Recent Developments in Pickering Emulsions for Biomedical Applications

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Abstract
Pickering emulsions, stabilised by organic or inorganic particles, offer long-term dispersibility of liquid droplets and resistance to coalescence. The versatility of stabilising particles and their ability to encapsulate and release cargo with high internal payload capacity makes them attractive in a wide variety of applications, ranging from catalysis to the cosmetic and food industry. While these properties make them an equally promising material platform for pharmaceutical and clinical applications, the development of Pickering emulsions for healthcare is still in its infancy. Herein, we summarise and discuss recent progress in the development of Pickering emulsions for biomedical applications, probing their design for passive diffusion-based release as well as stimuli-responsive destabilisation. We further comment on challenges and future directions of this exciting and rapidly expanding area of research.

1. Introduction
Emulsion-based systems have been applied for several decades in a wide variety of fields, from drug delivery and pharmaceutics to cosmetics and the food industry, thanks to their relative ease of formulation for poorly soluble drugs and other substances. Pickering emulsions, first described in the early 1900s,[1,2] are stabilised by solid particles rather than surfactants and can offer a plethora of advantages over traditional emulsions, including increased stability against solvent coalescence, lower toxicity, and added functionality, derived from the properties of the stabilising particles themselves.

Pickering emulsions stabilise the interface between two immiscible liquids by using solid nanoparticles, which reduce the interfacial energy of the system to produce a stable emulsion. Which of the two classes of emulsion that can be formed, water-in-oil (W/O) or oil-in-water (O/W), is determined by the wettability of the particles, as described by the Young equation and three-phase contact angle, θ.[3] Stable Pickering emulsions are generally formed when the contact angle is close to 90°. Particles with moderately hydrophilic surfaces tend to form O/W emulsions (due to θ<90°), whereas slightly hydrophobic particles form W/O emulsions (where θ>90°). If the affinity of the particles is too pronounced, the droplet will not be stabilised, resulting in a break-up of the emulsion and dispersion of the particles in the phase with the greatest wettability. The stability of Pickering emulsions is also dependent on the particle size, shape and concentration. These aspects are described thoroughly in a number of excellent review articles and therefore will not be discussed in detail in this article.[3–8]

Pickering emulsions have been applied in a number of areas of research and industrial importance, such as food manufacturing, cosmetics, agrochemicals and therapeutic delivery. Their popularity in biomedical applications (*i.e.* for use in healthcare, such as therapeutics, diagnostics or imaging), in particular, has increased dramatically in recent years, thanks to their high stability, capacity for superior cargo loading compared to conventional systems, and diverse range of stabilising particles, creating a broad library of available building blocks. For biomedical and pharmaceutical application, the choice of emulsifier is critical; it must be biocompatible, non-toxic, and be able to be excreted from the body (if necessary). In this article, we will review the latest developments in the design and application of Pickering emulsions for biomedicine, with a focus on stimuli-responsive Pickering emulsions as a route to the triggered release of a payload towards advanced therapeutic delivery strategies. Within this discussion, we will describe systems which have been applied in proof of concept and *in vitro* assessments and emphasise areas of potential future development.

2. Pickering Emulsions in Biomedical Applications

The unique potential of Pickering emulsions may be most evident in applications such as delivery of therapeutics and medical imaging,[9] due to their stability, high payload capacity, and potential for bespoke modification, particularly through the exploitation of the properties of the stabilising nanoparticles themselves. Emulsifiers for biomedical Pickering emulsions are typically based on inorganic or organic particles, such as silica (SiO_2) or magnesium hydroxide,[10–13] or polymer-based systems including poly lactic-*co*-glycolic acid (PLGA), poly(*N*-isopropylacrylamide) (pNIPAM), polystyrene (PS), or poly(methyl methacrylate) (PMMA). [14,15] More recently, there has been a drive to implement naturally-occurring polysaccharides, for example cellulose, starch, chitosan, or alginic acid, whose biocompatibility, non-toxic properties, and biodegradability are attractive for the development of biologically relevant Pickering emulsions.[16–19]

There are a number of challenges associated with implementing Pickering emulsions in biomedical applications, typically associated with the physiological environments they are likely encounter en route to their target sites. For example, penetration of topical formulations face the difficulties of skin permeation; orally applied systems will encounter high pH, enzyme concentrations and microbes in the oral and gastrointestinal (GI) tract which could affect their structural integrity; and (often) large Pickering emulsion droplet sizes may pose problematic in intravenous delivery. These obstacles must be considered at the design stage of Pickering emulsions to ensure they remain relevant and robust for potential clinical application.

A related challenge lies in preventing premature release of cargo from Pickering emulsion formulations. Some stabilising particles themselves have been directly linked to early release of cargo, often due to their porosity and structure.[20–23] Small (bio)molecules such as active pharmaceutical ingredients (APIs) can become entangled within the polymer chains (of polymer-based Pickering emulsions or microcapsules) or remain adsorbed on external emulsion surfaces, resulting in early ‘burst’ release.[20,22,23] Such issues can, of course, be avoided through judicious washing, or modification of components. Strategies such as increasing the shell thickness, cross-linking or solidification of the Pickering emulsion surfaces, or using a combination of particles for droplet stabilisation, can prevent untimely

cargo leakage.[21,23,24] There are, therefore, a number of considerations in the design of a successful therapeutic Pickering emulsion formulation.

2.1 Therapeutic Delivery using Pickering Emulsions

For the delivery of therapeutics, the emulsion stability is crucial with respect to the shelf life of the product and avoidance of systemic exposure in order to minimise side-effects. As a result, the majority of Pickering emulsions rely on therapeutic diffusion based delivery or distribution following emulsion destabilisation through degradation, for example in the low pH of the stomach. There are a number of routes for therapeutic delivery which have been explored and within these, significant modification of design principles must be used in order to develop effective delivery systems.

2.1.1 Topical Application

The topical administration of therapeutics involves local application to external surfaces such as skin or mucosa. Topical formulations are traditionally gels, creams, ointments, foams, aerosols, or lotions and their appeal stems from their ease of application by the end user (rather than requiring clinician application), local therapeutic effect and minimal adverse systemic side effects. For such agents to be successful, they must penetrate the epidermis, which can act as a barrier to the delivery of many impermeable therapeutics, and provide effective and sustained drug release. The adhesive ability and degree of penetration of a topically applied therapeutic is dependent on the product formulation itself. This remains the largest challenge in the development of dermally-applied Pickering emulsion systems, requiring significant development of the carrier system for effective function. Within this, careful consideration must also be given to ensuring that any formulation does not cause side effects, such as skin irritation or dermatitis. Pickering emulsions offer an interesting route to improving dermal drug permeation, since their formulation allows the incorporation of penetration-enhancing molecules, alongside their stability and high payload capacity.[6]

Pioneering work by Chevalier and co-workers demonstrated the first example of W/O silica particle-based Pickering emulsions for the transdermal delivery of caffeine.[10] Compared to a traditional classical surfactant-stabilised emulsion, this Pickering emulsion showed a 3-fold higher transdermal permeation rate. This was related to improved adhesion of the Pickering emulsions to the skin surface, as well as deep skin penetration of the stabilising silica nanoparticles, leading to enhanced drug release. Subsequent work on O/W Pickering emulsions demonstrated their capability for targeting different, in particular deeper, skin layers due to their slow release capacity.[11] More recent work has shown that the choice of formulation emulsifier and oil can affect the permeability of the Pickering emulsions, its depth of penetration within the skin, and accumulation of particles, therefore affecting drug efficacy.[18–20] For example, using oils such as glycerol and evening primrose as permeation promoters, Wang *et al.* observed increased therapeutic delivery which they related to the structural distortion of the *stratum corneum* skin layer by the oils.[20] Hu *et al*. further validated this idea, establishing that the structure of the oil was critical not only for the stability of the Pickering emulsion, but also for controlling depth of penetration and accumulation within skin.[18] Oils containing ring-structures allowed the highest permeation through the skin, with linear chain oils showing the highest skin retention. This again indicates that careful choice of Pickering emulsion formulations allow regulation of the skin target site, an important consideration in topical applications.

The topical application of Pickering emulsions can be beneficial not only for direct therapeutic delivery, but also for skin decontamination, as has recently been demonstrated by Salerno *et al.*, who developed Pickering emulsions for the removal of the chemical warfare agent VX.[12] In this case, the Pickering emulsion containing a warfare scavenging agent exhibited higher efficiency in the removal of the toxin than the scavenging agent alone. This was attributed to the strong adhesion of the emulsifiers to the skin surface, which aided in transfer of the chemical warfare agent from the skin to the oil phase of the Pickering emulsion (Figure 1a). Other recent work has used chitosan based Pickering emulsions as a method to enhance wound healing, where the synergistic effect of the cargo therapeutic and other components of the Pickering emulsion demonstrated improved functioning compared to the drug alone.[16] Another innovative topical application of Pickering emulsions is for sunscreens,[25,26] where the emulsifying particles can be physical UV filters in combination with an encapsulated active agent, such as melatonin.[27] Such formulations can present a stable and effective sunscreen with the added benefit of protection against oxidative stress, thanks to melatonin's free radical scavenger and antioxidant activity.[27] Silica particle-stabilised emulsions containing a dissolved UV filter have also recently been demonstrated to produce effective sunscreen films due to evaporation-induced effects.[26] Their unique combination of volatile and involatile components allows the UV filter to remain soluble throughout evaporation, maintaining excellent sun protection. These emulsion films offer advantages over solution sunscreen films, thanks to reduced film shrinking, which circumvents potential loss of sun protection.

These diverse applications of Pickering emulsions showcase their varied potential applications in topical biomedicine, with clear synergistic enhancements compared to traditional topical formulations. Increased activity and efficacy of the Pickering emulsions in these applications is linked directly to the design of the particulate emulsifier agents. These particles often demonstrate enhanced adhesion, resulting in increased skin adhesion and hence improved delivery efficacy, avoiding the requirement for chemical penetration enhancers. Such increased delivery efficiency, coupled with long shelf life and recent advances in the use of biocompatible and biodegradable emulsifiers,[14] exemplify the unique benefits of Pickering-based systems over traditional topical designs and offer an exciting new direction in topical formulations.

2.1.2 Oral Application

Orally applied therapeutics offer obvious opportunities to treat internal organs, in particular in the GI tract, and their ease of application makes them highly desirable. Oral application does, however, pose unique challenges due to the systemic distribution of a drug after entering the GI tract and subsequently the blood stream, which can result in unwanted interactions with receptors, tissues and organs, causing undesirable, and potentially dangerous side effects. Unpredictable adsorption from uncontrollable degradation by oral enzymes, microbe environments, and/or stomach acid additionally means that medicines often require a structural barrier or preservative such as an enteric coating, a challenge which is also pertinent to the use of Pickering emulsions for oral delivery routes. On the other hand, exploitation of the pH and enzymatic environments that a formulation will encounter during ingestion can facilitate the development of formulations whose release is enhanced by, or even relies on, these environments, for example, initiating release of an active pharmaceutical specifically in the oral or gastro-cavity.

Pickering emulsions designed on this basis promise advantages over traditional (enteric) coating methods, based on their high surface areas and bespoke surface functionality. Cossu *et al.*, for example, developed starch-based Pickering emulsion formulations for the treatment of oral infections of *C. albicans* with sensitivity to the oral enzyme *α*-amylase.[17] These O/W Pickering emulsions demulsified in response to the addition of *α*-amylase due to the enzymatic digestion of starch, initiating the controlled-release of the encapsulated active anti-fungal therapeutics thymol and amphotericin B. In a related effort, Sy *et al.* exploited the acidity of the GI tract for controlled destabilisation and cargo release of O/W Pickering emulsions based on the dissolution of the emulsifying $Mg(OH)_2$ particles at low pH.[28]

These tactics rely on the response of the emulsifier to the external environment to destabilise and release the therapeutic encapsulated in the Pickering emulsion. An alternative route has recently been described which exploits the therapeutic agent itself as the emulsifier.[29] The drug silybin, used to treat liver damage, has poor water solubility and bioavailability, however, silybin nanocrystals, which adsorb at the oil-water interface, have been demonstrated to behave as both an emulsion stabiliser and an active therapeutic. High drug release (compared to silybin alone) occurs due to the partial dissolution of the drug into the oil phase of the Pickering emulsion, leading to ready release and high efficacy. This is attributed to the formation of lipid-like drug solutions which interact with endogenous solubilising species (for example phospholipids, cholesterol or bile salts) and promote transfer into the aqueous phase for improved bioavailability. Careful choice of the stabilising particle therefore has the opportunity to transform the efficacy of Pickering emulsions.

2.1.3 Parenteral Application

Pickering emulsions further offer potential for parenteral applications, such as intramuscular, intravenous, and subcutaneous routes. As with oral applications, parenteral administration is systemic, therefore, enhancing the targeting ability of a formulation is beneficial to reduce undesirable side effects. Exploiting targeting agents has recently shown enhanced efficacy of W/O Pickering emulsions of oxaliplatin, a liver tumour chemotherapeutic, and Lipiodol stabilised with biodegradable PLGA particles, designed for intravenous delivery.[30] Key to this work was the targeting ability of the Lipiodol, an oil-based radio-opaque contrast agent which shows preferential tumour uptake. In comparison to conventional W/O emulsions, sustained release of the chemotherapeutic was observed in combination with reduced systemic exposure. Due to the reduced toxicity to non-diseased organs, these findings could lead to an extension of the therapeutic window, *i.e.* the ability to increase chemotherapy doses without the usual associated systemic side effects, which would be of vast importance in future patient therapies.

A challenge associated with intravenous formulations is designing their controlled, sustained release, which can significantly lower systemic exposure to non-target organs, and aids in significant release of the therapeutic at the target site. Neufeld and co-workers have been working on such slow-release systems for a number of years,[31,32] most recently preparing W/O Pickering emulsions stabilised by glycerol monostearate for the delivery of an anti-cancer therapeutic oseltamivir phosphate which targets mammalian neuraminidase 1 involved in multistage tumorigenesis in a number of cancer types.[33] Efficient encapsulation of the active drug into the Pickering emulsions provided a stable formulation with slow-release properties, however the excellent stability led overall to only a low fraction of the active compound being released. The addition of a surfactant to the system, in this case sorbitan monooleate,

facilitated increased therapeutic release as a result of surfactant adsorption onto emulsifier particle surfaces. This altered their wetting behaviour and stimulated emulsion destabilisation. Sustained drug release was observed over a 30-day period, increasing the therapeutic effect against pancreatic cancer cells. Further work in this area to enable tight control over the duration of the therapeutic release could offer a unique opportunity for future patient treatments.

In an alternative, but related subcutaneous delivery application, Pickering emulsions have very recently been explored as adjuvants towards new vaccine formulations.[34] PLGA-stabilised Pickering emulsions with immobilised antigens produced by Xia *et al.* provided the force-dependent deformation and mobility necessary to enable multivalent interactions with antigen-presenting cells, enhancing cellular internalisation of the emulsion droplets (Figure 1b). These properties provided significant advantages over conventional emulsions, with enhanced antigen binding, uptake and activation making this a potent adjuvant for vaccine delivery with enormous potential. Similar sustained delivery of vaccine antigens has been observed using polymeric bioresorbable amphiphiles as emulsifying agents for W/O systems, enhancing vaccine efficacy.[35]

Whilst parenteral application of Pickering emulsions clearly shows strong promise, enabling targeting and sustained release, a major challenge is the physical construct of the formulation itself. Pickering emulsion droplets can be relatively large (up to several microns in size), which may prove problematic for effective delivery, and evasion of the mononuclear phagocytic system (MPS).[36] The subsequent biodistribution of such emulsions, as well as their breakdown products (*i.e.* stabilising particles following demulsification/dissolution) also require careful consideration. It has been noted that the shape and size of injected particles can have an effect on their biodistribution and accumulation within organs.[37] This is rarely mentioned in articles describing Pickering emulsions for therapeutic delivery in the literature, but it is a sizeable problem for translation to the clinic, and should be afforded more consideration in future investigations.

2.2 Pickering Emulsions in Biosensing and Bioseparation

Pickering emulsions can additionally be used for biorecognition and bioseparation by harnessing molecular imprinting technology. This technique traditionally uses polymeric matrices to design materials (molecularly imprinted polymers, MIP) capable of molecular recognition with strong binding affinities and high selectivity towards a (bio)molecule of interest, mimicking natural recognition systems such as antibodies and biological receptors.[38,39] Whilst already an established field, there are some reservations surrounding MIP generated though polymerisation, as the generated polymers often have limited control over the chain length, resulting in irregular morphologies or shapes.[40] Pickering emulsion polymerisation, on the other hand, where polymers are formed within the emulsion internal phase, typically generates polymers with controlled and well-defined lengths thanks to their regulation by the emulsion droplet size.[40] A variety of different biomolecules and chemicals have been imprinted in this way, facilitating targeting of proteins,[41] steroids,[42] bacteria,[43] and APIs.[40] A recent interesting application of Pickering emulsion enabled MIP is shown in the work of Hajizadeh *et al*., who developed MIP immobilised in cyrogels for the capture and purification of haemoglobin Hb protein from cell homogenate suspension and non-purified red blood cells lysate.[24] This work demonstrated clear advantages over traditional immobilisation strategies, with the Pickering emulsion-formed MIP exhibiting high binding

capacity and enhanced selectivity towards Hb proteins as a result of excellent accessibility of the active MIP groups. This bioseparation behaviour of MIPs formed using Pickering emulsions has been demonstrated in a number of other works, demonstrating the utility of Pickering emulsions in diverse biomedical applications.[21,44]

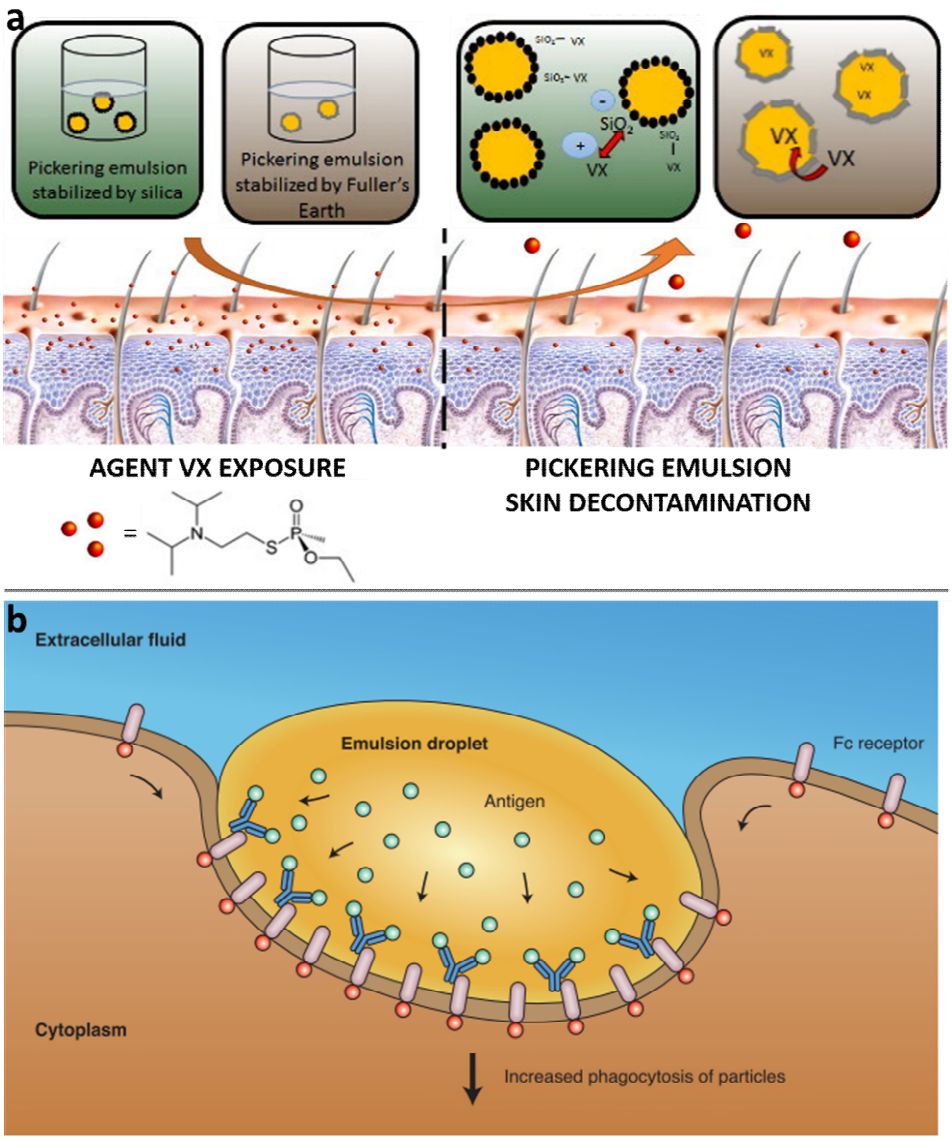

Figure 1. Examples of the use of Pickering emulsions in different therapeutic delivery approaches: a) Schematic showing the topical application of Pickering emulsions for skin decontamination with enhanced scavenging and removal of a chemical warfare agent due to migration into the oil phase and electrostatic interactions; image adapted, with permission, from Elsevier copyright 2016.[12] b) Schematic showing a Pickering emulsion adjuvant system with enhanced cell delivery of an antigen (green sphere). Increased contact of the emulsion droplet with the cell surface, due to shape deformation, facilitates antigen-antibody (blue "Y" symbol) binding at the interface (Fc receptor-mediated process), boosting cellular internalisation of the emulsion droplets; image adapted with permission from Nature Publishing Group copyright 2018.[34,45]

3. Stimuli-responsive Pickering Emulsions

Conceptually, it is evident that colloidal stability and stimuli-induced demulsification are key to the controlled release of cargo. All of the Pickering emulsion based delivery systems described thus far have been relatively stable systems, which rely on slow diffusion-based release or known exposure to specific environments (such as low pH stomach acid or enzymes) to allow destruction and hence therapeutic 'escape' from the stable emulsions. However, the concept of a Pickering emulsion that remains stable until the application of an external trigger, offers opportunities to control therapeutic delivery directly at the disease site.[46] This could increase efficacy, reduce overall required doses and potentially diminish side effects – of enormous benefit to the patient.

Tissues, organs and cells are precision machines, and small changes in their microenvironment and behaviour can be indicative of the presence of diseased tissues and tumours. For example, certain enzymes are well-known to be linked with specific disease pathologies, including stroke, cardiovascular or neurodegenerative inflammatory responses and cerebral ischemia;[47] metal ions play vital roles in a number of important signalling pathways in the body, with changes in concentrations being indicative of diseases such as Alzheimer's (increased Zn^{2+} levels);[48] pH can also be monitored in the detection of ischemia or metabolic disorders.[49] The presence or variation of such species has previously been exploited in order to produce useful biomedical systems, such as therapeutic delivery from nanoparticles as well as diagnostic imaging agents,[46,50] however Pickering emulsions possessing this responsive capability have been less widely probed.

The design of Pickering emulsions which can be manipulated by the use of external stimuli has received increasing attention in recent years, with examples of droplet destabilisation in response to pH, salt concentrations, chemical or biological entities, temperature, light, shear, microfluidic collision, electric and magnetic stimuli.[9,51–57] In general terms, a transformation in the emulsifier upon exposure to a stimulus can result in a change in the emulsion stability. This transformation may distort the size of the particle, forcing it to swell or shrink; or initiate phase inversion due to a change in emulsifier wettability; or cause complete demulsification and disassembly of the emulsion (which can be reversible or irreversible). Stimuli-responsive Pickering emulsions have been reported for various applications in product recovery, oil recovery, and catalysis,[6] however their potential in biomedical applications has only started to emerge in the past decade.[58]

3.1 pH Responsive Pickering Emulsions

Variation of pH in different regions of the body is well known and can be a useful indicator of the presence of disease. Malignant tumours present with pH ranging from 6.8 to 7.2, and the presence of hypoxia, tumour growth and metastases are generally indicated by regions of greater acidity than blood and healthy tissue.[59] pH changes can therefore prove useful for triggered therapeutic release directly at a site of disease and is one of the most popularly probed release mechanisms in stimuli-responsive Pickering emulsions.

For the purposes of drug delivery *via* this stimulus, it is important to ensure the stability of the Pickering emulsion at physiological pH, with the cargo stably encapsulated until release at the desired pH trigger location.[46] Traditionally, highly charged small molecules or surfactants are employed to stabilise the surface of the emulsifying nanoparticle in a physiologically relevant pH range through electrostatic interactions.[60–63] Variation in pH subsequently

breaks these electrostatic interactions through protonation/deprotonation, leading to demulsification due to changes in particle wettability and subsequent cargo release. The same principles of triggered demulsification due to changes in electrostatic stabilisation and wettability can be exploited with the use of polymer-grafted inorganic nanoparticle emulsifiers.[64,65] Phase inversion can be observed with carefully-designed long-chain polymeric emulsifiers, such as polyurethanes or amphiphilic Janus particles.[66,67] In all these systems, care must be taken to ensure the species employed are biocompatible, and do not cause irritation, or unsought responses.

Biocompatible materials including polysaccharides like chitosan,[68,69] soy peptides,[70] lignin[71] and alginic acid[72,73] show excellent potential as emulsifiers and emulsifier-modification agents in stimuli-responsive Pickering emulsions. This is due to the abundance of pH-responsive functional groups in their structures, such as amines, hydroxyls, and carbonyls, which can cross-link and dissociate or decompose accordingly to stabilise or destabilise the emulsion systems.[74] The future of pH-responsive systems may lie within combining natural polymers and inorganic materials to form so-called double Pickering emulsion systems comprising multiple components, each capable of tailored and controllable release of different therapeutics systematically. Recent efforts towards this by Guo *et al*., have used graphene oxide (GO), polylactic acid (PLA), and hydroxyapatite (HA) to construct core@shell@shell GO@PLA@HA colloidosomes as a multistage drug-release system. This multi-component system was prepared *via* the double Pickering emulsion method and microcapsules were formed following volatile solvent escape from the initial droplets. The materials within the composites were chosen for their biocompatibility and differing surface chemistry which permits drugs of differing hydrophobicity (rose Bengal, coumarin and 5-fluorouracil) to be encapsulated (Figure 2a).[51] The pH-sensitivity of the HA outer shell, which undergoes acid degradation, enabled controlled drug release of this multicomponent system, with efficient drug release at pH 5.0. The multi-layer system additionally facilitated staged and sustained release of the different drug components, as the emulsion degraded. This example of a solidification of a double Pickering emulsion system shows exceptional promise and inspiration can be taken for the next generation of drug-delivery carriers, where multi-drug systems can increase therapeutic efficacy, in particular for efficient tumour therapy.

One of the most important considerations in the development of pH-responsive Pickering emulsions is the sensitivity and pH range of the release mechanism. The pH environment within the body that a formulation may encounter varies dramatically between organs, blood, tumour or infection sites. This necessitates that designed formulations remain stable across a wide pH range and only exhibit a narrow well-defined pH-responsive window, such that their triggered release occurs only at the desired site. While many of the systems described herein demonstrate stability over a relatively wide pH range, and release at a specific pH range, it remains unclear how robust and narrow the pH window remains under physiological conditions. More work is required before any translation to *in vivo* studies could be considered.

3.2 Photoresponsive Pickering Emulsions

Premature release can be a major issue associated with exploiting internal biological markers as a trigger for Pickering emulsion destabilisation and therapeutic release. A great deal of research has hence focussed on the use of stimuli which can be controlled *ex situ* by an end user or clinician.[75] Light-based clinical treatments are already popular, for example the use of near-infrared (NIR) radiation in photothermal therapy (PTT) for the treatment of cancer[76]

and photodynamic therapy (PDT) in the treatment of skin cancer and dermatological issues such as acne, cutaneous infections, or inflammatory disorders.[77] The benefit of these stem for the precise placement of the light source, minimising exposure and hence side effects, although poor tissue penetration means that the utility of such treatments can be limited.

Light-responsive Pickering emulsions for biomedical applications are a steadily expanding area of research, although only a handful have been described in recent years. Similarly to the pH-responsive systems, their mechanism of release follows light-irradiation triggered changes in emulsifier particle wettability, leading to Pickering emulsion inversion[78–80] or coalescence.[52,81] Changes in wettability are again proffered by the surface modification of the stabilising particle. The optically sensitive molecule spiropyran (which undergoes a conformational change with light irradiation), when associated with silica particles, for example, produces an amphiphilic system which switches from being hydrophobic to hydrophilic upon UV illumination, resulting in emulsion inversion.[78,79] This approach has been demonstrated to be particularly useful for biocatalysis, where inversion aids product recovery and emulsifier recycling.[79] Stenhouse adducts, an alternative class of photoactive donor-acceptor molecules, have very recently been examined as an alternative emulsifier modification route to visible light triggered inversions of Pickering emulsions.[80] Their photoactivated transition between hydrophobic to zwitterionic species efficiently and quickly alters particle wettability and is the first example exploiting these interesting compounds for cargo release, as demonstrated using model dye compounds.

Photocatalytically active materials, such as TiO_2, have clear advantages as Pickering emulsion stabilisers for the production of light-responsive systems. They rely on the formation of surface defects upon light illumination; the production of oxygen vacancies at bridging sites results in the conversion of Ti^{4+} to Ti^{3+} species which favour dissociative water adsorption, producing the necessary change in wettability to cause emulsion destabilisation.[52,81] Importantly, this triggered demulsification can be carried out using UV, NIR or visible light, when TiO_2 or N-doped TiO_2 nanocomposites are employed as emulsion stabilisers (Figure 2b).[52,81] Bai *et al.* have demonstrated this mechanism for the triggered release of an encapsulated API, astragalus polysaccharides.[52]

Despite the relatively few examples of light-actuated Pickering emulsions for biomedical applications, the potential of these systems is clear. When designing light-responsive Pickering emulsions, consideration must be taken when choosing a light source; UV light, for example, is a major contributor to skin cancer development.[82] NIR, on the other hand, has deeper biological tissue penetration and low scattering, making it a useful non-invasive clinical tool. In addition, the impact of reactive by-products, such as reactive oxygen species, on non-targeted cells must be minimal or non-existent to prevent damage to healthy cells.

3.3 Thermoresponsive Pickering Emulsions

Another approach to remote-controlled Pickering emulsion cargo release is the use of temperature. Thermal ablation is a common clinical treatment, for example in the hyperthermic treatment of cancer. Heat application is therefore readily available and can have slightly deeper tissue penetration than light irradiation. The exploitation of varying temperature within the body may be an alternative route of triggering therapeutic release; due to their increased metabolism, it is well-known that cancerous tissue locally presents with slightly elevated temperatures (40-42 °C) compared to healthy tissue (37 °C). This small thermal window has

been explored in other release and diagnostic systems and may be exploited for emulsion destabilisation.[83]

In order to achieve thermally sensitive Pickering emulsions, control over stabilising particle wettability can be harnessed through the exploitation of thermoresponsive polymers. Their functionality is typically based on a conformational transformation with changing temperature. When utilised in Pickering emulsions, this change in geometry can cause destabilisation or increased permeability, causing cargo release.[84] Poly(*N*-isopropylacrylamide), pNIPAM, is one of the most extensively used thermoresponsive polymers for biomedical applications as its conformational transition temperature is close to biological temperatures (32 °C) and it can be easily modified. Within Pickering emulsion research, pNIPAM can be used independently as the emulsifier[85] or grafted onto other materials to achieve a responsive stabilising agent.[22,84,86–88] Below the polymer transition temperature, in its hydrophilic state, Pickering emulsions remain stable, however when raised above this temperature, their hydrophobic transformation alters particle wettability and disintegrates the emulsion. This approach holds advantages due to its reversibility and the narrow temperature range and timeframe of transition.

Thermoresponsive materials are not only limited to drug delivery. Recent work by Chen *et al*., developed similar systems for biosensing/bioimaging applications.[9] In this study, carbon dots (CD) were incorporated into pNIPAM and grafted onto cellulose acetate nanocrystals (CA). It was observed that the formed composites had temperature dependent ‘on/off’ fluorescence switching behaviour. Below the transition temperature, fluorescence was turned on, however above it, fluorescence was turned off (Figure 2c).

Alternatively, thermally-responsive Pickering emulsions can be achieved through emulsifier particle grafting with a stabilising surfactant whose weak interaction with the core stabilising particle can be broken through a change in temperature. Binks and co-workers recently demonstrated this approach using silica particles stabilised with the non-ionic surfactant alkyl polyoxyethylene monododecyl ether.[89] Hydrogen bonding between the oxygen atoms of the polyoxyethylene headgroup and nanoparticle surface silanol groups facilitated adsorption and stabilisation of the emulsion at low temperatures (25 °C). Loss of hydrogen bonding and hence emulsion destabilisation occurred when the temperature was raised (45 °C). The drawback to this approach was the time taken for demulsification to occur (up to 45 mins). Although such behaviour this may reduce efficacy of stimuli-induced drug delivery at a target site, it may hold advantages in the slow release of therapeutic, of benefit for bolus-delivery.

While the potential for thermoresponsive systems is clear, issues could arise in its translation to clinic; the window in temperature difference between healthy and cancerous cells is narrow and therefore careful and precise design of the Pickering emulsion is critical to prevent destruction or contamination of healthy cells.

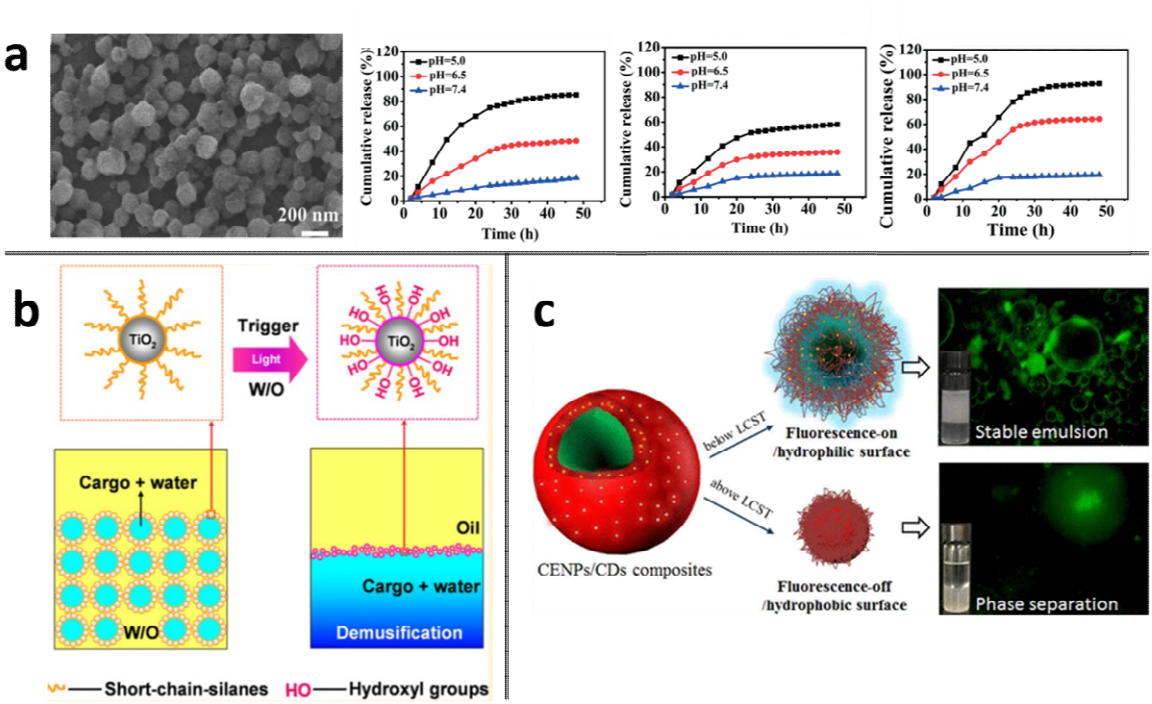

Figure 2. Examples of stimuli responsive Pickering emulsions. a) Left to right: SEM image of pH-responsive core@shell@shell GO@PLA@HA composite microcapsules formed from W/O/W Pickering emulsions and cumulative release profiles of rose Bengal, coumarin and 5-fluorouracil, respectively, from the composites containing each of the 3 drugs. Different rates of drug release were observed at different pHs, with staged and sustained release from the multi-component system; image adapted, with permission, from Wiley copyright 2017.[51] b) Light responsive destabilisation of silane-modified TiO_2 Pickering emulsions, which occurs following light irradiation as a result of increased dissociative water adsorption onto TiO_2 particle surfaces, changing wettability and destroying the stable Pickering emulsion. The use of N-doped TiO_2 particles extends light response to the visible range; image adapted, with permission, from the American Chemical Society copyright 2016.[52] c) Temperature-responsive core/shell nanospheres of cellulose acetate encapsulated by poly(*N*-isopropylacrylamide) (pNIPAM) with incorporated fluorescent carbon dots (CDs). Reversible emulsion breakage can be triggered through thermal changes, exploiting the conformational transition temperature of the pNIPAM layer. These composites exhibited fluorescence 'on/off' switching behaviour in response to thermal triggers and changes in the emulsion stability; image adapted, with permission from the American Chemical Society copyright 2018.[9]

3.4 Magnetically Responsive Pickering Emulsions

The use of magnetic materials in biomedicine has been popular for several decades, with applications as contrast agents for medical imaging as well as therapeutic delivery and bioseparation thanks to their attractive magnetic properties.[90,91] Within Pickering emulsions, inorganic magnetic nanoparticles have been explored as emulsifier agents, most commonly with the aim of producing systems whose direction and motion can be controlled using an externally applied magnetic field whilst maintaining the integrity of the Pickering emulsion.[92–94] Such species are promising for magnetic targeting to enhance drug release at a specific site whilst minimising systemic exposure,[93] though little work has shown practical demonstrations of this behaviour *in vitro* or *in vivo*. An interesting application of magnetic particle-stabilised Pickering emulsions is for scavenging and removal of unwanted

species. Lee and co-workers showed the absorbance of a model dye compound into the aqueous phase of a magnetic Pickering emulsion, which can then be magnetically removed and recycled.[94]

The magnetic properties of the particles within magnetic Pickering emulsions may also be exploited for triggered emulsion destabilisation and cargo release. This can be through the application of an alternating magnetic field which results in heating of the particles in a manner comparable to that used in hyperthermic treatments. This approach, usually combined with a thermoresponsive polymer, relies on destabilisation of the Pickering emulsion by wettability changes dictated by the polymer's thermal transition, as described in section 3.3.[95] In fact, there are few examples of the direct effect of the application of an external magnetic field to a magnetic particle stabilised Pickering emulsion.[96] Of particular relevance to biomedicine is work by Fuller and co-workers, who observed reversible magnetically-triggered phase separation of a magnetic particle stabilised Pickering emulsion leading to emulsion destabilisation.[97] In their highly-tuned systems, the force of the movement of magnetic particles towards the magnetic field caused pressure which forced the films between droplets to thin and destabilise, removing the particles from the droplet entirely. Without a doubt, the ability to break an emulsion reproducibly using an externally applied magnetic field is extremely promising from a biomedical perspective, due to the low cost of the required magnetic systems, the depth of penetration and the fast triggering of the demulsification. This is an area which deserves further attention.

3.5 Multi-stimuli Responsive Pickering Emulsions

The future of stimuli-responsive Pickering emulsions for biomedical applications may lie within dual or multi-stimuli responsive systems, enabling controlled and staged release of therapeutics, or multi-stage biosensing, providing greater control, enhancing efficiency and selectivity. Combination (or multi-drug) anti-cancer therapy, for example, has become popular as a route to overcoming drug resistance, with ideal "cocktail therapies" capable of controlled release of each drug individually to maximise synergistic effects.[98] Acidic and mildly hyperthermic microenvironments of cancerous tissues could also be exploited as dual triggers for the targeted delivery of therapeutics directly at a site of disease. There has hence been a surge of research in the area of multi-responsive Pickering emulsions in the last 5 years for various applications, including industrially relevant processes such as catalysis and sensing.[99,100] Though promising, only a handful are directly applicable to or have been demonstrated for biomedical applications. [53,101]

A range of stimulus combinations have been investigated, such as CO_2 and light,[99] pH and light,[100] CO_2 and redox environments,[102] temperature and ionic strength,[103] pH and temperature,[104–106] pH and magnetic fields,[101,107–109] and magnetic fields and temperature.[23,110] Many systems employ emulsifiers composed of a single amphiphilic polymer with multi-functionality or co-polymer systems bearing different stimuli-sensitive groups (often based on poly(*N*-isopropylacrylamide) or poly(methyl methacrylate) species), either as a polymeric emulsifier or *via* modification of an inorganic particle.[23,99,100,105,106] These polymers undergo a conformational change in response to different stimuli, usually based on a conversion from hydrophilic to hydrophobic state leading to a change in wettability and demulsification[105] or phase inversion,[99] or alternatively result in swelling/shrinking of the emulsifying particles,[100] leading to reduced emulsion stability. A noteworthy example is the use of amphiphilic double dynamers which exploit both supramolecular and intramolecular

dynamics to provide dual pH and temperature sensitivity resulting from morphological transitions leading to emulsion destabilisation (Figure 3a).[104]

Most studies combining magnetic responsiveness allow sensitivity to some primary stimulus (*e.g.* pH), with the magnetic component additionally facilitating directional motion.[23,107,108] The group of Meng and co-workers have exploited a magnetic field to trigger emulsion coalescence and a chemical reaction only in the presence of UV light in a truly multi-responsive manner (Figure 3b).[109] Pickering emulsions formed using a dual-emulsifier system of magnetic and titania particles aggregated near to an applied magnetic field. Upon UV irradiation, water surface adsorption onto titania particles (following the mechanism described in section 3.3)[52,81] led to a change in wettability and coalescence between the aggregated neighbouring droplets. This facile approach would facilitate a reaction between two cargoes, allowing difficult, highly reactive or toxic reactions to take place in a controlled manner at a site of interest. An alternative use of magnetic particles is to harness their magnetic heating behaviour through the application of an alternating magnetic field. This was originally used over a decade ago to provide (magnetic) directionality as well as hyperthermia-generated thermal demulsification,[110] but more recently has demonstrated enhanced pH-triggered Pickering emulsion destabilisation.[101] In the presence of an alternating magnetic field, destabilisation of magnetic nanocellulose stabilised Pickering emulsions occurred at alkaline pHs, due to the dual effect of droplet deformation upon magnetisation of the emulsifier, as well as the local field-induced thermal heating effect. This caused increased particle wettability due to increased surface adsorption of water, behaviour not observed in the absence of a field.

Another interesting recent example of a multi-responsive system by Hong *et al.* describes the use of a O/W Pickering emulsion to form microcapsules with Au nanoparticles mutually connected by *α*-synuclein proteins, through the solidification of the Pickering emulsion.[53] These systems, designed to be sensitive to disease-specific physiological properties, demonstrated protease-dependent release. As a result of disruption of the *α*-synuclein-*α*-synuclein interaction, controlled cargo release was facilitated, which, in combination with light sensitivity, provided photoelectronic and photothermal effects such as localised heating of the Au-based emulsifier particles. These solid colloidosomes could hold exceptional promise towards targeted cargo-carrying Pickering emulsions capable of precise pathological site recognition, of use for future sensor and therapeutic applications.

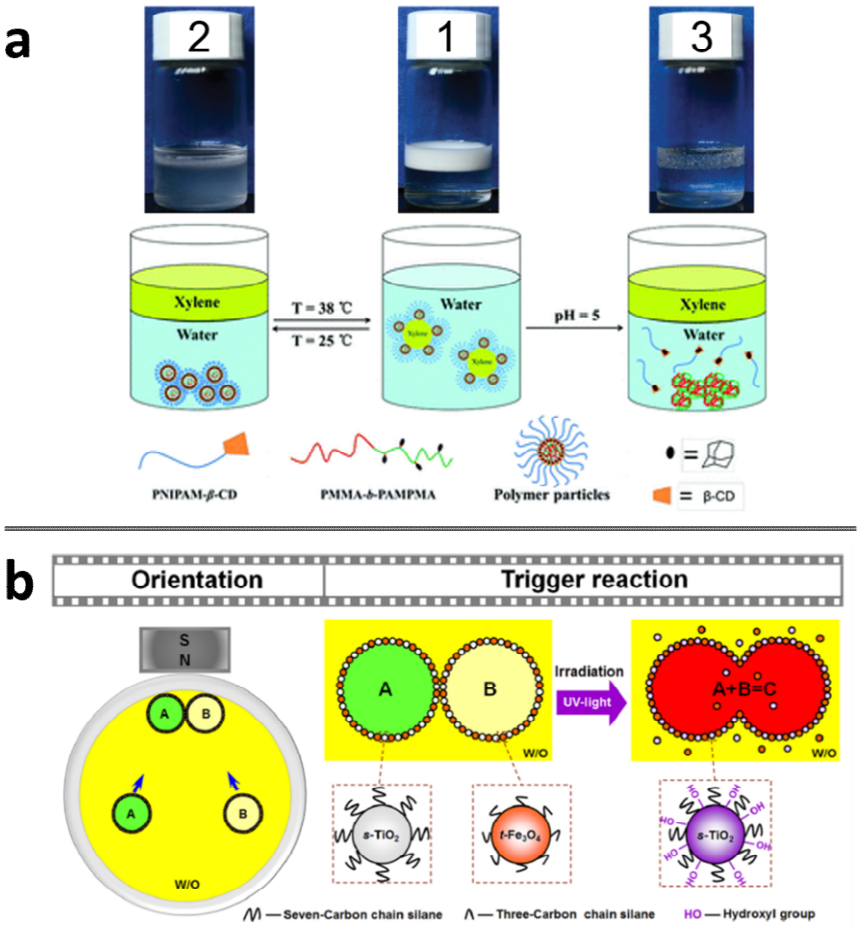

Figure 3. Examples of multi-component Pickering emulsions capable of responsiveness to multiple stimuli. a) Top panel shows photographs of an amphiphilic double dynamer stabilised Pickering emulsion (1), a broken emulsion upon thermal treatment (2) and a broken emulsion upon pH treatment (3). Photographs correspond to the behaviour shown in the schematic in the bottom panel; images adapted, with permission, from the Royal Society of Chemistry copyright 2018.[104] b) Schematic showing dual magnetic and UV responsive Pickering emulsions stabilised by magnetic and titania particles. In the left panel, orientation of stable emulsion droplets occurs alongside a magnet. In the right panels, UV-triggered coalescence and chemical reaction can occur; image adapted, with permission from the American Chemical Society copyright 2017.[109]

4. Conclusions and Future Directions

Since their first description by Pickering and Ramsden over a century ago, particle stabilised emulsions have been widely investigated for a variety of applications. Their improved biocompatibility, stability and ease of modification/tunability based on the chosen particle design, make them a favourable alternative to conventional surfactant-stabilised emulsions. Whilst Pickering emulsions are widely used in the food and cosmetics industry, advances in material design have not been widely translated to clinical applications such as biosensing and therapeutic delivery. The use of Pickering emulsions for biodelivery has been probed in the form of topical, oral and parenteral delivery formulations relying on diffusion-based therapeutic release (Figure 4a). Future research directions of this broad topic are already beginning to emerge. Recently, there have been efforts to utilise naturally occurring biodegradable and biocompatible materials. Li *et al*., for example, have developed Pickering

emulsions using combinations of corn prolamine zein and polysaccharide gum Arabic to encapsulate thymol, a natural anti-microbial agent.[111] This approach may overcome issues associated with poor biocompatibility of stabilising particles, and biodegradation may potentially facilitate sustained cargo release.

The development of stimuli-responsive Pickering emulsions is a rapidly growing field, thanks to their potential for targeted delivery directly at a site of disease and the possibility of remote control, either by a trained clinician, or through exploiting a disease's own pathology and microenvironment to trigger therapeutic delivery. This level of control could improve therapeutic efficacy and reduce side effects through decreased systemic exposure, of massive importance to the safety and well-being of patients. Stimuli-responsive Pickering emulsions can be categorised based on their sensitivity to external environments such as pH, light, temperature, magnetic fields or (bio)chemical entities, such as disease pathology-specific enzymes, proteins or acidity (Figure 4b, Tables 1 and 2). The pre-existence of clinical hardware, such as NIR for photodynamic therapy, which could be used to trigger light-stimulated Pickering emulsions, for example, could make these systems even more attractive to the pharmaceutical and clinical industry.

Further enhancement of the idea of triggered-delivery is more recently moving towards Pickering emulsions which are sensitive to a number of stimuli. The future of this area, we believe, lies in multi-component stabilising particle emulsion systems, wherein a number of different emulsifiers, each with their own independent response to a stimulus, are exploited. These would enable either staggered release from multi-shelled Pickering emulsions, or else release only at a site with the 'perfect' cocktail of stimuli. Whilst the benefits of such precise-release systems are clear, current research needs to push further to explore the full potential of these multi-responsive dynamic systems, in particular towards *in vitro* and *in vivo* behaviour. It is clear, therefore that the area of Pickering emulsions for biomedical applications has enormous potential, with a lot still to be achieved, and we should see continuing and increased activity in coming years.

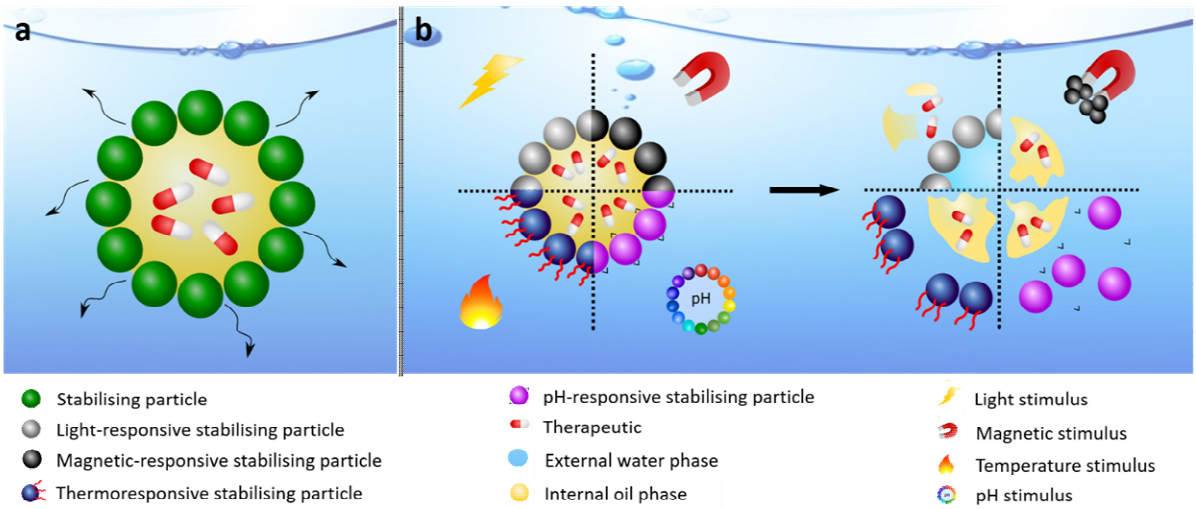

Figure 4. a) Schematic showing passive diffusion-controlled release of cargo from a Pickering emulsion. b) Schematic showing actuated release of cargo from stimuli-responsive Pickering emulsions. Clockwise: exposure to a magnetic field results in removal of magnetic nanoparticles and demulsification; alteration of pH causes a change of surface charge and wettability, destabilising the emulsions; temperature dependent conformation changes of

polymer-based Pickering emulsions result in demulsification; and irradiation of light can lead to phase inversion of the Pickering emulsion.

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Declaration of Interest
None.

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