International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Emerging Applications of Pickering Emulsions in Pharmaceutical Formulations: A Comprehensive Review

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Abstract: Over the past two decades, particle-stabilized Pickering emulsions (PEs) have emerged as a versatile platform in pharmaceutical formulations, demonstrating distinct advantages over surfactant-based systems through enhanced stability, reduced toxicity, and tunable interfacial properties. These systems exhibit unique drug delivery potential through their precisely controllable architecture, particularly in achieving spatiotemporal drug release patterns, tissue-specific targeting, and enhanced therapeutic payload encapsulation. In this review, the characteristics of PEs are first detailed, followed by an introduction to the main preparation methods and the key parameters for controlling the type, droplet size, and stability of PEs. The third section categorizes and discusses the advantages and disadvantages of various solid particles as emulsifiers. Lastly, emphasis is placed on the application of PEs in the pharmaceutical field, including functionalized designs and various administration routes to enlighten the rational design of PEs for effective drug delivery.

Keywords: Pickering emulsions, drug delivery, solid particle emulsifiers, controlled release

Introduction

Emulsions play a vital role in the pharmaceutical industry. They are widely used in drug delivery systems because they enhance the solubility of hydrophobic drugs, improve pharmacokinetics, and help reduce adverse effects. These formulations are commonly applied in oral, injectable, and topical therapies.[1] However, being thermodynamically unstable systems that disperse immiscible liquids with synthetic surfactants, emulsions have drawbacks including loss of moisture in the epidermis, skin irritation, and challenges in drug distribution and elimination.[2,3] To address these challenges, alternative stabilization approaches have been explored. Among them, Pickering emulsions (PEs), introduced by Pickering in 1907, utilize solid particles as emulsifiers, offering superior stability against droplet coalescence compared to traditional emulsions. The strategic selection of particles is essential for preparing stable PEs, which have shown promise in drug stability, encapsulation of bioactive ingredients,[4] slow-release, and targeted drug delivery. Compared with surfactants, solid particles are able to adsorb and be permanently anchored at the oil-water interface.[5] Notably, recent research has demonstrated the application of pH-responsive PEs in co-encapsulating immune checkpoint inhibitors and chemotherapeutic drugs, presenting a viable approach for oncology treatment.[6]

PEs have found diverse applications in various fields of research and industry such as pharmaceuticals, food production, cosmetics, and agrochemicals. Among these applications, their role in pharmaceutical formulations has garnered particular attention, as they offer enhanced biocompatibility, reduced toxicity, and improved control over drug release.[7] Unlike conventional surfactants, most solid particles do not typically result in significant in vivo toxicity in formulations and are generally well-tolerated by the body, making them highly suitable for various drug delivery applications. In pharmaceutical formulations, PEs not only enhance drug solubility and bioavailability but also provide sustained release and enzymatic protection, making them valuable for oral and transdermal drug delivery. Their rigid particle-stabilized interface improves skin adhesion, potentially enhancing drug penetration.[8] Additionally, in injectable

Received: 30 December 2024
Accepted: 24 April 2025
Published: 7 May 2025

formulations, PEs contribute to controlled drug release, prolonged circulation time, and targeted accumulation in tumor therapy.[9] These advantages underscore their potential in modern drug delivery systems, warranting further research into their functionalization and in vivo performance.[10–12]

This review will first summarize the properties and preparation techniques of PEs. Subsequently, the benefits and limitations of current particulate stabilizers in pharmaceutical systems will be discussed. Special attention will be given to the functional designs that endow specific properties to PEs, such as controlled drug release, targeted drug release, stimuli-responsive drug release, etc. In the end, this review will also put specific focus on the use of PEs in various administration routes, helping to address critical formulation challenges in oral, transdermal, subcutaneous, intravascular and intratumoral delivery systems.

Characteristics and Preparation of PEs

The discovery of PEs is credited to S.U. Pickering, whose publication was believed to be the first to report the stabilization of O/W emulsions by solid particles adsorbed on the surface of oil droplets. However, Pickering's findings did not gain significant attention until recently. PEs are composed of two immiscible liquids and are stabilized by either organic or inorganic solid particles. Similar to conventional emulsions, PEs can be categorized as O/W, W/O, W/W, O/O, or multi-type (such as W/O/W or O/W/O).[13–15] In PEs, the active pharmaceutical ingredient (API) can be encapsulated not only within the inner phase but also within the solid particles or attached to the particle surface or the water-oil interface. For instance, Candiani et al successfully encapsulated vitamin D3 within droplets stabilized by flaxseed meal particles.[16] It is worth noting that while most medicinal PEs are predominantly O/W, there is a diverse range of W/O/W and O/W/O PEs that have been developed. Multiple emulsions are particularly interesting for pharmaceutical applications as they allow for the co-encapsulation of three APIs: one within the internal droplets, the second within larger droplets, and the last within the particles.[17]

The robust stability of PEs has garnered significant research attention, with its stabilization mechanism primarily revolving around two main types: the interfacial film theory and the three-dimensional network mechanism. The interfacial film theory involves solid particles, such as spherical and rod-shaped nanoparticles and nanofibers, creating a dense film encasing dispersed droplets, preventing coalescence when droplets come into coalescence.[18] Furthermore, oil droplets can become ensnared within particle arrays during particle aggregation in the continuous phase, forming a three-dimensional network that restricts particle mobility and bolsters emulsion stability, exemplified by fat crystals.[19] The stability of PEs is influenced by various factors, with particle wettability being a crucial parameter for solid particles to stabilize these emulsions. For particles to be adsorbed at the interface, they need to be wetted by both liquids. The empirical Finkle's rule states that the type of emulsion depends on the relative wettability of the particles in the two liquids.[20] Hence, the wettability of particles at the oil-water interface, quantified by the contact angle, is of great importance. Hydrophilic particles with a contact angle less than 90° tend to favor the formation of oil-in-water emulsions, while hydrophobic particles with a contact angle greater than 90° prefer water-in-oil emulsions (Figure 1). Additionally, factors such as the particle size and shape, pH, external magnetic field, temperature, ionic strength, the crystallinity of the particles, and oil-water ratio can also impact the stability of PEs.[21,22] Similarly, the coverage of the surface particles, along with their wettability and concentration, also plays a critical role, as higher particle concentration and surface coverage can provide stronger interfacial resistance, thus improving stability. All these key factors that stabilize PEs are interlinked and may influence the nanoparticle wetting properties and, consequently, the obtained emulsion and its stability.[23–26]

Furthermore, the use of nanoparticles allows for the formation of PEs at the micron or even nanometer scale. For example, Chen et al successfully created nanoscale superstructures by compressing nanogels at the water-oil interface.[27] These superstructures were then used to stabilize nanodroplets loaded with paclitaxel (PTX), resulting in a slow drug release profile, enhanced cytotoxicity, and prolonged in vivo blood circulation. This innovative approach offers a versatile strategy for fabricating nanoscale superstructures with deformable nanoparticles, demonstrating the capacity of PEs in the field of nanomedicine.

PEs represent a highly stable form of emulsion, allowing for the utilization of existing surfactant-based emulsion preparation techniques. Currently, PEs are created through rotor-stator homogenization, ultrasonic emulsification, high-

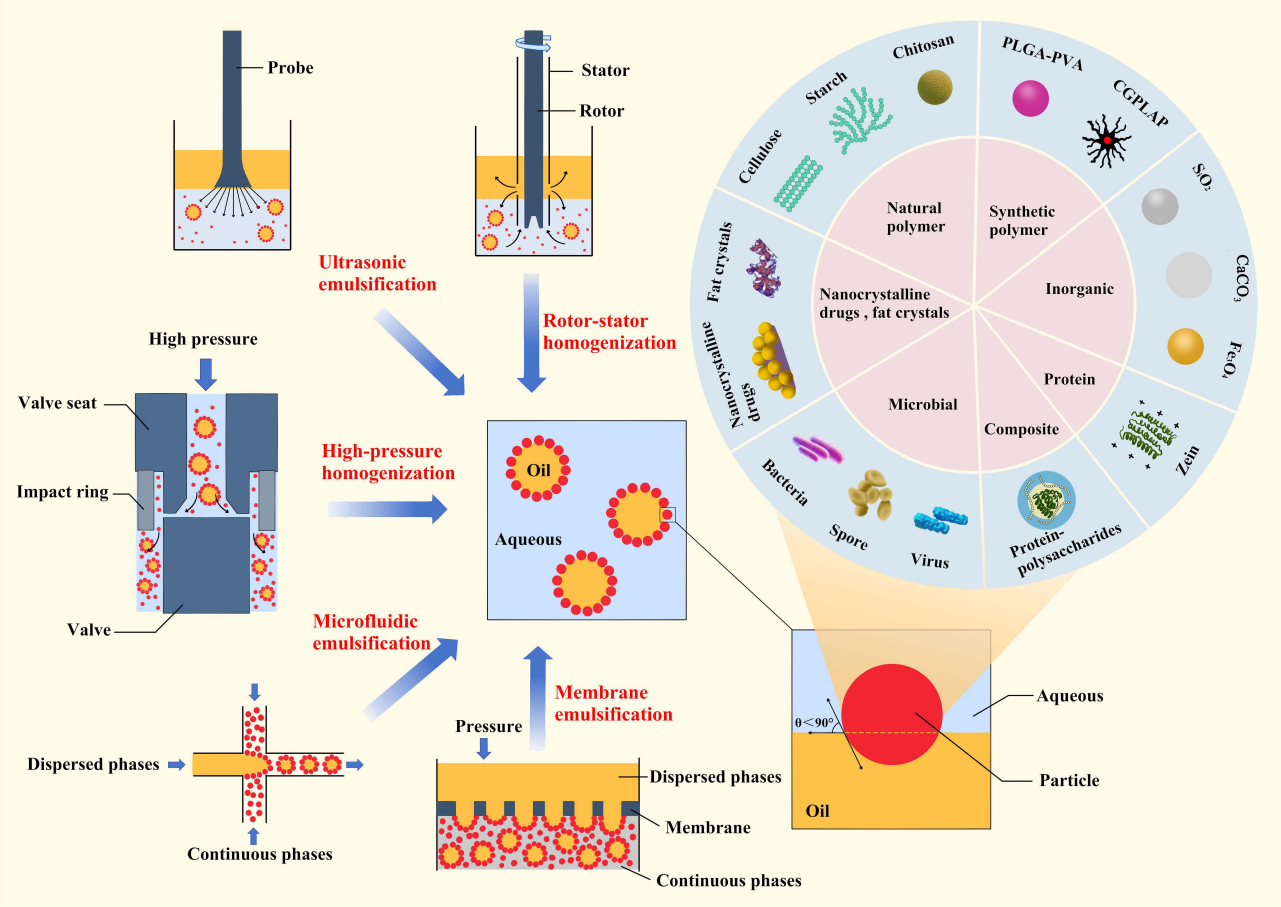

Figure 1 Schematic representation of the main preparation methods and on the micro and nano scales for O/W PEs. The figure on the right shows a fan schematic of solid particle classification.

Abbreviations: PLGA-PVA, poly(lactic-co-glycolic acid)- poly(vinyl alcohol); CGPLAP, cashew tree gum grafted with polylactide; SiO_2, silicon dioxide; $CaCO_3$, talcum carbonate; Fe_3O_4, ferric oxide.

pressure homogenization, microfluidic emulsification, and membrane emulsification (Figure 1). Among these methods, rotor-stator homogenization, ultrasonic emulsification, and high-pressure homogenization are the most commonly employed for PEs preparation. For instance, during rotor-stator homogenization, a powerful shear field is rapidly generated between the rotor and stator, resulting in the uniform dispersion of the oil and water phases along with the added particles. The droplets interact with solid particles dispersed in the system, promoting particle adsorption at the oil-water interface and contributing to the stabilization of the PEs. It should be noted that while rotor-stator homogenization is frequently used, the shear forces involved can present challenges such as particle aggregation, particle damage or excessive heating. Therefore, precise control of process parameters such as rotational speed, gap size, processing time, and particle concentration, as well as optimization of these parameters, is crucial for obtaining stable PEs with desired properties.[17] The size of PEs' droplets achieved through the mentioned techniques exhibits some degree of variation. The high pressure homogenization method enables the production of nanoscale droplets through the repetition of multiple cycles. Alternatively, the rotor-stator homogenization method achieves similar results by utilizing high-speed stirring.[28]

Solid Particle Emulsifiers

Solid particles play a vital role in PEs by decreasing oil-water interfacial tension and thus preventing droplet coalescence. Many natural organic particles, like polysaccharides, proteins, and solid lipid particles, are considered ideal materials for drug delivery using PEs. Several studies have confirmed the safety of these organic particles and their versatility for various applications, including pharmaceuticals and the food industries. Notably, starch, cellulose, alginate, albumin, and

https://doi.org/10.2147/IJN.S514928

poly(lactic-co-glycolic acid) (PLGA) are examples of organic particles that are approved for clinical use in drug delivery systems.[4,29–32] In addition, inorganic particles, fat crystals, microbial particles, and other particles shown in Solid Particle Emulsifiers are suitable for stabilizing PEs. Different types of solid particles used to stabilize PEs not only exhibit varying toxicity profiles but also significantly influence the emulsions' physical stability and drug release behavior. For instance, synthetic particles such as strongly cationic silica nanoparticles or non-degradable iron oxide particles often exhibit systemic toxicity due to prolonged tissue retention in vivo. In contrast, natural macromolecules such as proteins and bacterial derivatives tend to be more biocompatible, though they have the potential risk of eliciting immunogenicity risks.[33,34] Furthermore, the physicochemical characteristics of these particles, such as wettability, size, concentration, storage stability, and responsiveness to environmental stimuli, play a critical role in determining the overall stability of PEs. A rational selection of particle materials, properties, and concentrations is imperative when designing PEs. In fact, some formulations are engineered so that surface-bound particles can degrade, aggregate, or detach from the oil–water interface in response to internal stimuli (eg, changes in pH, redox conditions, or enzymatic activity) or external triggers (eg, light or temperature).[35–37] This controlled destabilization mechanism is harnessed to achieve stimulus-responsive drug release. Collectively, these factors underscore that the selection and design of the stabilizing particles are pivotal not only for optimizing the emulsions' stability and in vivo toxicity but also for their efficacy in targeted drug delivery.

Natural Polymer Nanoparticles

In emulsions, it is important to prevent droplets from coalescence to maintain stability. Some polysaccharides, which are natural polymers, are insoluble in both water and oil. For instance, the most representative polysaccharides such as gum Arabic, modified cellulose, and starch can be utilized to stabilize emulsions.[38] In recent years, polysaccharide-based nanoparticles have shown tremendous capacity for applications in the fields of biotechnology, pharmaceuticals, and food industries. The information detailed is succinctly presented in Table 1.

Cellulose, a widely found biopolymer, is an ideal material option due to its sustainability, biodegradability, and non-toxic nature. Cellulose nanocrystals (CNCs) and cellulose nanofibrils are the primary forms of cellulose nanoparticles.[39] CNCs, prepared by acid hydrolysis, possess a highly crystalline structure and have rod-like nanosizes. They can form a stable interfacial film at the oil-water interface, thereby maintaining the stability of the emulsion.[63] Dong et al successfully synthesized spherical cellulose nanocrystals (S-CNCs) with diameters ranging from 30 nm to 60 nm using mixed acid hydrolysis of mercerized microcrystalline cellulose combined with ultrasonic treatment.[39] The PEs' droplets stabilized by S-CNCs showed remarkable stability across a wide range of pH, ionic strength, and temperature variations. Consequently, the utilization of S-CNCs as novel stabilizers for PEs presents promising opportunities in the fields of biomedical, cosmetic, and food applications. Furthermore, bacterial cellulose nanocrystals (BCNs) proved to be another promising emulsifier for the preparation of stable oil-in -water PEs.[40] Bacterial cellulose (BC) can be further purified with sodium hydroxide to yield a form of BC with an endotoxin value below 20 endotoxin units, meeting the acceptable range for implant applications as defined by the US Food and Drug Administration. This suggests that BCNs may be suitable for intravenous applications.[64] However, the wider application of nanocellulose-based PEs is hindered by safety concerns, and there is a lack of established protocols for evaluating the immunotoxicity, genotoxicity, and nutrient absorption associated with these emulsions. Additionally, the lack of standardized nanocellulose products, the limited number of manufacturers, and high production costs pose significant challenges.[65]

Starch, the second most abundant natural polymer after cellulose, finds extensive usage in the food and pharmaceutical industries.[66] The inherent hydrophilic structure of natural starch granules restricts their ability to effectively stabilize the oil-water interface. Consequently, chemical modifications were performed to enhance their hydrophobic properties, thereby facilitating improved adsorption at the oil-water interface.[67] One commonly used modification method is the application of octenyl succinic anhydride (OSA). For instance, Wang et al conducted a study in which enzymatically branched glutinous maize and potato starch were recrystallized to form starch globule crystals.[42] These crystals were then modified with OSA to increase their hydrophobicity, ultimately serving as emulsifiers for the preparation of PEs. The researchers discovered that the resulting octenyl succinate starch spherocrystals played a role in protecting the stability of encapsulants and slowing down lipid oxidation. This

Table 1 Examples of PEs Stabilized by Solid Particles

Particles			Emulsion			References
Composition		**Shape**	**Types**	**Droplet size**	**Emulsification Method**	
Natural polymer nanoparticles	Cellulose nanocrystals	Spherical	O /W	≈32.17–32.83 μm	Ultrasonic pulverization (30%, 3min)	Dong et al, 2021[39]
	Bacterial cellulose nanocrystals	Needle-like	O /W	≈4 μm	Ultrasonic device (2 W/mL, 20s)	Kalashnikova et al, 2011[40]
	Microfibrillated cellulose	Fiber	O /W	≈28.44–29.10 μm	High-pressure homogenizer (pre-emulsion high-speed homogenizer)	Bouhoute et al, 2021[41]
	Starch globule crystals modified with OSA	Spherical	O /W	≈1-50 μm	High-pressure homogenizer (300 bar) (pre-emulsion high-speed homogenizer)	Wang et al, 2017[42]
	Butyric acid -modified porous starch	Spherical	O/W	≈15-30 μm	Homogenizer (18000 r/min, 120 s)	Ma et al, 2023[43]
	Chitosan nanoparticles	–	O/W	–	Sonicated (0.2 kW, 3min)	Alehosseini et al, 2021[44]
	Lignosulfonate nanoparticles	Spherical	O/W	≈2-18 μm	Ultrasonic Homogenizer (160W, 1min)	Shomali et al, 2022[45]
	Alkaline lignin-graft-PNIPAM copolymer nanoparticles	Spherical	O/W	≈180-200 μm	Sonicator (50%, 30s)	Dai et al, 2019[46]
Synthetic polymer nanoparticles	Cashew tree gum grafted with polylactide	–	O/W	≈1-3.5 μm	Spontaneous emulsification	Richter et al, 2018[47]
	Plga	Spherical	W/O	≈25 μm	Three-way stop cock	Deschamps et al, 2019[48]
Inorganic nanoparticles	SiO_2 nanoparticles	Spherical	O/W	≈60 μm	Rotor-stator homogenizer (14,000 rpm, 6 min)	Heidari et al, 2022[49]
	Phosphatidylcholine-kaolinites	Octahedral	O/W	–	High-shear homogenizer (8000rpm, 30s)	Tang et al, 2019[50]
	Pbs quantum dots	Spherical	O/W	≈0.5–10 μm	Homogenizer	Huang et al, 2022[51]
	Titania (tio_2) and iron oxide (Fe_3O_4) nanoparticles	Spherical	W/O	≈100 μm	Ultrasonic Vibration Processor (200 W, 3 min)	Xie et al, 2017[52]
Protein nanoparticles	Recombinant oil bodies protein nanoparticles	Spherical	O/W	≈10 μm	High-pressure homogenizer (100bar,5 cycles) (pre-emulsion high-speed blender)	Sun et al, 2023[53]
	Groel-derived protein nano-ring	Ring-like	O/W	≈200-400 nm	Ultrasound equipment (40%, 2min)	Xu et al, 2020[54]
	Sodium caseinate-modified zein nanoparticles	Spherical	O/W	≈10-50 μm	A high-speed homogenizer (12000rpm, 2min)	Feng et al, 2016[55]

(*Continued*)

Table 1 (Continued).

Particles			Emulsion			References
Composition		**Shape**	**Types**	**Droplet size**	**Emulsification Method**	
Nanocrystalline drugs, fat crystals	Curcumin nanocrystalline	Spherical	O/W	≈156.88–170.44 nm	A high-pressure homogenizer (800 bar, 50 cycles)	Wang et al, 2023[56]
	Diacylglycerol-based solid lipid nanoparticles	Spherical	W/O	≈20 μm	A rotor-stator homogenizer (10000 rpm, 2min)	Li et al, 2021[57]
Microbial nanoparticles	Tobacco mosaic virus-like nanorods	Rod-like	O/W	≈2-8 μm	Shaken by hand (2 min)	Wang et al, 2017[58]
	Ganoderma lucidum spores particles	Oval	O/W	≈60-70 μm	A Branson digital 450 W Sonifier (50%, 20min)	Zhu et al, 2019[59]
	Baker's yeast and lactic acid bacteria	Spherical and rod-like	O/W	≈30-100 μm	Vortexing or impeller-type mixing	Firoozmand et al, 2016[60]
Composite particles	Cellulose nanofibrils modified by soy protein isolate nanoparticles	Spherical and fiber	O/W	≈10-40 μm	Homogenized (16000rpm, 2min)	Zhang et al, 2019[61]
	Fe_3O_4 cellulose nanocrystal	Rod-like	O /W	≈7.5 μm	Ultrasound (60W, 3min) (pre-emulsion high-speed homogenizer)	Low et al, 2019[62]

https://doi.org/10.2147/IJN.S514928

finding contributes to our current understanding of emulsifiers for edible particles. To address the inherent limitations of OSA modification, Ma et al successfully synthesized butyric acid (BA)-modified porous starch (PS) with varying degrees of substitution.[43] Through an esterification reaction, BA-PS with high degree of substitution can effectively stabilize the encapsulation of PTX in PEs, significantly enhancing emulsification and PTX retardation capabilities. This suggests that BA-PS has the capacity to be utilized as an emulsifier for slow-release drug delivery. Furthermore, there is still ample room for exploration in the application and development of environmentally friendly methods for producing starch granules to stabilize PEs.[68]

Chitosan is derived from chitin through deacetylation in the presence of hot alkali, and it possesses remarkable properties such as biocompatibility, biodegradability, mucous adhesion, and low toxicity.[69] In comparison to traditional emulsions, PEs incorporating chitosan enhance the bioavailability of various compounds. The stability of the PEs can be achieved through the use of self-aggregated chitosan particles,[70] chitosan nanocrystals (also known as chitosan whiskers, nanowhiskers, or rod-shaped chitosan), or complexes of chitosan with proteins[71,72] such as corn protein or gelatin.[73] As an example, Alehosseini et al tried to explore the PEs based on chitosan nanoparticles (CSNPs) as food-grade delivery systems for d-limonene, which is a bioactive compound.[44] If they are able to provide data related to the in vivo safety studies of the obtained emulsion, the stable PEs of CSNPs holds promise for application in the delivery of active drug nanoparticles.

Moreover, both lignin and agarose (agarose microgels)[74] are natural polymers. Lignin, a phenolic polymer, creates a three-dimensional network structure in the cell wall.[75] Lignin has extensive applications in packaging materials, hydrogels, and even as a carrier for bioactive substances like enzymes and drugs.[76] Nevertheless, the limited solubility and dispersibility of structurally diverse lignin pose challenges for its advancements in the realm of green energy and materials. Consequently, diverse approaches must be employed to improve its properties. For instance, Shomali et al utilized carboxylated lignosulfonate with different grafted alkyl side chains to synthesize lignosulfonate nanoparticles (LNPs).[45] By adjusting the length of the alkyl chains, the resulting LNPs exhibited a higher affinity to the oil-water interface. As a result, a green, environmentally friendly, and simple water-based acid precipitation process was employed to obtain emulsions with smaller and more stable droplet sizes. In addition, Zhang et al have reported a green and simple method for the production of LNPs using beet alkaloid and lactic acid deep eutectic solvent through water droplet-induced self-assembly, which effectively addresses the issue of environmentally unfriendly organic solvents.[76] Moreover, Dai et al have developed a novel multi-functional PEs stabilized by LNPs to enhance the stability and thermal-controlled release of trans-resveratrol.[46] The research findings suggest that LNPs-based PEs hold great capacity in the storage and thermal-controlled release of light-unstable and poorly water-soluble drugs.

While certain natural substances such as proteins or polysaccharides are utilized in the formulation of these emulsions, the resultant particles typically exhibit polydispersity, instability, or excessive hydrophilicity, rendering them inadequate for emulsion stabilization. Indeed, the challenges associated with quality control of natural materials, influenced by factors like production locale and processing parameters, further complicate matters.[77] Consequently, research pertaining to PEs in pharmaceutical applications warrants further exploration.

Synthetic Polymer Nanoparticles

Biodegradable polymer particles have garnered attention specially in the field of drug delivery due to their reduced toxicity, ability to control drug release kinetics, and enhanced biocompatibility.[78] Biodegradable polymers comprise synthetic polymers like polylactic acid (PLA), and polyglycolic acid, as well as their copolymers, such as PLGA, and polycaprolactone.[17] For instance, to enhance Amphotericin B (AmB) oral bioavailability and control drug release, Richter et al first reported the utilization of self-assembled cashew gum grafted with PLA nanoparticles, obtained through nano-precipitation, to obtain stable AmB-loaded PEs through spontaneous emulsification.[47] Biodegradable particles made of PLGA offer the advantages of biocompatibility and rapid clearance from the body, which can help prevent inflammatory reactions due to accumulation. In a separate study, Deschamps et al employed a simple emulsification technique using two connected syringes to incorporate PLGA nanoparticles into the aqueous phase, resulting in the formation of an oil-in-water lipiodol emulsion with an average droplet size of

approximately 40 μm, which is comparable to the diameter of blood vessels near tumors.[48] They loaded doxorubicin (DOX) into the internal phase and found that complete release of DOX from the stable lipiodol emulsion required up to 10 days, demonstrating the capacity of these solid particle-stabilized emulsions for efficient encapsulation and sustained release of chemotherapy drugs for the treatment of tumors. In line with prior research, in vitro experiments have revealed that PLGA nanoparticles exhibit no discernible toxicity until reaching relatively high concentrations of 3 mg/mL.[79] However, the toxicity of PLGA up to 3 mg/mL needs further exploration, because stabilization of PEs requires larger concentrations of solid particles than this. Notably, in a significantly dynamic physiological environment, the interaction between nanoparticles and cellular components would occur at a reduced concentration level necessitating continuous fluid replenishment, thereby mitigating the risk of cytotoxic effects.[48] As a result, more in-depth studies on toxicity tests including genotoxicity assay are needed, which hold significance for use in the injectable administration of chemotherapeutic drug.[80]

Inorganic Nanoparticles

Inorganic solid particles commonly employed for the preparation of PEs comprise SiO_2, TiO_2, ZnO, $CaCO_3$, Fe_3O_4,[81] carbon nanotubes, kaolin, quantum dots (QD), and various modified inorganic solid particles. Extensive research has demonstrated that modified solid particles can enhance the stability of PEs and regulate their demulsification.[82] Silica nanoparticles, also known as nano-silica, are extensively utilized owing to their cost-effectiveness, favorable biocompatibility, low in vivo toxicity, and antibacterial properties. Therefore, SiO_2 is a frequently utilized material in the synthesis of PEs.[83] For example, Heidari et al employed the Taguchi approach to modify SiO_2 nanoparticles using cetyltrimethylammonium bromide to stabilize PEs, making them bioactive compounds delivery system.[49] In the study by Tang et al, natural kaolinite was modified to prepare phosphatidylcholine-kaolinite and used to stabilize PEs encapsulating curcumin (Cur).[50] The resulting PEs were effectively absorbed by cells, non-toxic, and biocompatible, and they could completely release Cur in the intestines to improve the bioavailability of Cur. These findings may contribute to the effective encapsulation of lipophilic food or drugs in PEs to enhance their bioavailability. Some inorganic particles also exhibit characteristics of responsiveness to external stimuli. For example, Huang et al developed QD-based nanoreactors by creating amphiphilic PbS QD-stabilised PEs through the formation of Janus ligand shells. Their research offers valuable insights for enhancing the effectiveness of nanoreactors and microemulsions in facilitating multiphase photocatalytic reactions.[51] In addition, Xie et al proposed a photomagnetic dual-responsive PEs micro-reactor, in which photosensitive TiO_2 and Fe_3O_4 nanoparticles are co-adsorbed at the oil-water interface of the emulsion droplets.[52] By approaching each other under an external magnetic field, the reactants came into contact and triggered a chemical reaction under ultraviolet light irradiation. Their research has opened up broad prospects for the construction of multifunctional PEs. Further research could investigate the utilization of visible light instead of ultraviolet light in photomagnetically driven PEs microreactors, offering significant potential for advancements in the field of life sciences. However, there is relatively limited research on the in vivo safety of these inorganic nanoparticles, which hinders their application as drug carriers.[84]

Protein Nanoparticles

Protein nanoparticles possess several advantages that make them well-suited for the preparation and stabilization of traditional PEs. These advantages include their natural origin, non-toxicity, biocompatibility, biodegradability, potential health benefits, good surface activity, and emulsion stability.[85] In the context of PEs, protein nanoparticles can take on various shapes, including non-deformable solid spherical nanoparticles,[53] nanofibers, nanotubes, nanogels, nanocages,[86] and plate-like nanoparticles. Protein-based PEs have greater applications in the food and pharmaceutical industries compared to traditional inorganic particle-stabilized PEs. These applications include substituting partially hydrogenated fats in food,[87] encapsulating, stabilizing, and releasing active ingredients,[53] and inhibiting lipid oxidation.[88] For instance, in the work of Sun et al, the recombinant oil bodies protein (ROP) was induced using guanidine hydrochloride.[53] In this approach, the ROP first formed a core-shell structure to encapsulate Cur, and then the formed ROP-Cur colloidal particles were used to stabilize PEs for the preparation of a double-chamber microdroplet system to achieve co-encapsulation of Cur and vitamin D. This study provides an important avenue for developing nutrition delivery systems and improving the stability and bioactivity of hydrophobic nutrients. Furthermore, Xu et al utilized a GroEL-derived

protein nanoring from Escherichia coli to stabilize PEs for encapsulating β-carotene.[54] In the context of promoting biocompatibility and sustainability, this work offers a more environmentally friendly solution for emulsion-based applications. Moreover, Feng et al successfully prepared a nanocomplex of corn zein and sodium caseinate by surface adsorption, which enhanced the stability and dispersibility of corn zein colloidal particles in the aqueous phase.[55] This approach was employed to explore a novel method of utilizing food-grade protein surface modification to stabilize PEs. The aforementioned studies indicate that proteins have the ability to stabilize emulsions. However, it is important to note that protein-stabilized PEs are highly susceptible to alterations in environmental factors such as pH, ionic strength, and temperature. If these conditions surpass certain thresholds, the PEs have a tendency to flocculate and expedite the destabilization process. Consequently, further adjustments are required in order to utilize protein particles effectively in the future for the production of PEs.[89,90]

Nanocrystalline Drugs, Fat Crystals

Recently, a new delivery system called drug nanocrystal (NC) self-stabilized PEs (NSSPE) has been developed for poorly water-soluble drugs. This system is stabilized by insoluble drug nanocrystals, eliminating the need for additional stabilizers. NSSPE offers the combined benefits of NC and PEs while addressing the side effects associated with inorganic solid particles like silica. One of the key advantages of NSSPE is its ability to enhance the water solubility of insoluble drugs such as quercetin, geraniol,[91] and silymarin flavonoids,[92] leading to improved oral bioavailability.[93] This delivery system, consisting of just three components (water, oil, and drug), significantly increases the drug loading capacity as the drug no longer needs to be dissolved in the oil phase.[94] In the work by Sheng et al, Cur was adopted as a typical Biopharmaceutics Classification System (BCS) IV drug, and a stable PEs of Cur-NCs was prepared using either poorly digestible (isopropyl palmitate, IPP) or easily digestible (soybean oil, SO) oils.[94] After optimization, they found that the concentration of Cur in the formulation far exceeded its solubility in IPP or SO. Their research provides a new strategy for improving the oral bioavailability of Cur and other BCS IV drugs. Additionally, Wang et al proposed the introduction of traditional Chinese medicine volatile oil - turmeric oil as the oil phase in the concept of "drug excipient combination" to prepare a drug called NSSPE, and Cur-NSSPE lyophilized powder was prepared using the freeze-drying method.[56] This Cur-NSSPE lyophilized powder showed more significant advantages in its anti–inflammatory effects both in vitro and in vivo compared to Cur-API and Cur-NCs.

Solid lipid nanoparticles (SLNs), commonly referred to as fat crystals, have been employed as colloidal nanocarrier systems in drug delivery.[95] Nevertheless, there is a lack of pharmaceutical applications that utilize fat crystal stabilized PEs. These fat crystals, however, have demonstrated their capability as suitable candidates for this purpose due to their exceptional biocompatibility, minimal toxicity, ability to safeguard thermally unstable molecules against degradation, and their specific targeting capabilities. Lipid crystals, such as triglycerides, contain small amounts of monoglycerides and diglycerides and can serve as solid particles with unique temperature-responsive properties.[57] They provide stability to W/O emulsions and effectively build the emulsion droplet by forming an interfacial film and a crystalline network, creating the desired texture.[19,96] In the work of Li et al, they developed SLNs based on medium- and long-chain diglycerides (MLCD) as interface stabilizers for W/O PEs.[57] By using MLCD as the lipid core and controlling the crystallization curve, crystal form, contact angle, and interface adsorption curve through the selection and concentration of surfactants, the rigidity of SLNs can be adjusted. The high rigidity of SLNs makes water-in-oil PEs a viable option for reducing saturated fatty acid levels and serving as a carrier for water-soluble bioactive compounds. While researchers have demonstrated the safety of the SLNs, the inclusion of surfactants to enhance SLNs properties in the formulation of PEs drug delivery systems necessitates further research to ensure safety.[97]

Microbial Nanoparticles

Various microscopic particles can be found in nature, including viruses, spores, bacteria, and yeast, at both micro- and nano-scale levels. These particles exhibit uniform size distribution and can be tailored for pharmaceutical purposes.[17] For example, virus-like nanoparticles lack genetic material and consist of protein shells. They are robust structures capable of encapsulating drug molecules at the nanoscale. Within nanomedicine, viruses have been engineered as intelligent carriers

for targeted drug delivery.[98] Nonetheless, concerns regarding the immunogenicity, cytotoxicity, inflammatory response, and other toxicities associated with mammalian viral vectors have prompted the exploration of plant viruses or plant virus nanoparticles as alternative nanocarriers.[99] Extensive research has revealed the ability of these natural particles to stabilize PEs, enhancing biocompatibility, bioactivity, and bioavailability in body fluids while reducing toxicity. Notably, the Tobacco mosaic virus can self-assemble into nanorods with amphiphilic properties and inherent self-assembly capability, demonstrating significant potential for drug delivery and viral detection.[58,99] Similarly, Ganoderma lucidum spores have been identified as effective stabilizers of PEs due to their unique organic composition and structure.[59] Furthermore, in a study by Firoozmand et al, yeast and lactic acid bacteria were employed as micrometer-sized colloidal particles to stabilize oil-in-water emulsions, resulting in long-term stability of the dispersed oil droplets (lasting over one year) upon optimization.[60] These microbial cells have demonstrated the ability to produce a monophasic emulsion with high oil volume fractions, characterized by closely packed oil droplets arranged in a polyhedral manner. This innovative method of emulsification stabilization holds great capacity for various food applications; however, the research in the realm of drug delivery remains limited, necessitating further exploration by the scientific community.[100]

Composite Particles

The utilization of emulsifiers such as starch and cellulose to stabilize emulsions may be limited by certain properties of the particles. To overcome this limitation, composite particles can be created through interactions between particles with different properties, resulting in more stable PEs. For instance, solid biopolymer nanoparticles with prolonged coalescence lifetimes were successfully produced by leveraging effective associative interactions between proteins and polysaccharides.[101] These composite particles, exemplified by lactoferrin nanoparticle-inulin polysaccharide,[102] were utilized to stabilize the oil-water interface and shield protein particles from pepsin, thus enhancing the kinetic stability of the emulsions under gastric conditions. Moreover, Zhang et al demonstrated a sustainable approach by modifying the surface of bacterial cellulose through the physical adsorption of soybean isolate proteins onto cellulose protofibrils. The resulting complexes effectively stabilized PEs with diameters ranging from 10 μm to 40 μm, and subsequent in vivo digestion studies revealed enhanced resistance to lipid hydrolysis in these emulsions.[61] These findings underscore the capacity of composite particles in the stabilization of PEs. Composite particles are increasingly being designed as multifunctional systems, offering simultaneous stabilization and active functionalities such as antibacterial effects, drug delivery, or environmental responsiveness. This has driven the exploration of advanced emulsion types, including multiple emulsions and double PEs, expanding their application capacity in the pharmaceutical field. Additionally, innovations in nanocomposite particles provide precise control over emulsion properties and enhanced interfacial performance, further advancing their role in complex formulation systems.

Functional Designs of PEs

Sustained or Controlled Drug Release

PEs have emerged as a reliable method for encapsulating and delivering active pharmaceutical ingredients, utilizing solid particles to create a protective barrier.[7] Indeed, the solid particle film acts as a hindrance, slowing down the diffusion of therapeutic drugs from the emulsion to the target site. This controlled release mechanism offers numerous advantages, including prolonged drug persistence, protection against degradation, reduced administration frequency, and enhanced patient compliance.[103] For instance, a recent study demonstrated that pea isolate protein (PPI) could be transformed into nanoparticles at pH 3.0,[104] leading to the development of a stable gel-like emulsion with sustained β-carotene release properties through microfluidic emulsification.[105] Moreover, to overcome the disadvantages of high toxicity of antimicrobial peptides, high hemolysis of human cells, short circulating plasma half-life and poor stability in vivo, researchers have stabilized PEs with Parasin I-interacted lecithin and chitosan nanoparticles.[106] The results of the in vitro study indicated that the emulsion exhibited the ability to enhance membrane damage and coalescence area upon bacteria binding. Furthermore, the study revealed that the peptide-composite nanoparticles used to stabilize emulsions enabled the sustained release of Parasin I, ultimately boosting their antimicrobial efficacy. In addition, the sustained drug release properties of PEs are also beneficial to cancer treatment. For instance, oil-in-water lipid iodine

emulsion remains the preferred choice for localized chemotherapy in hepatocellular carcinoma treatment.[107] These findings underscore the benefits of utilizing PEs for the sustained or controlled release of active drugs, such as vitamins, antimicrobial peptides, and anticancer drugs.

Targeted Drug Delivery

Targeted delivery is a key benefit of drug delivery systems, offering the competence to minimize adverse effects and enhance therapeutic effectiveness by facilitating the accumulation of substances in specific tissues.[108] PEs play a crucial role in enabling precise drug delivery through mechanisms such as particle adsorption on interfaces, bonding with target cells, and increasing cellular binding of modified target ligands by expanding the contact area.[109] For instance, in the context of cancer vaccine administration, conventional liquid mixtures of immunostimulants, antigens, and target molecules often struggle with diffusion and degradation issues, hindering an optimal immune response.[110] In contrast, PEs can be strategically formulated to encapsulate various components with diverse characteristics, such as size, hydrophobicity, or charges. To illustrate, Du et al utilized the recognition ability of mannose by antigen-presenting cell surface receptors to create mannose-based PEs for delivering complex vaccines aimed at synergistically combating tumors in conjunction with PD-1 antibodies.[111] This targeted approach not only amplified the cellular immune response but also heightened the anti-tumor effects synergistically. Insights gained from these findings shed light on the ability of PEs-based targeted drug delivery strategies. Moreover, the effectiveness of drug delivery from PEs is closely tied to the properties of the particles involved. For example, researchers have successfully stabilized β-carotene emulsions with PPI nanoparticles at pH 3.0 for intestinal targeting, leveraging the isoelectric point nature of protein particles to suit different parts of the digestive system.[105]

Stimulus Responsive Drug Delivery Systems

In numerous application scenarios, the surface characteristics of solid particles can undergo various physical or chemical changes triggered by environmental factors like pH, temperature, specific reagents, light, and magnetic fields. These changes can impact the wettability, charge, or size of the particles and disrupt the arrangement of the emulsion's interface[112](Figure 2). Consequently, PEs can serve as responsive delivery systems by striking a balance between droplet stability and controlled rupture, enabling researchers to achieve controlled or targeted drug release. For instance, in environments with weakly acidic conditions like inflammation sites, lysosomal compartments, or tumor tissues that necessitate in vivo treatment, researchers have harnessed the acid sensitivity and degradability of acetalized starch-based nanoparticles to enhance the efficacy of targeted drug delivery systems for anticancer medications, such as Cur.[113] Moreover, studies have explored thermosensitive PEs, exclusively stabilized by SLNs, for drug encapsulation and delivery like ketoprofen. These SLNs exhibited controlled drug release upon experiencing specific temperature changes, such as partial melting at 37°C.[114] The versatility of PEs, whether responsive to pH or temperature changes, introduces novel opportunities for precise drug delivery systems. Notably, nano delivery systems activated by external stimuli, like photothermal responses, offer distinct advantages over those reliant on internal triggers such as pH and heat, due to their ease of manipulation and precise treatment control. Furthermore, owing to its excellent tissue penetration capacity, near-infrared radiation (NIR)-light responsive drug delivery systems present a promising avenue in cancer treatment.[115] Recent research has explored the use of polydopamine (PDA) bowl-shaped mesoporous nanoparticles as Pickering stabilizers, resulting in pH-responsive emulsions with notable photothermal responsiveness under NIR light due to PDA integration.[116] These properties hold significant potential for diverse biomedical applications, including drug delivery. It is important to note that the release of drugs is influenced by factors like the rupture and deformation of PEs, which could affect their stability. Hence, future stimulus-responsive PEs are likely to focus on achieving a balance between stability and effective drug release mechanisms.

Multilayer Structure

In cancer treatment, combining various medications through cocktail therapy has proven to be a promising strategy for combatting tumor regression and multidrug resistance.[119] However, the challenge lies in effectively delivering multiple drugs with diverse hydrophobicity and targets in a spatiotemporal manner.[109] Hence, there is a demand for the

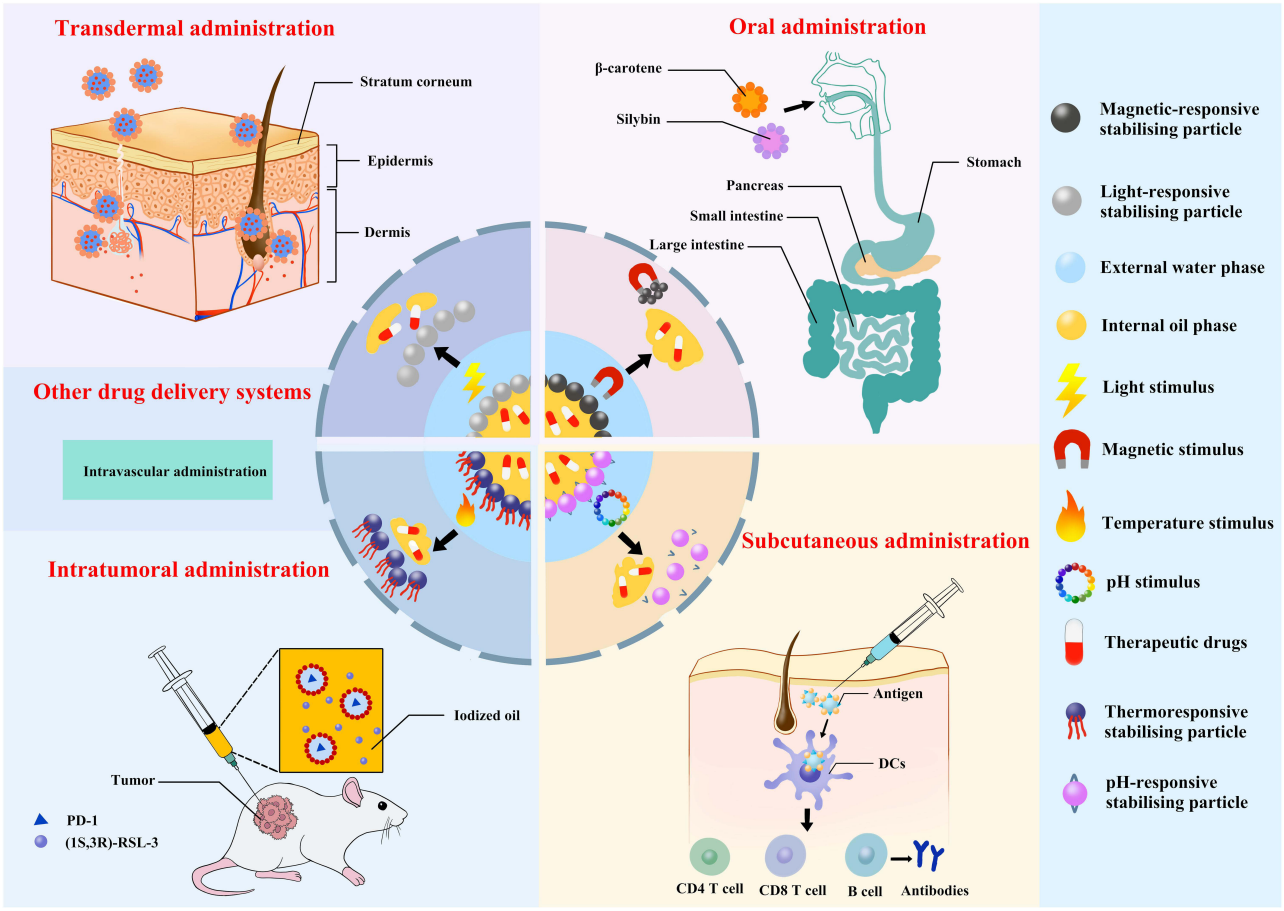

Figure 2 Schematic representation of stimulus-responsive drug release and routes of administration of PEs. The oral and intratumoral administration of PEs is referenced to Li et al,[117] Yi et al,[92] and Dai et al.[118]

development of multi-drug delivery systems to enhance the bioavailability and effectiveness of treatments. PEs, known for their intricate structure, serve as an efficient multi-drug delivery system. The multilayer configuration of W/O/W or O/W/O emulsions offers a better solution for loading different components with varying hydrophobicity or charge.[120] For instance, a recent study by Tang et al introduced PEs loaded with betanin and Cur, where betanin and Cur were dissolved in the inner aqueous and oil phases, respectively, to create the W/O emulsion. The W/O emulsion was then combined with betanin-bovine serum albumin nanoparticles dispersed in the outer aqueous phase to form a composite W/O/W emulsion.[121] The synergistic effect of betanin and curcumin in inhibiting A549 cell growth highlights the capability of this multilayer structure for co-delivering multiple drugs with diverse properties, suggesting its significance in future clinical applications. Furthermore, the multilayer structure of PEs can be further combined with active targeting ligands, stimuli-responsive designs, or sustained-release techniques to achieve precise and sequential drug delivery of multiple drugs.

Delivery Routes of PEs

PEs have shown significant applications in the pharmaceutical field, particularly in drug delivery systems. When administered via different routes, such as oral, subcutaneous, intravascular, or intratumoral, the characteristics of the stabilizing particles (size, surface properties, and biodegradability) must be carefully optimized to enhance therapeutic efficacy and ensure safe delivery. For instance, Pickering particles for oral administration should be suitable for strongly acidic environment and protect bioactive drugs.[122] Furthermore, PEs encapsulating chemotherapeutic agents for

intravascular and intratumoral administration may use particle stabilizers that respond to the tumor environment and release the drugs.[35]

Oral Administration

PEs are primarily used for the oral delivery of hydrophobic as well as poorly bioavailable drugs in the expectation of increasing the stability and improving the aqueous solubility of orally administered drugs. Poorly water-soluble drugs present challenges in formulating oral drug products due to their inconsistent bioavailability and limited dissolution in the gastrointestinal tract.[123] Lipid-based formulations have been explored to enhance the oral bioavailability of such drugs, but the high surfactant content in these formulations may cause gastrointestinal irritation, leading to reduced drug effectiveness and bioavailability.[124] PEs offer a novel drug delivery approach using solid particles instead of surfactants, which can minimize irritation. For instance, Eudragit® RL100 nanoparticles have been utilized to stabilize PEs, extending the efficacy of drugs like ketoprofen and reducing the dosing frequency.[125] Furthermore, recent advancements in PEs involve utilizing solid particles to create a protective barrier at the water-oil interface, safeguarding the drug core from degradation in particularly acidic environments or under various stress conditions. Li et al successfully enhanced the bioavailability of β-carotene by encapsulating it in PEs stabilized with chitosan hydrochloride-carboxymethyl starch nanogels[117] (see Table 2). The Pickering particles should be biocompatible and able to withstand or respond to the acidic environment of the stomach and the enzymatic conditions of the gastrointestinal tract. For instance, Hu et al hypothesized that media-milled black rice particle-stabilized PEs would be a good oral delivery vehicle for 5-demethylnobiletin (5-DMN), which has the potential to enhance 5-DMN absorption and metabolic conversion in the colon (Figure 3).[126] Black rice particles are high in dietary fiber and phenolic compounds, which could be selectively broken down by the colonic microbiota. They found that black rice-stabilized PEs encapsulated 5-DMN targeting the colon could alleviate dextran sulfate sodium-induced weight loss and diarrhea. However, comprehensive data on the pharmacokinetics and bioavailability of PEs remain limited, with in vitro lipolysis models commonly employed to assess their suitability for oral drug delivery. Moreover, utilizing refractory drug nanocrystals to stabilize emulsions for oral drug delivery systems can increase drug loading capacity without the need for surfactants or polymer stabilizers.[92] Besides, the elucidation of the in vivo degradation of PEs, encompassing particle stabilization and emulsion digestion, holds paramount importance. The employment of a pioneering bioimaging methodology reliant on aggregation-induced burst fluorescent probes presents a promising avenue to address this intricate issue.[127,128]

Transdermal Administration

PEs demonstrate promising capabilities in the topical administration of antibiotics for skin infections and in the transdermal delivery of lipophilic drugs, as evidenced by research findings. Topical drug delivery is a challenging field with many advantages, including extended administration duration, reduced frequency of dosing, and minimized systemic side effects.[130] While conventional emulsions with surfactants may compromise the skin barrier, PEs offer a promising solution due to their low toxic, non-carcinogenic nature and excellent dermal compatibility. PEs could enhance the skin permeation of drugs by augmenting the moisture level within the stratum corneum, while certain solid particles may induce changes in the structure of the stratum corneum proteins.[143] Recent research by Frelichowska et al demonstrated that PEs effectively enhance the delivery of lipophilic drugs like retinol into the skin, particularly within the stratum corneum, when compared to traditional emulsions.[129] These nanoparticle-stabilized emulsions exhibit unique characteristics suitable for targeting the stratum corneum or enabling controlled drug release. This phenomenon could be attributed to the capacity of PEs for coalescence in contrast to surfactants-stabilized droplets, potentially stemming from differences in droplet flexibility. Moreover, in the context of skin barrier damage and associated bacterial infections, topical application of antibiotics via PEs shows capability for treating infections and preventing further complications.[130] While PEs hold promise for sustained antibiotic delivery to prevent wound infections, further research is needed to investigate their skin penetration and safety profiles in vivo.[8] Techniques like confocal laser scanning microscopy were employed to track particles and investigate the penetration capability of emulsion droplets through the stratum corneum into the deeper layers of the skin. This

Table 2 Examples of Different Delivery Routes for PEs

Delivery routes	Emulsion			Drug /localization	Functional designs	References
	Type	Particles	Droplet size			
Oral	O/W	Eudragit RL100 nanoparticles	≈220 nm	Ketoprofen/ oil	Controlled Release	Dieng et al, 2020[125]
	O/W	Chitosan hydrochloride/carboxymethyl starch complex nanogels	≈5-8 μm	β-carotene/ oil	–	Li et al, 2020[117]
	O/W	Silybin nanocrystal	≈24.2–30.4 μm	Silybin/ NPs	–	Yi et al, 2017[92]
	O/W	Pea protein isolate protein	≈3-8 μm	β-carotene/ oil	Stimulus response and targeted delivery	Shao et al, 2016[105]
Transdermal	O/W	Silica particles	≈2-4 μm	Retinol/ oil	Sustained release	Frelichowska et al, 2009[129]
	W/O	Aluminum starch octenyl succinate particles	–	Minocycline hydrochloride/ water	Controlled release	Marto et al, 2019[130]
	W/O	Chitosan/collagen peptides nanoparticles	≈7.63–15.72 μm	–	–	Sharkawy et al, 2021[131]
	O/W	Carboxymethyl chitosan - sodium alginate nanoparticles	≈5 μm	Curcumin/ oil	Controlled release	Wu et al, 2022[132]
Subcutaneous injections	O/W	PLGA-PEG-mannose nanoparticles	≈1 μm	Lipopeptide ovalbumin/ oil-water interface	Targeted delivery	Du et al, 2022[111]
	O/W	Alum microgels	≈4 μm	SARS-CoV-2 spike protein/ oil-water interface	Targeted delivery	Peng et al, 2020[133]
Intravascular administration	O/W	Poly(N-isopropylacrylamide-co-allylamine) nanogels	≈1.5 μm	Paclitaxel/ oil	Sustained release and targeted delivery	Chen et al, 2011[27]
	O/W	CTAB and LA	≈294-502 nm	CTAB and LA/ NPs	Targeted delivery and stimulus response	Chen et al, 2023[134]
	W/O	PLGA nanoparticles	–	Oxaliplatin/ water	Sustained release	Deschamps et al, 2018[135]
	O/W	Poly (N-isopropylacrylamide-co-acrylic acid) nanogels	≈1-10 μm	–	Stimulus response	Li et al, 2021[136]

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Intratumoral administration	W/O	PLGA nanoparticles	≈37-47 μm	Ipilimumab/ water	Sustained release	Tselikas et al, 2020[137]
	O/W	CTAB	≈91.72–96.44 nm	Paclitaxel/ oil	Sustained release	Xu et al, 2016[138]
Other drug delivery systems	O/W	Chitin nanocrystals	≈3.5 μm	–	–	Yu et al, 2024[139]
	O/W	Galactose-functionalized hydroxyethyl starch-grafted polycaprolactone nanoparticles	≈140 nm	Doxorubicin and indocyanine green/ oil	Targeted delivery and stimulus response	Hu et al, 2017[140]
	O/W	Poly(N-isopropylacrylamide-co-acrylic acid) nanogel	≈150 nm	Doxorubicin/ oil	Targeted delivery and stimulus response	Shang et al, 2019[141]
	O/W	OSA-modified starch particles	–	Nile red/ oil	Stimulus response and controlled release	Zheng et al, 2022[142]

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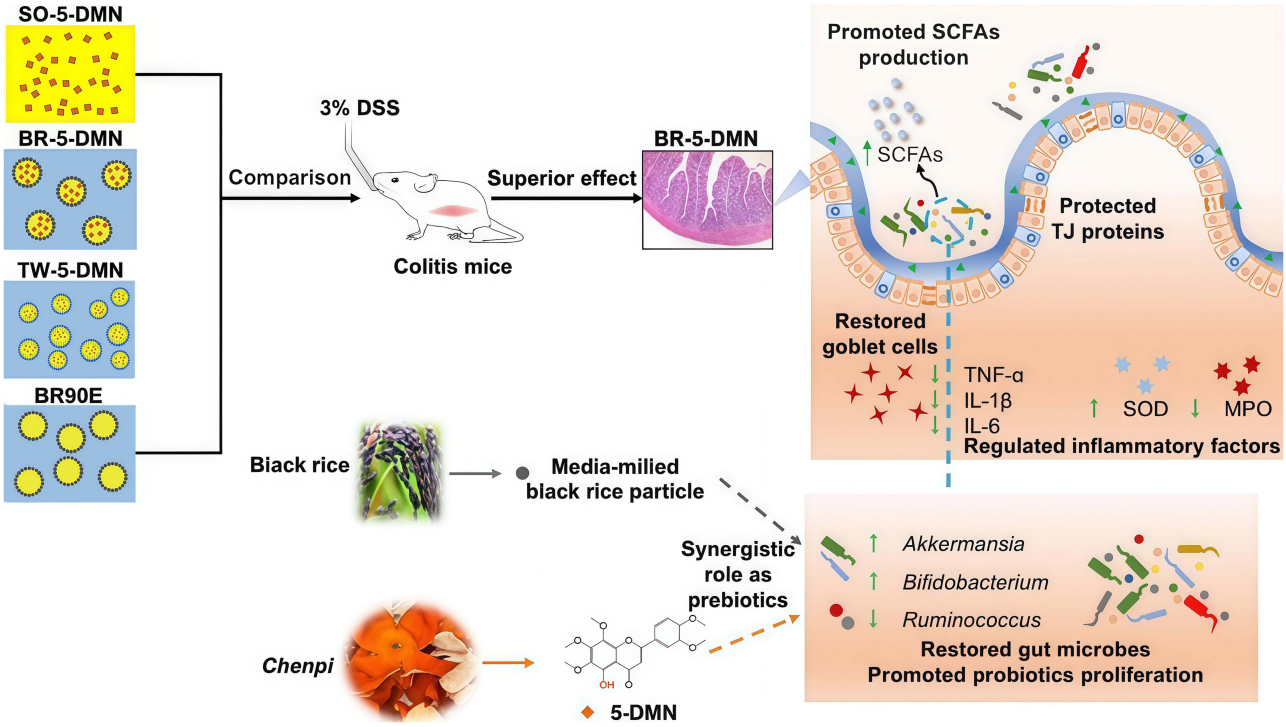

Figure 3 A milled black rice particle-stabilized PEs (BR-5-DMN) has been developed as a delivery vehicle for 5-DMN to treat colitis. Reprinted with permission from Hu H, Wang Y, Zhao D-G, Lu X. Oral Delivery of 5-Demethylnobiletin by Media-Milled Black Rice Particle-Stabilized PEs Alleviates Colitis in Mice: Synergistic Effects of Carrier and Loaded Bioactive. J Agric Food Chem. 2025;73(2):1257–1272. *Copyright © 2025, American Chemical Society.*[126]

method was utilized to assess the potential entry of the topically administered drug into the bloodstream, enabling the evaluation of in vivo skin penetration and safety of PEs.[131] However, the application of PEs to transdermal drug delivery has some limitations because of emulsions with strong mobility. Consequently, certain researchers have explored the application of PEs in conjunction with a gel matrix containing Cur to address skin wound treatment, thereby extending drug retention on the skin.[132] In addition, the potential for irritation caused by particles and emulsions on the skin, mucous membranes, and damaged skin is a critical consideration for ensuring the safety of drug delivery systems, which is essential for the advancement of future research.

Subcutaneous Administration

Subcutaneous injections of PEs are predominantly utilized in vaccines. A significant obstacle in vaccine development involves producing highly effective and safe adjuvants to assist antigens to elicit strong humoral and cellular immune responses.[144] Research on adjuvants has particularly concentrated on utilizing particulate carriers that imitate the characteristics of microorganisms or diseased cells.[145] PEs, which utilize solid particles as stabilizers, have shown promise in maintaining the deformability and migration of presented antigens while offering high biosafety and antigen-loading capabilities.[146] To improve vaccine delivery efficiency, Du et al have developed a multicomponent cancer vaccine delivery system by incorporating target molecules, immunostimulants, and antigens into these emulsions.[111] In the B16-MUC1 tumor model, the large interfacial area of PEs enhanced interactions between antigens and antigen-presenting cells (APCs), thereby improving antigen uptake and promoting immune activation. Notably, no signs of inflammation or toxicity were observed in the treated mice, indicating a favorable biosafety profile and effective tumor suppression. Furthermore, adjuvants, in the form of solid particles, can stabilize PEs, as demonstrated by Peng and collaborators, who created an aluminum-stabilized PEs by adsorbing alum within squalene/water, based on the nature of the microgel of alum.[133] This approach not only addresses the limitations of alum in eliciting T-cell responses but also enables effective co-loading of antigens and adjuvants to enhance immune reactions. Analogously, Guo et al designed PEs loaded with adeno-associated viruses (AAVs), stabilized by biomineralized manganese nanoparticles and aluminum

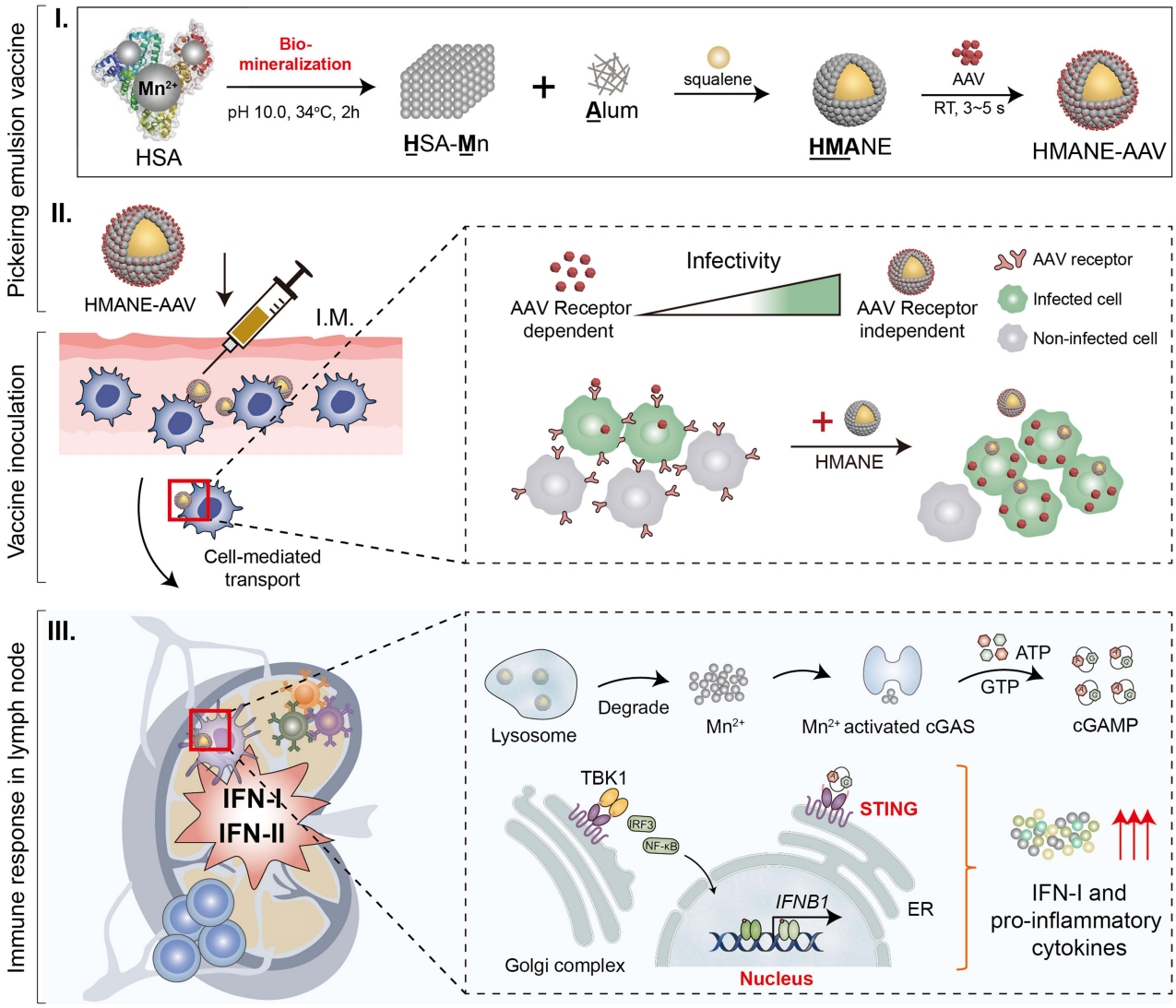

Figure 4 Schematic illustration of a biomineralized manganese nanoparticles and aluminum hydroxide stabilized PEs vaccine for enhancing AAV transduction and immune response. Reprinted from Guo Z, Wu F, Guo C, et al. Metalloparticle-engineered Pickering emulsion displaying AAV-vectored vaccine for enhancing antigen expression and immunogenicity against pathogens. Adv Mater. 2025;37(8):2412627.. *Copyright © 2025 John Wiley & Sons, Inc.*[147]

hydroxide.[147] This platform conferred AAVs with favorable in vivo distribution kinetics and improved the safety of AAVs vaccine, ultimately enhancing AAVs infection efficiency in APCs (Figure 4). Furthermore, compared to the AAVs vaccination dose, the PEs with one-fifth AAVs induced effective immune responses. Stimuli-responsive PEs offer a promising approach for the controlled delivery of antigens and adjuvants tailored for cancer treatment requirements. For instance, researchers have successfully created PEs stabilized with Fe_3O_4 cellulose nanocomposites via ultrasound-assisted in situ co-precipitation.[148] This magnetic emulsion shows promise as a smart nanotherapeutic carrier for biomedical and drug delivery applications. Coating this Fe_3O_4-stabilized emulsion with antigens allowed for lymph node retention of the vaccine via subcutaneous delivery and external stimulation, thereby achieving strong activation of APCs.

Intravascular Administration

Intravascular administration of PEs is mainly used as the form of nanodroplets, especially in the treatment of tumors. Recent researchers have demonstrated that nanodroplets can passively target tumor tissues through enhanced penetration

and retention effects.[6] For instance, utilizing the temperature-sensitive properties of poly(N-isopropylacrylamide), researchers have developed nanoscale droplets encapsulated with PTX,[27] inducing higher accumulation of the drug at the tumor site and demonstrating the capability of PEs for cancer therapy in the realm of nanomedicine. However, the tightness of the arrangement of nanoparticles at the water-oil interface may have an effect on the stability of the nanoemulsion. Consequently, more stable nano-PEs loaded with active molecules could be created using deformable or soft building blocks as nanoparticle emulsifiers, which were able to form stronger interfacial barriers to resist droplet-droplet coalescence.[27] Notably, once nanocarriers enter cells via endocytosis, they are typically captured by lysosomes, reducing the efficiency of drug delivery.[149] To address this issue, various delivery vectors with different lysosome escape mechanisms have been designed.[150,151] For instance, PEs stabilized by hybridized nanoparticles (HNPs) composed of cetyl trimethylamine bromide (CTAB) and linoleic acid (LA) possessed the lysosomal escape ability. In an acidic environment, HNPs disintegrated the emulsion upon protonation, with CTAB disrupting lysosomal membranes and LA acting on lysosomal and mitochondrial membranes through interactions involving lysosomal iron ions, leading to tumor cell death.[134] In vivo studies in a CT26 melanoma tumor-bearing mouse model demonstrated that PEs stabilized by HNPs had no potential off-target toxicity in major organs, supporting the good biocompatibility of this formulation. If employed in the transportation of anticancer medications, these nanocarriers have the possibility to generate a more potent anti-tumor effect. While scholars have investigated the safety profile of the emulsion in healthy cells and animal models, establishing its remarkable tumor-targeting specificity with minimal off-target tissue accumulation, the cellular toxicity of CTAB warrants careful consideration. Further experimentation is imperative to delineate the safety parameters comprehensively.[152]

Furthermore, hepatic artery injection embolization serves as a temporary reservoir for chemotherapeutic agents, allowing a controlled drug release into hepatic tumor tissues, thus minimizing systemic exposure.[153] Lipiodol, a radiopaque contrast agent, preferentially accumulates in liver tumor tissues and was adjuvanted with chemotherapeutic drugs to create stable PEs.[135] Li et al developed temperature-sensitive nanogels with a shell-and-core structure using two gel materials, resulting in Pickering gel emulsions with a temperature-sensitive sol-gel phase transition in vivo, enhancing intravascular embolization properties and long-term angiography of lipiodol in orthotopic liver cancer mice.[136] The Pickering gel emulsion has been shown to have 7.0 times higher mechanical strength than hairy p(NIPAM-acrylic acid) nanogels and better plugging properties through creep testing. In a recent study, calcium phosphate nanoparticles-stabilized lipiodol PEs were prepared for hepatocellular carcinoma, which encapsulated a clinically approved vascular disrupting agent. The emulsion responded to the tumor microenvironment and released combretastatin A4-phosphate to disrupt tumor nutrient delivery.[154] Therefore, these studies hold great promise for potential clinical translation of vascular embolization lipiodol PEs.[12,154]

Overall, when formulating PEs for intravascular drug delivery systems, it is imperative to prioritize factors such as sterility and non-pyrogenicity to ensure both the safety and regulatory compliance of the system, thereby optimizing its therapeutic efficacy.[155]

Intratumoral Administration

PEs are recognized for their suitability in delivering drugs within tumors as they exhibit excellent stability and the capability to regulate drug release effectively. Numerous research studies have revealed that administering low-selective chemotherapeutic agents systemically may lead to severe side effects due to dosage constraints. Over the past few decades, there have been significant advancements in the technology of directly injecting long-acting liquid formulations into tumors, effectively achieving high concentrations within the targeted tumor area.[156] Local administration of immunotherapy emerges as a promising strategy to mitigate the autoimmune and inflammatory toxicity associated with systemic delivery, thereby enhancing the therapeutic effectiveness of such treatments. Consequently, researchers developed a radiopaque PEs by dispersing an anti-CTLA-4 antibody in lipiodol with PLGA nanoparticles as stabilizers. The results demonstrated that the anti-CTLA-4 antibody's structure remained intact and retained its anti-tumor efficacy in vivo when released from this PEs.[137] In addition, Dai and his team designed a W/O PEs

gel loaded with PD-1 antibody in the internal phase and iron death inducer (1S, 3R)-RSL-3 (RSL-3) in the continuous phase, which promoted iron death of the tumor cells and activated the body's immune response upon intratumoral administration[118] (Figure 2). Furthermore, numerous studies have explored the incorporation of small molecule inhibitors and anti-tumor drugs into PEs, which, when administered intratumorally, collaborate to enhance anti-tumor efficacy.[6,36,83] These findings underscore the ability of intratumoral injections to effectively target the entire tumor and its microenvironment, showcasing significant promise in the field of oncology. PEs, with their unique slow-release property, deformability, and capacity to transport various medications, present a promising approach for intratumoral administration and controlled release of a diverse array of antineoplastic agents, showing great capability for therapeutic use in oncology.

Other Drug Delivery Systems Based on PEs Preparation Methods

It is challenging to achieve the encapsulation of two or more drugs in the same carrier using traditional nanocarriers. PEs, with their unique structural features, can fulfill this requirement. Researchers have utilized PEs' droplets as templates to develop multi-drug co-delivery systems, especially for tumor treatment. The fundamental concept of this method involves utilizing solid particles to stabilize oil-in-water emulsions, then fixing the solid particles through cross-linking or volatile oil phases to create hollow structures resembling microspheres.[139] These structures hold great ability as carriers for drug delivery. For instance, Hu et al employed galactose-functionalized hydroxyethyl starch-polycaprolactone nanoparticles as templates to create carbon nanotubes encapsulating DOX/indocyanine green.[140] These nanotubes demonstrated strong tumor-targeting capabilities through intravenous injection, enhanced tumor penetration, and facilitated photothermal effects. The researchers also identified these nanocolloids as a beneficial drug delivery system for actively targeting tumors in imaging-guided combination therapies for conditions like hepatocellular carcinoma.[140] Nanocapsules present an appealing approach to achieving highly efficient anti-cancer drug delivery. Traditional techniques like emulsion-diffusion and nanoprecipitation, which involve small-molecule surfactants, often result in high toxicity issues. To address this concern, researchers have utilized the Pickering technique to produce polymer nanogels for stabilizing nanocapsules, incorporating a cyclic peptide for enhanced tumor targeting and disulfide bond for stimulus-response. The capsules containing these are proposed as a great nanocarrier for precise drug release and targeted delivery.[141] Furthermore, hydrogel-based drug delivery systems offer significant advantages in safeguarding bioactive compounds from degradation and improving their bioavailability. When integrated with PEs, a novel stimuli-responsive drug delivery system is created, characterized by improved stability and controlled drug release kinetics. For example, a hydrogel composed of carboxymethyl cellulose, sodium alginate, and knotted cold gel was utilized as a carrier for loading PEs containing hydrophobically active drugs, representing a promising immobilization and pH-responsive controlled drug release approach.[142]

Conclusion

PEs, stabilized by solid particles, offer a superior alternative to surfactant-based systems in pharmaceutics due to their enhanced stability, biocompatibility, and reduced toxicity. Unlike conventional emulsions, PEs enable controlled drug release, protect labile therapeutics, and facilitate co-delivery of multiple agents—critical for complex applications like cancer therapy and vaccine development. The versatility of particle stabilizers allows tailored formulations for diverse routes, including oral, transdermal, and intratumoral delivery.

However, despite their potential, there is a lack of commercial products and clinical applications for PEs, requiring more input from researchers in this field. Patent applications for PEs mainly focus on methods of preparing emulsions using solid particles, as well as applications in detergents and cosmetics. Only a limited number of patents exist for PEs intended for pharmaceutical and food purposes. Moreover, there is a lack of detailed in vivo toxicity studies of PEs, and more researchers are needed to fill the gaps in toxicity testing. Optical microscopy provides a simple and rapid way to observe PEs, but there are limitations in observing interfacial, phase, and morphological features of solid particles. Confocal laser scanning microscopy with appropriate dyes has been identified as one of the most suitable methods for evaluating emulsion properties.[157,158] Some scholars are utilizing

neural network models to assess emulsion properties through object detection algorithms.[159] Moreover, research often lacks comparisons between different dosage forms or formulations against PEs for drug delivery in disease treatment. The industrial-scale production of PEs is still in its early stages, presenting challenges in predicting cost-effectiveness.[8] Future studies are likely to focus on the preparation of versatile and stable PEs using safe and stable particles to cater to diverse delivery requirements.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (82003683), the Sichuan Science and Technology Program (2023NSFSC1684), and the Fundamental Research Funds for the Central Universities, Southwest Minzu University (ZYN2024155).

Disclosure

The authors report no conflicts of interest in this work.

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