often used however because there are commercially available grades of "hydrophobized" silica having organosilanes chemically grafted to their surface (Barthel 1995). Wetting of such silica surfaces is controlled by the grafting degree of the organosilane. Adsorption of organic molecules such as surfactants, polymers, or even small surfactant-like organic molecules, to the solid particles, allows adjusting the surface properties of the stabilizing particles so as to achieve the desired emulsion type and optimum stability (Gelot et al. 1984; Hassander et al. 1989; Midmore 1998a, b, 1999; Ghouchi Eskandar et al. 2007, 2011; Akartuna et al. 2009; Drelich et al. 2010). However, surface-active molecules that adsorb at the surface of solid particles may also adsorb at the oil-water interface and contribute to the emulsion stability in the same way as classical surfactants do. Adsorption of solid particles is very strong when partial wetting conditions are met. The strongest adsorption and the maximum stability of emulsions are reached when the contact angle is 90° (Binks and Lumsdon 2000a). Obviously, large particles having a larger area contacting oil and water show larger adsorption strength. Even small solid nanoparticles also adsorb to the oil-water interface quite strongly. Stabilizing solid particles do not show surface activity, which is a definite difference compared to surfactants (Vignati et al. 2003; Dong and Johnson 2003).

Stabilization of Pickering emulsions occurs because the layer of adsorbed solid particles forms a rigid coating that acts as a mechanical barrier against coalescence. Such a rigid protective coating has been compared to an eggshell. The origin of its mechanical strength is the two-dimensional aggregation of solid particles at the droplet surface by means of capillary forces. A supplementary three-dimensional aggregation takes place in some instances, building a thick solid layer of solid particles. Therefore, the stability of Pickering emulsions is very high compared to classical emulsions. It allows the preparation of either concentrated emulsions (high internal phase ratio) or coarse emulsions (emulsion with droplet size in the millimeter range) that conventional surfactants would not be able to stabilize with sufficient efficiency. Solid particles may also prevent coagulation if they cause thickening of the continuous phase. This effect is similar to the stabilizing action of polymeric thickeners that are often included in the formulation of conventional emulsions.

Numerous particles are able to stabilize Pickering emulsions. They are either inorganic or organic. Hydrophobized silica and clay (montmorillonite, laponite, kaolin) are the most common inorganic particles. Latex and carbohydrate nanocrystals (cellulose, chitin) are examples of suitable organic particles.

### 19.2.2 Emulsion Type, Emulsion Inversion, and Double Emulsions

The emulsion type is controlled by the wettability of the solid particles (Aveyard et al. 2003; Binks and Lumsdon 2000): hydrophilic particles stabilize o/w emulsions and hydrophobic particles stabilize w/o emulsions. Examples of hydrophilic particles are silica, clay, titanium dioxide, and zinc oxide. Examples of hydrophobic particles are "hydrophobic" silica (grafted with organic silanes), "hydrophobic bentonite" (montmorillonite coated with

fatty quaternary ammonium salts) polystyrene, and polytetrafluoroethylene (PTFE, Teflon®). Too much hydrophilic (or hydrophobic) particles are totally wet by water (or oil) however; partial wetting is an absolute requirement for solid particles adsorption at the oil-water interface. This is very similar to the Bancroft rule for emulsifiers stating that a hydrophilic emulsifier (high HLB) gives rise to an o/w emulsion type, while a hydrophobic emulsifier (low HLB) gives rise to a w/o emulsion type. Accordingly, a HLB-like rule has been introduced for solid particles by Kruglyakov (2000). The relevant quantity is the contact angle in water, $\theta_w$, defined by the Young's law (Eq. 19.1): o/w emulsions form when $\theta_w < 90°$, and w/o emulsions form when $\theta_w > 90°$. In contrast with the behavior of emulsifiers, the contact angle for optimum stability is close to $\theta_w = 90°$. Therefore, "balanced particles" are efficient stabilizers, whereas "balanced surfactants" behave as poor emulsifiers. As an example, the well-known lecithin is a "balanced surfactant" that cannot stabilize emulsions; it needs being mixed with either a hydrophilic surfactant in order to stabilize o/w emulsions or with a hydrophobic surfactant for o/w emulsions. In other words, optimum emulsifiers are shifted apart from the HLB of "balanced surfactants"; conversely, "balanced particles" are at optimum. As a corollary, the same type of solid particles meets the stabilization criteria of either o/w or w/o emulsion type. The Bancroft rule for solid particles is less a clear-cut rule than for emulsifiers. Phase inversion does not take place when the contact angle is close to 90°. Catastrophic phase inversion upon progressive addition of the continuous phase does not happen as readily as for surfactants. Apart from the wetting behavior, supplementary parameters such as the relative water and oil contents, the medium where the solid particles have been initially dispersed, have a definite influence on the emulsion type (Binks and Lumsdon 2000a, b, c; Binks and Rodrigues 2003). Another consequence of both o/w and w/o emulsion types being at optimum for $\theta_w = 90°$ is a strong hysteresis in phase inversion experiments (Binks and Rodrigues 2003; Kruglyakov and Nushtayeva 2004).

Multiple emulsions of the w/o/w type are attractive dosage forms for encapsulation of hydrophilic drugs such as proteins and nucleic acids. The stabilization of multiple emulsions using emulsifiers is a difficult task because the stability is lost when the emulsifiers adsorbed at the surfaces of the w/o internal and w/o/w droplets mix together. The strong adsorption of solid particles to the various oil-water interfaces is an obvious benefit because particles keep retained at the right interfaces and do not mix.

A classical two-step process was used to prepare w/o/w multiple emulsions of medium-chain triglycerides: a primary w/o emulsion was stabilized by hydrophobic silica particles (coated with grafted dimethylsilyl groups at 49 % coverage); the obtained primary w/o emulsion was then dispersed in water using hydrophilic silica particles (coated with dimethylsilyl groups at 21 % coverage) as stabilizing particles, yielding a stable w/o/w emulsion (Barthel et al. 2003).

### 19.2.3 Control of Emulsion Properties by Formulation and Process Parameters

Once the emulsion type and the nature of the ingredients have been chosen, the droplet size and the rheological behavior are the main physicochemical properties of emulsions that matter in regard to their skin delivery. Such properties are controlled by the formulation (the type and concentration of the ingredients) and the emulsification process.

#### 19.2.3.1 Droplet Size of Pickering Emulsions

The concentration of solid particles controls the droplet size. This meets expectations as it is similar to the effect of the concentration of surfactants. Indeed, a larger amount of stabilizing species allows a larger interfacial area to be formed, thus smaller droplets. Under conditions such that solid particles adsorb as a dense monolayer, the total oil-water interfacial area is in proportion to the amount of solid particles, and the mean droplet diameter is given by the following relationship (for an o/w emulsion) based on simple geometrical considerations (Wiley 1954; Arditty et al. 2003; Frelichowska et al. 2010):

$$Diam = \frac{6}{\rho_{oil}\alpha_{solid}} \frac{M(\text{oil})}{M(\text{solid})} \quad (19.2)$$

where $M$(oil)/$M$(solid) is the mass ratio of oil (dispersed phase) to solid particles, $\rho_{oil}$ is the density of oil (kg m$^{-3}$), and $a_{solid}$ is the interfacial area covered per mass of adsorbed solid particles (m$^2$ kg$^{-1}$). Such a linear relationship has often been experimentally verified (Arditty et al. 2004, 2005); but cases of departure from Eq. 19.2 have also been reported (Wang and Hobbie 2003; Binks and Whitby 2004; Frelichowska et al. 2010). Incomplete coverage by solid particles may also lead to stable Pickering emulsions; however, there are several microscopic observations of such emulsions (Fig. 19.1) (Binks and Kirkland 2002; Horozov and Binks 2006; Destribats et al. 2010).

The mechanisms being responsible for the droplet size in surfactant-based and Pickering emulsions are different. The reduction of droplet size by increasing surfactant concentration results from two phenomena: on one hand, the simple geometrical argument given above holds; on the other hand, fast surfactant adsorption during the emulsification process causes a decrease of the interfacial tension that makes the droplets fragmentation easier under shear. On the contrary, adsorption of solid particles does not change the interfacial tension (Vignati et al. 2003; Dong and Johnson 2003) (unless the particles contain surface-active impurities or they are associated with a surfactant).

In the case of a low amount of solid particles, a "limited coalescence" ripening phenomenon may occur: the poorly stabilized emulsion droplets undergo coalescence till the total interfacial area matches the area that the solid particles can stabilize (Wiley 1954; Arditty et al. 2004). Successful limited coalescence requires that the emulsion remains stable during the ripening process; otherwise emulsification fails as a part of the oil is released (Frelichowska et al. 2010; Avendaño Juárez and Whitby 2012). Under conditions of low particle content, large droplets can only be stabilized. A suitable emulsification process yields stable coarse emulsions having droplets within millimeter size range (Zhai and Efrima 1996; Arditty 2003). Formation of poorly stabilized Pickering emulsions is controlled by both formulation and emulsification process parameters.

On the basis of the geometrical relationship between droplet diameter and oil/solid mass ratio (Eq. 19.2), very fine emulsions might be prepared at a high content of solid particles. Such expectation is based on the hypothesis of droplet-size control by the amount of stabilizing particles. A high-power emulsification process is required for the fragmentation of droplets. In the case of lack of power, the smallest droplets that the process can create do form, and only a part of the stabilizing particle is used for reaching full coverage of the droplets. The remaining part of the stabilizing particles is not used for the stabilization; such excess particles are left free in the continuous phase.

As a summary, three distinct regimes are encountered depending on the mass ratio of solid particles to the dispersed phase (Fig. 19.2). In the first regime at low solid content, either emulsification fails or coarse emulsions are prepared provided a suitable process has been designed. In the second regime, the droplet size is controlled by the ratio $M$(particles)/$M$(oil) according to Eq. 19.2. The third regime is reached when the emulsification process is not able to create the interfacial area that the amount of solid particle might stabilize. The droplet size gets controlled by the emulsification process parameters such as homogenizer type, design of the instruments (propeller, rotor-stator, etc.), and stirring speed. The crossover from the second to the third regime depends on the power of the emulsification process.

#### 19.2.3.2 Rheology of Pickering Emulsions

The viscosity of emulsions is an important property regarding their use as formulations for topical administration. Indeed it controls the materials transfer from the emulsion droplets to the skin. When all solid stabilizing particles are adsorbed to the emulsion droplets, the rheological behavior of Pickering emulsions is the same as that of surfactant-based emulsions. Emulsions are fluid as long as the concentration of droplets remains low; strong thickening appears in concentrated

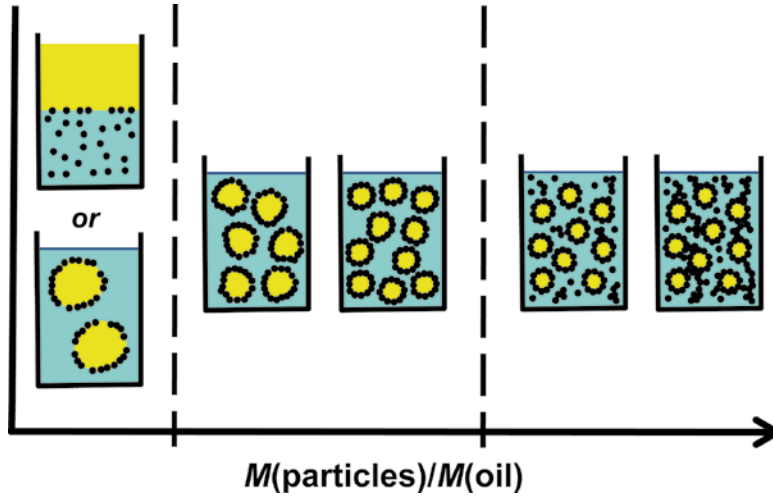


**Fig. 19.2** Scheme of the different behaviors taking place according to the mass ratio *M*(particles)/*M*(oil). In the first regime at low particle/oil ratio, either emulsification process fails or a stable coarse emulsion is formed. Full adsorption of solid particles takes place in the second regime where the droplet size is controlled by the formulation (amounts of solid particles and oil). The droplet size is controlled by the emulsification process in the third regime at high particle/oil ratio; excess solid particles is dispersed in the aqueous phase and possibly particles aggregate, forming a percolating continuous network in case of strong aggregation or large amount of excess particles

emulsions when the volume fraction of droplets reaches 50–60 %. High internal phase ratio emulsions (HIPEs, gel emulsions) are viscoelastic materials found for concentrations above 60–70 %. A specific feature of Pickering emulsions is the thickening action of excess of free particles (non-adsorbed) present in the aqueous phase (of o/w emulsions). In general, the solid particles that are able to adsorb onto oil droplets also tend to self-aggregate in water because they are not hydrophilic enough to remain well dispersed. As an example, the hydrophobic fumed silica particles used for the stabilization of Pickering emulsions have been primarily made commercially available as thickening agents (Barthel 1995).

A nice example of gelation induced by solid particles in Pickering emulsions is given by Abend and Lagaly (1998, 2001). A percolating network of flocculated solid particles has been built by heterocoagulation of two types of particles. The adsorbed particles prevented coalescence; the remaining part caused thickening and prevented coagulation. Interestingly, X-ray microscopy observations (Fig. 19.3) have shown that the oil droplets coated by solid particles were stuck to the network of solid particles, so that the oil droplets were part of the gel (Neuhäusler et al. 1999; Thieme et al. 1999).

The flocculation of excess solid particles can be induced in a controlled manner by physicochemical parameters such as salinity of the aqueous phase. Thus, low salinity leave well-dispersed or weakly flocculated particles and the emulsion is fluid (either Newtonian or rheo-thinning fluid); high salinity induces the formation of a continuous network of solid particles in the continuous phase that causes gelation of the emulsion. The rheological properties of practical relevance, in particular the yield stress, can be adjusted by means of simple addition of electrolytes (Horozov et al. 2007; Whitby et al. 2011).

## 19.3 Skin Delivery of Drugs

Topical application of drugs loaded in Pickering emulsions is of particular relevance for pharmaceutical and cosmetic applications. It shows advantage due to the surface properties of droplets covered by solid particles and the possible controlled drug release through the barrier of solid particles present

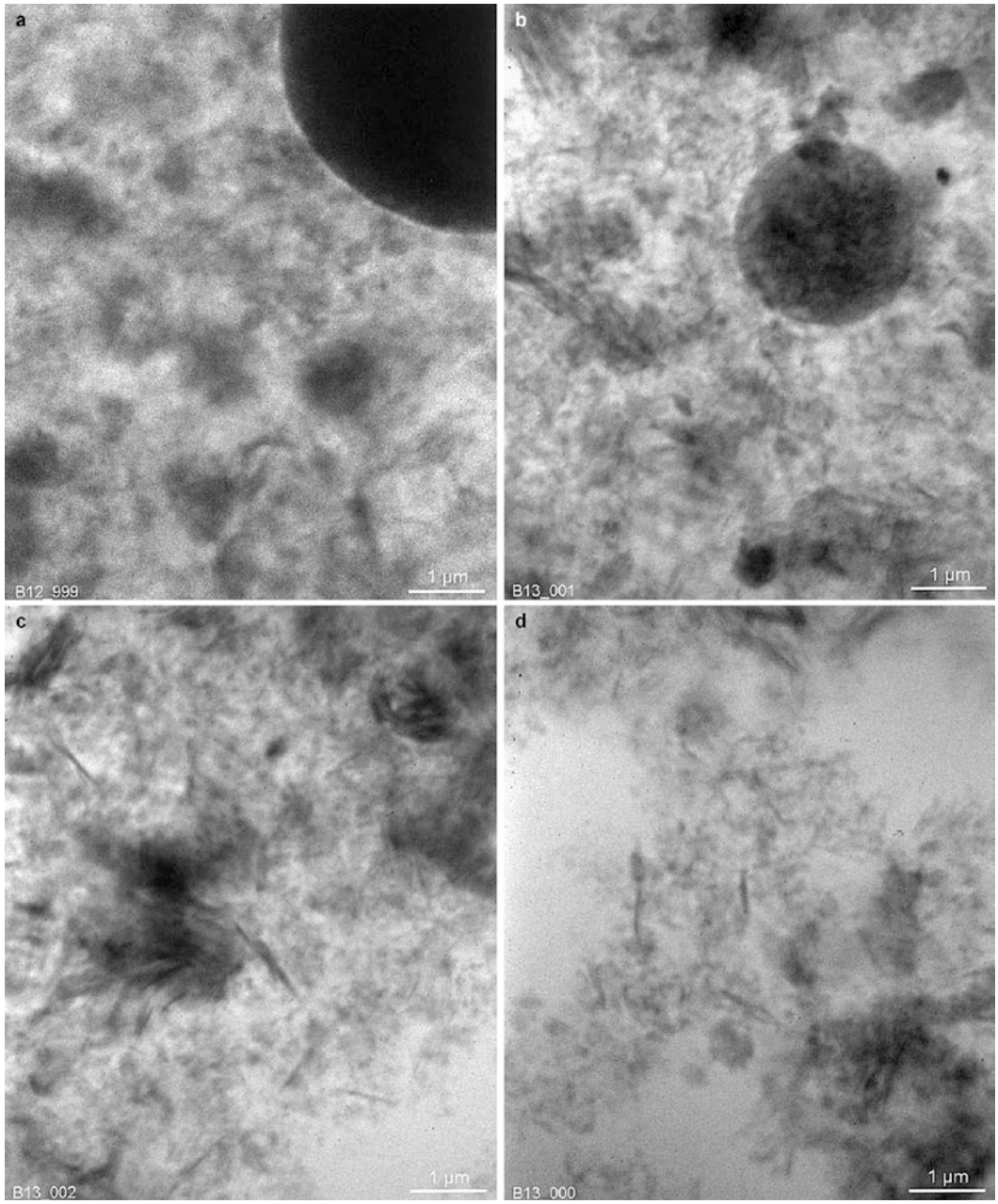


**Fig. 19.3** X-ray microscopy images of o/w Pickering emulsion stabilized by mixed montmorillonite and layered double hydroxide particles that underwent heterocoagulation. A continuous network of aggregated particles is seen in the continuous phase, as well as entrapped oil droplets appearing as large black circles. Montmorillonite particles appear as platelets and layered double hydroxide appear as particles of nearly spherical shape (Thieme et al. (1999), with permission)

at the surface of droplets. An important benefit for cosmetic applications is the surfactant-free character of these emulsions which enables the avoidance of irritancy caused by surfactants. Skin delivery of drugs by Pickering emulsions has been approached in comparative investigations of Pickering and surfactant-based emulsions by several groups as reported in the following.

Pickering emulsions behave as penetration enhancers in some instances where the skin permeation of a drug loaded inside the droplets of a Pickering emulsion was faster than for a conventional emulsion or a homogeneous solution. Although the mechanism of accelerated transport is not clearly established yet, it is quite obvious that Pickering emulsions do not behave as classical penetration enhancers that increase the permeability of the stratum corneum by fluidization of the intercellular lipids. Pickering emulsions cause a faster permeation in some instances. They may also cause accumulation of drugs inside the stratum corneum. In conclusion, there are definite differences with respect to surfactant-based emulsions. Such effects are discussed in the following as being a generalized penetration enhancement behavior.

### 19.3.1 O/W Pickering Emulsions

Skin penetration of a hydrophobic drug, all-trans retinol, from o/w Pickering emulsions has been compared to the penetration from a classical surfactant-based emulsion (Frelichowska 2009b). For the comparison to make sense, the fundamental properties of both emulsions were set identical: the two emulsions had the same chemical composition, but the stabilizing ingredients were different (either solid particles or surfactant molecules), and they had the same droplet size and the same viscosity. The purpose was to investigate the influence of the droplet coating composed of solid particles better than comparing a Pickering emulsion to an emulsion taken from a commercial product.

Owing to its high lipophilic character ($\log P_{\text{octanol}} = 5.68$), the main part of retinol remains stored in the lipidic medium of stratum corneum. As consequence, permeation is negligible for both Pickering and classical emulsions. Accumulated amounts of retinol have been measured in the skin layers of excised pig skin after 24 h exposure to o/w Pickering and classical emulsions of medium chain triglycerides loaded with 0.1 % retinol and a solution in oil as reference. The skin penetration from emulsions was much larger than from the solution. A significant contribution to faster absorption from classical emulsion has often been ascribed to the penetration enhancer action of the emulsifiers (Brinon et al. 1998; Montenegro et al. 2008; Otto et al. 2009). Such an effect cannot hold for Pickering emulsions. That a surfactant-free emulsion causes high penetration rate casts doubts on the role of emulsifiers as the origin of improved skin penetration from conventional emulsions. The total amounts of retinol found in the skin were identical for both emulsions, but the distribution of retinol along the various skin layers showed large differences. Thus, retinol absorbed from the Pickering emulsion was strongly retained in the stratum corneum, and it consequently reached the viable epidermis and dermis to a lesser extent in comparison to the surfactant-based emulsion. Tape-stripping experiments have shown that storage of retinol in stratum corneum took place especially in its outermost layers when Pickering emulsion was used (Fig. 19.4).

A very similar investigation of skin delivery of retinol has been carried out independently at the same time from a medium chain triglycerides emulsion stabilized by mixed particle/surfactant (fumed silica nanoparticles + either anionic soybean lecithin or cationic oleylamine) (Ghouchi Eskandar et al. 2009). Interestingly, similar conclusions were reached although the stabilizing system of the Pickering emulsion was different. Retinol was accumulated in the outermost layers of the skin. The in-depth distribution of retinol in the skin was measured by cutting the skin into several horizontal 100 μm thick slices that were analyzed for their retinol content. A full comparison with the study by Frelichowska et al. (2009b) is difficult because of the low in-depth spatial resolution of the method based on parallel slicing compared to that of tape stripping (Touitou et al. 1998). Thus, the first slice containing the largest amount of retinol included the full stratum corneum and a large part of the viable epidermis. The "Pickering" emulsions were basically surfactant-based emulsions to which silica was added, so that it is difficult to conceive the relative contribution of solid particles and surfactant molecules. The skin absorption was larger than in the study by Frelichowska et al. (2009b) pertaining to true Pickering emulsions (free of surfactant); in particular, the second and third slices corresponding to 100–300 μm depth contained

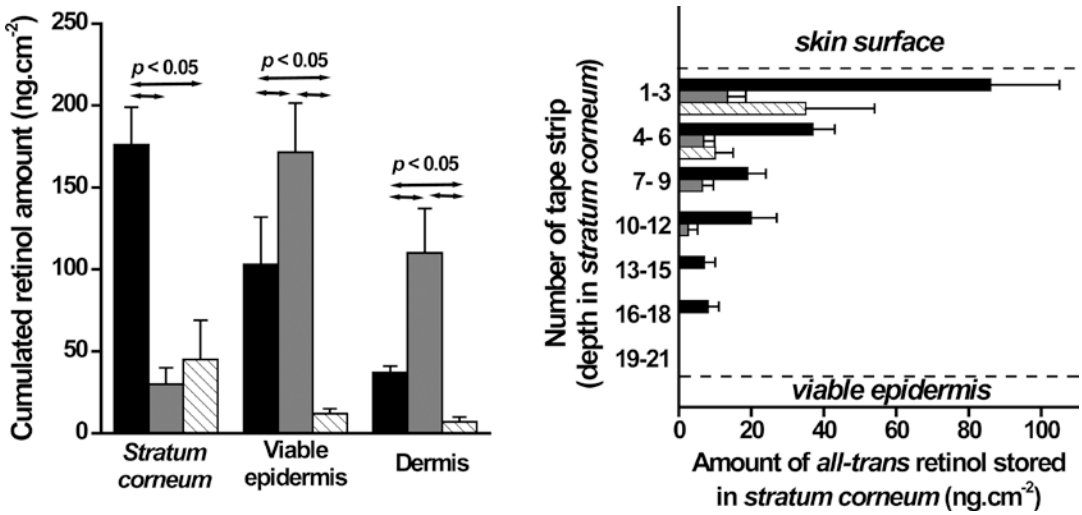


**Fig. 19.4** Distribution of retinol in skin layers after 24 h exposure to Pickering emulsion (*black*), classical emulsion (*gray*), and solution in medium chain triglycerides (*dashed*). *Left*: Cumulated amount in stratum corneum, viable epidermis, and dermis (applied dose = 400,000 ng·cm$^{-2}$). *Right*: Distribution inside the stratum corneum obtained by the tape-stripping technique

large amounts of retinol. Such differences with respect to surfactant-free Pickering emulsions were probably caused by the penetration-enhancing action of the surfactants (especially the oleyl-chained oleylamine) present at a fairly high concentration (1 % for 10 % oil content). Indeed the infrared spectrum of stratum corneum lipids was altered by the presence of the oleylamine surfactant in the emulsion. The presence of silica particles significantly increased the absorption of retinol with respect to the silica-free emulsion (only surfactant-based). Silica could be considered as a penetration enhancer in such systems or silica acted in synergy with the surfactants, which showed definite difference with the surfactant-free Pickering emulsions.

Accelerated skin absorption of drugs has recently been shown for o/w Pickering emulsions loaded with molecules of medium polarity. The steady-state permeation flux of methyl salicylate (log$P$=2.5) loaded in a Pickering emulsion was twice higher than the aqueous solution (Marku et al. 2012). The permeation and accumulation inside skin of the fluorescent probe acridine orange 10-nonyl bromide (AONB) was enhanced by the presence of silica particles adsorbed at the surface of an o/w emulsion stabilized by the lecithin emulsifier (Ghouchi Eskandar et al. 2010). AONB loaded in the lecithin-stabilized emulsion was mainly retained in the stratum corneum, whereas its penetration was deeper in the epidermis when loaded in the emulsion stabilized by mixed silica/lecithin. However, the effects of solid particles were hardly perceptible in the same experiments performed with oleylamine as emulsifier instead of lecithin. Two effects explain this result: loading of the cationic AONB inside oil droplets was low because of the electrostatic repulsions with oleylamine emulsifier, and the strong penetration-enhancing effect of oleylamine screened the possible effect of the presence of solid particles.

As summary, accumulation inside the stratum corneum and less penetration to the deeper skin layers has been observed for the highly hydrophobic retinol. This is not a general phenomenon however. Less hydrophobic drugs loaded in o/w Pickering emulsion showed also accelerated penetration to the dermis and permeation into receiver compartment.

### 19.3.2 W/O Pickering Emulsions

Skin delivery of a hydrophilic drug, caffeine, from a w/o Pickering emulsion has been studied in the same way as the retinol absorption from

o/w emulsions. Permeation of caffeine was measured from a Pickering emulsion compared to a surfactant-based emulsion having the same chemical composition (but the stabilizing layer being composed of emulsifier molecules instead of silica nanoparticles), the same droplet size, and the same viscosity (Frelichowska et al. 2009c). Results of the in vitro drug diffusion through excised pig skin revealed a higher transdermal flux of caffeine through excised skin (Fig. 19.5). Such higher permeation in an in vitro experiment suggests that a larger delivery to the deep dermis and hypodermis would occur with regard to application to full skin in vivo. A higher concentration in the dermis correlates with the larger permeation.

### 19.3.3 Mechanisms of Enhanced Skin Absorption

The origin of the faster penetration has mainly been discussed by Frelichowska (2009c) for the skin absorption of caffeine from w/o Pickering emulsions. Several transport phenomena have been considered; experiments have been performed in order to evaluate their relative contributions and finally disclose the main origin of the faster permeation through the skin. The different pathways of the drug molecule from the emulsion droplets to the deep skin layers are considered.

The first step is drug release from inside the emulsion droplets to the surrounding medium; the release behavior is often referred to as the bioavailability. Since the dense coating of solid particles around the emulsion droplets efficiently stabilizes the emulsion with respect to emulsifier-based emulsions, it is presumed that such layer acts as a barrier to diffusion of molecules. The Pickering emulsion droplets may behave as an encapsulation system that delays the release of drugs to the continuous phase. Experimental evidence of sustained release has been given for particular o/w emulsions made of cross-linked polydimethylsiloxane coated with adsorbed silica particles (Simovic and Prestidge 2007). Sustained release of caffeine from w/o emulsion droplets to a bulk aqueous phase has been indeed measured by Frelichowska (2009c). Transfer of the drug from Pickering emulsion droplets to the aqueous phase was slowed down by a factor 1.5 with respect to the emulsifier-based emulsion.

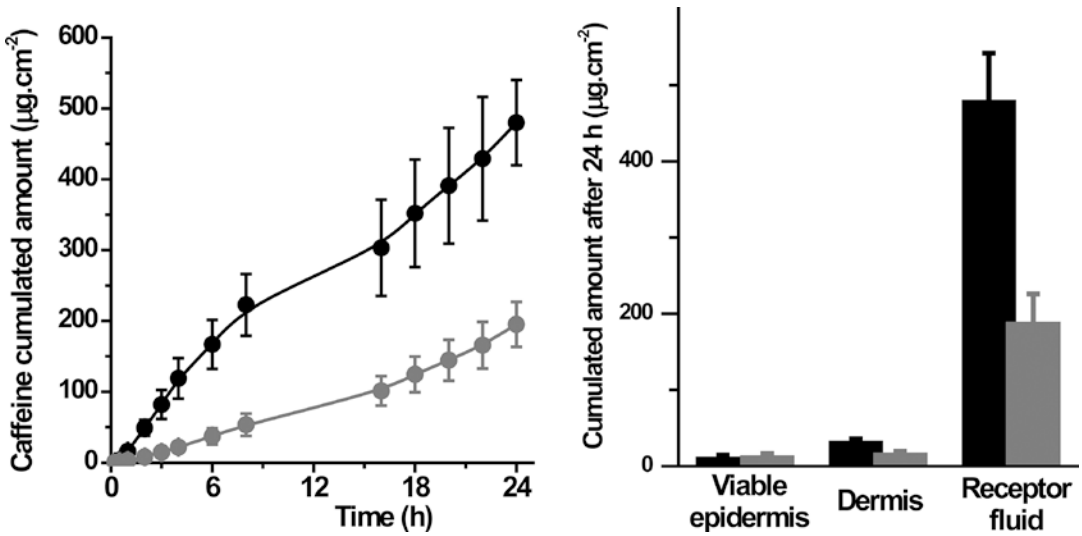


**Fig. 19.5** Skin absorption of caffeine from w/o emulsions: Pickering emulsion (*black*) and classical emulsion (*gray*). *Left*: Permeation profile over 24 h exposure to different emulsions. *Right*: Distribution of caffeine inside skin layers after 24 h exposure to different emulsions (applied dose = 3,000 µg.cm$^{-2}$)

Permeation of the drug through the skin should have been slower accordingly; on the contrary, it has been measured to be faster.

The direct transfer of drug molecules from emulsion droplets to the skin surface appeared the most relevant contribution to the accelerated permeation of caffeine. Such direct transfer occurs when droplets come in contact with the skin surface. Stronger adhesion of the w/o Pickering emulsion droplets to the skin has been disclosed from measurements of adhesion energy of water drops to the skin surface immersed in an oil medium. Thus, the adhesion energy was 3.3 $J \cdot m^{-2}$ for drops covered with silica particles ("Pickering drops") emulsions against 0.27 $J \cdot m^{-2}$ for drops from emulsifier-coated drops (and 3.3 $J \cdot m^{-2}$ for bare drops). Higher adhesion energy meant a longer contact time of the water droplets to the skin surface, and consequently a faster transfer of the caffeine molecules contained in water droplets to the skin. According to such mechanism of transfer during the contact of droplets with the skin surface, emulsion droplets are not considered as carriers, and no penetration of emulsions droplets into the skin is involved. It is believed that emulsion droplets cannot penetrate the skin as intact particles. Accelerated transfer of the drug from the emulsion droplets to the skin overcompensates the encapsulation-like sustained release of caffeine into the continuous phase, as well as the possible penetration-enhancing effect of the emulsifier contained in the classical emulsion, so that the overall effect is an acceleration of the drug delivery by Pickering emulsions.

Penetration of silica particles into the skin gives a possible supplementary transport mechanism for the drug. Indeed, the polar caffeine molecule may adsorb at the surface of silica particles that penetrate the nonpolar medium of the stratum corneum. Penetration of silica particles is limited however as discussed in the next section. The depth of penetration of silica particles upon 24 h exposure to a Pickering emulsion was 5 μm, that is, half of the thickness of the stratum corneum. Therefore, the contribution of this phenomenon is limited.

For the o/w emulsions, storage of silica particles in the stratum corneum may be the origin of a higher storage of retinol in the stratum corneum. Indeed retinol probably adsorbs at the surface of silica particles in the lipidic medium of stratum corneum in the same way as fatty alcohols do in nonpolar organic solvents. The larger storage of retinol in the stratum corneum after exposure of the skin to the o/w Pickering emulsion may result from such adsorption of the drug to silica particles that do not penetrate deeper. In case where silica particles penetrate the skin deeper, the transport of drug adsorbed to silica particles may occur. Such situation was claimed by Ghouchi Eskandar et al. (2010) on the basis of a correlation between concentration profiles of fluorescent penetrant molecule and silica nanoparticles measured from confocal fluorescence microscopy and SEM on histological transversal sections, respectively.

Easier direct transfer from emulsion droplets to the skin may also be operative as in the case of w/o Pickering emulsions. Indeed, it should compensate the penetration-enhancing activity of the surfactant in the classical emulsion taken as reference, so that the total amounts of absorbed retinol measured for Pickering and classical emulsions are the same. Although the mechanism of improved transfer coming from a higher adhesion of emulsion droplets has not been studied for o/w emulsions, this phenomenon is likely operating in the same way as for w/o emulsions. This holds for o/w Pickering emulsions loaded with drugs of medium polarity that are able to permeate through the skin (Ghouchi Eskandar et al. 2010; Marku et al. 2012).

The measurement of the adhesion energy of emulsion droplets to the skin surface can be performed quite easily taking macroscopic drops as mimicking the emulsion droplets (Frelichowska 2009c). The size of macroscopic drops is ~1,000 times larger than the size of emulsion droplets. The adhesion energy of a droplet deposited on a (skin) surface is

$$E_{\text{Adhesion}} = \gamma_{\text{w-o}} \left(1 + \cos\theta_{\text{w}}\right) \qquad (19.3)$$

where $\gamma_{\text{w-o}}$ is the interfacial tension between oil and water in the presence of either solid particles or surfactant molecules and $\theta_{\text{w}}$ is the contact

angle of the drop of dispersed phase deposited on the (flat and smooth) skin surface immersed in the continuous phase. Both $\gamma_{w\text{-}o}$ and $\theta_w$ can be easily measured with the standard laboratory equipment (drop shape analysis tensiometer).

### 19.3.4 Fate of the Stabilizing Solid Particles

The deep skin penetration of solid particles may be considered as an issue regarding possible health concerns of nanoparticles. Such topic has been largely addressed concerning inorganic particles used in sunscreen formulations, titanium dioxide, and zinc oxide (Mavon et al. 2007; Nohynek at al. 2008; Bolzinger et al. 2011). There is a wealth of experimental data showing that such inorganic particles do not penetrate the skin deeply and that their penetration is restricted to the stratum corneum upon reasonable exposure durations (hours to days). The same trend has been observed for silica particles used for the stabilization of Pickering emulsions. Figure 19.6 shows scanning electron microscopy (SEM) pictures of corneocytes collected by means of tape stripping after 24 h exposure of the skin to a w/o Pickering emulsion. Silica particles are readily visible at the surface of corneocytes; their abundance decreases as a function of the skin depth

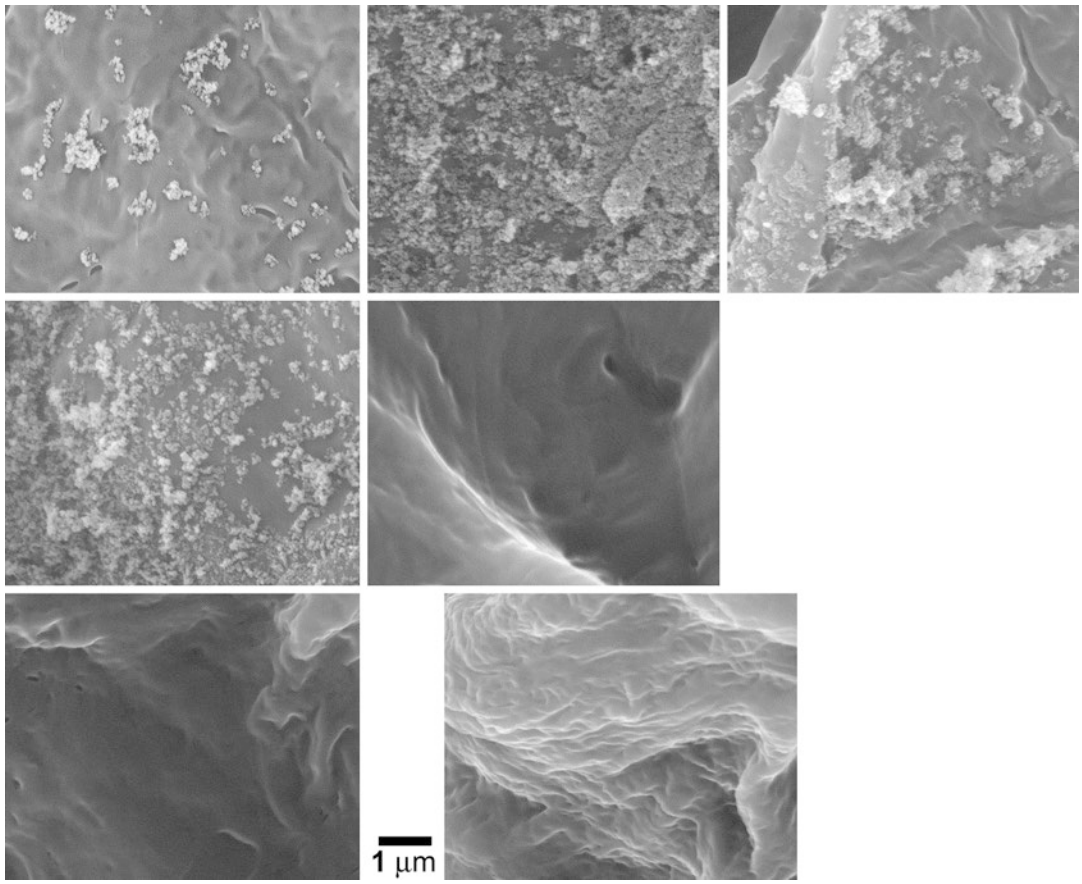


**Fig. 19.6** SEM pictures of corneocytes peeled off the stratum corneum by the tape-stripping technique after 24 h exposure to Pickering emulsion. A less amount of silica particles is observed upon going deeper into the stratum corneum; no more particles are detected beyond the 10th strip corresponding to half the thickness of stratum corneum. From *top* to *bottom*: skin surface, 1st, 7th, 10th (2 pictures), 15th, and 19th strip

and no more silica particles have been detected beyond the 10th strip corresponding to 5 μm skin depth (half of the stratum corneum thickness).

Ghouchi Eskandar et al. (2010) reached the same conclusion from observations of histological sections of the skin. Silica particles appeared as white areas in SEM pictures under backscattered electron detection. The images revealed a uniformly white layer corresponding to the stratum corneum that contained a high amount of silica, and several white spots dispersed at random in the viable epidermis and dermis. The amount in the stratum corneum was obviously much higher than the cumulated amounts in the deeper layers of skin. Unfortunately, the quantitative analysis of silicon by EDX has been averaged over the whole histological section, so that a quantitative assessment of the fractions of silica in the stratum corneum and viable layers of skin was not available. Their measurements are particularly interesting because in their studies drug penetration was favored by other ingredients of the formulation that acted as penetration enhancers. The stabilizing layer was made of mixed surfactants and solid particles, so that the solid particles might have penetrated easier because of the penetration-enhancing properties of the surfactant, in particular oleylamine, which acts as a penetration enhancer.

Alternatives to inorganic nanoparticles are biodegradable organic particles. Biodegradable Pickering emulsions are attractive for skin delivery applications, as well as for other fields such as food applications, development of emulsifier-free environmentally sustainable formulations, etc. Several types of such particles can stabilize Pickering emulsions of edible or biodegradable oils: fat crystals (Rousseau 2000), cellulose (Kalashnikova et al. 2011, 2012), chitin (Tzoumakia et al. 2011), or block copolymer micelles (Laredj-Bourezg et al. 2012).

### Conclusions

Solid particles can be advantageously used as emulsifiers for the stabilization of Pickering emulsions. They also influence the skin absorption of drugs loaded inside the droplets of dispersed phase. The parameters allowing the control of the emulsion properties and skin absorption pertain to both the formulation (choice of the ingredients and their concentration) and the emulsification process. The physicochemical properties of the skin surface are such that Pickering emulsion droplets show strong adhesion to the skin, thus allowing faster transfer of drugs to the skin. The penetration-enhancing activity of Pickering emulsions mainly relies on this adhesion phenomenon. Other phenomena specific to Pickering emulsions modulate skin absorption, even if they are not sensu stricto penetration enhancer actions: lower bioavailability due to sustained release and penetration of solid particles inside the stratum corneum causing immobilization of adsorbed drug molecules.

Manufacture of Pickering emulsions can be easily implemented since the replacement of classical emulsifiers by solid particles is quite a direct substitution, and fabrication process is the same as for conventional emulsions.

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