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REVIEW

The Role of Microemulsions in Enhancing the Stability of Biopharmaceuticals

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Abstract: Biopharmaceuticals, especially protein- and nucleic acid-based drugs, have demonstrated remarkable therapeutic efficacy in the treatment of various diseases. However, their complex molecular structures make them prone to physical and chemical instabilities such as aggregation, degradation, and hydrolysis, which severely limit their clinical applications. Microemulsions, as thermodynamically stable and spontaneously formed nanoscale colloidal dispersion systems, have emerged as an effective strategy to improve the stability of biopharmaceuticals owing to their excellent encapsulation capacity, structural stability, and formulation flexibility. This review systematically summarizes the basic composition and structural characteristics of microemulsions, as well as their mechanisms in regulating drug release behavior. Using representative examples such as ketorolac, curcumin, resveratrol, and quercetin, it further analyzes the potential of microemulsions to enhance drug permeability, prolong pharmacological action, and improve therapeutic efficacy. In addition, the review discusses current technical challenges faced by microemulsion technology and explores its future prospects in targeted delivery and gene therapy applications, aiming to provide a theoretical basis and practical reference for microemulsion-based strategies to enhance the stability of biopharmaceuticals.

Keywords: microemulsion, biopharmaceutical stability, protein aggregation, nucleic acid drugs, drug delivery system, self-microemulsifying drug delivery system, bioavailability

Introduction

Biopharmaceuticals, produced by living organisms using recombinant DNA (rDNA) technology, are bio-based products derived from nucleic acids and genetically engineered cells. These include recombinant hormones, vaccines, and recombinant tumor necrosis factor (TNF).[1,2] With their high affinity for cell surface receptors or extracellular target proteins, biopharmaceuticals interact specifically with extracellular subunits to initiate induced biological responses. They have demonstrated remarkable therapeutic efficacy in treating a wide range of diseases, from cancer and viral infections to neurodegenerative disorders.[3,4] In the past five years, regulatory agencies in the US and the EU approved a 36% increase in the number of biosimilar drugs compared to previous years, and the approval rate for biosimilars continues to rise.[5–7]

However, alongside the flourishing development of biopharmaceuticals, issues related to the instability of raw materials during drug development and storage remain a significant challenge. Studies have shown that the interactions between active pharmaceutical ingredients and excipients in formulations can impact drug stability.[8–10] Therapeutic agents can be delivered to their cellular targets via drug delivery systems. However, this delivery process may trigger protein aggregation, thereby reducing the optimal bioavailability, distribution, sustained release, and formulation stability of the biopharmaceuticals.[11] Additionally, chemical degradations such as deamidation, oxidation, and racemization have been identified as critical factors influencing formulation stability and efficacy in biopharmaceuticals.[12] Furthermore,

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environmental factors such as light, heat, radiation, and reactions with other components in containers or mixtures can induce instability during storage.[9]

To address these issues, microemulsion technology has been innovatively applied in the development of biopharmaceuticals in recent years. Due to its excellent ability to reduce interfacial tension and enhance solubility, microemulsions have found wide applications in biopharmaceuticals.[13,14] A microemulsion is an isotropic colloidal dispersion system spontaneously formed by water, surfactants, cosurfactants, and oil.[15] As a branch of nanofluids, microemulsions offer significant advantages in thermodynamic stability and do not separate or break after prolonged storage or even centrifugation.[16,17]

Given the current advancements, biopharmaceuticals have gradually opened up the pharmaceutical markets in the US and EU due to their exceptional clinical efficacy in treating various indications.[1] However, the pressing issue of improving the stability and bioavailability of protein-based therapeutics remains unresolved. Therefore, further research to elucidate the role and mechanisms of microemulsion technology in enhancing the stability of biopharmaceuticals holds high practical significance and value.

This study will systematically investigate the effects of microemulsion technology on inhibiting protein aggregation, enhancing bioavailability, and improving formulation stability of protein-based biopharmaceuticals, and elucidate the underlying mechanisms. The aim is to provide a theoretical foundation and technical support for the efficient application of microemulsions in the field of biopharmaceuticals.

Basic Concept of Microemulsions

A microemulsion is an optically isotropic and chemically stable system formed by two immiscible liquids (water and oil) with the assistance of amphiphilic substances, typically including surfactants and cosurfactants.[18] In 1943, Hoar et al first reported that a transparent or translucent system could be spontaneously formed by mixing water, oil, surfactants, and cosurfactants (usually alcohols of medium chain length).[16,19] On a microscopic scale, the droplet size of microemulsions typically ranges from 1 to 150 nm. The small droplet size and thermodynamic stability endow microemulsions with unique properties, enabling them to be widely applied across various fields, including pharmaceuticals, cosmetics, food, petroleum recovery, and the adsorption of nanomaterials.[20–28] Figure 1 summarizes the formation, properties, and applications of microemulsions.

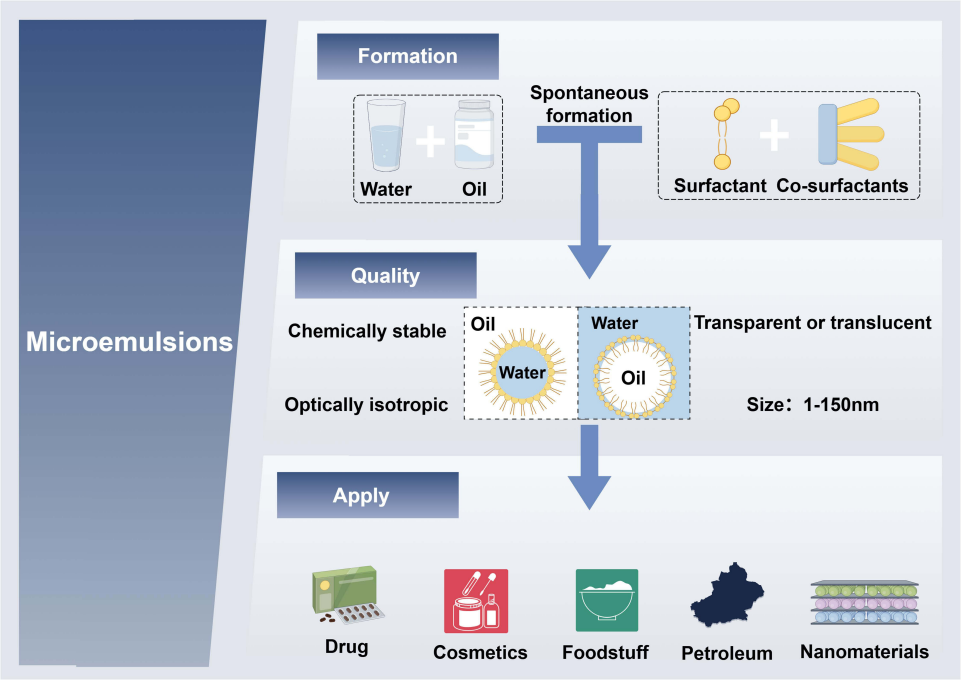

Figure 1 Formation, Properties, and Applications of Microemulsions. (Drawn by Figdraw).

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Stability Types

Winsor classified systems based on the influence of amphiphilic molecules and solvents on droplet curvature, describing four types of phase equilibria.[29] Winsor I type (oil droplets dispersed in an aqueous phase – O/W): a system formed by a surfactant-rich aqueous phase (lower phase) mixed with a surfactant-poor oil phase; Winsor II type, primarily consisting of a surfactant-rich oil phase and a surfactant-depleted aqueous phase; Winsor III type, characterized by a surfactant-rich middle phase coexisting with surfactant-poor water (lower layer) and oil (upper layer) phases; Winsor IV, a single-phase homogeneous mixture.

Phase Inversion Types

The structure of nonionic surfactant-stabilized microemulsions is highly sensitive to temperature changes, with each system characterized by a narrow temperature range.[14] In these systems, there exists a specific phase inversion temperature (PIT) at which the curvature of the membrane shifts from positive to negative. Shinoda et al defined these critical points for microemulsion formation,[30–32] which can be summarized as follows:[33] T < PIT, O/W microemulsion (Winsor I); T > PIT, W/O microemulsion (Winsor II); T = PIT, a middle-phase microemulsion (Winsor III). This illustrates the transition from a low-temperature, high-water-content O/W microemulsion to a near-PIT bicontinuous microemulsion and a high-temperature W/O microemulsion. Figure 2 systematically summarizes the impact of surfactants on microemulsions.

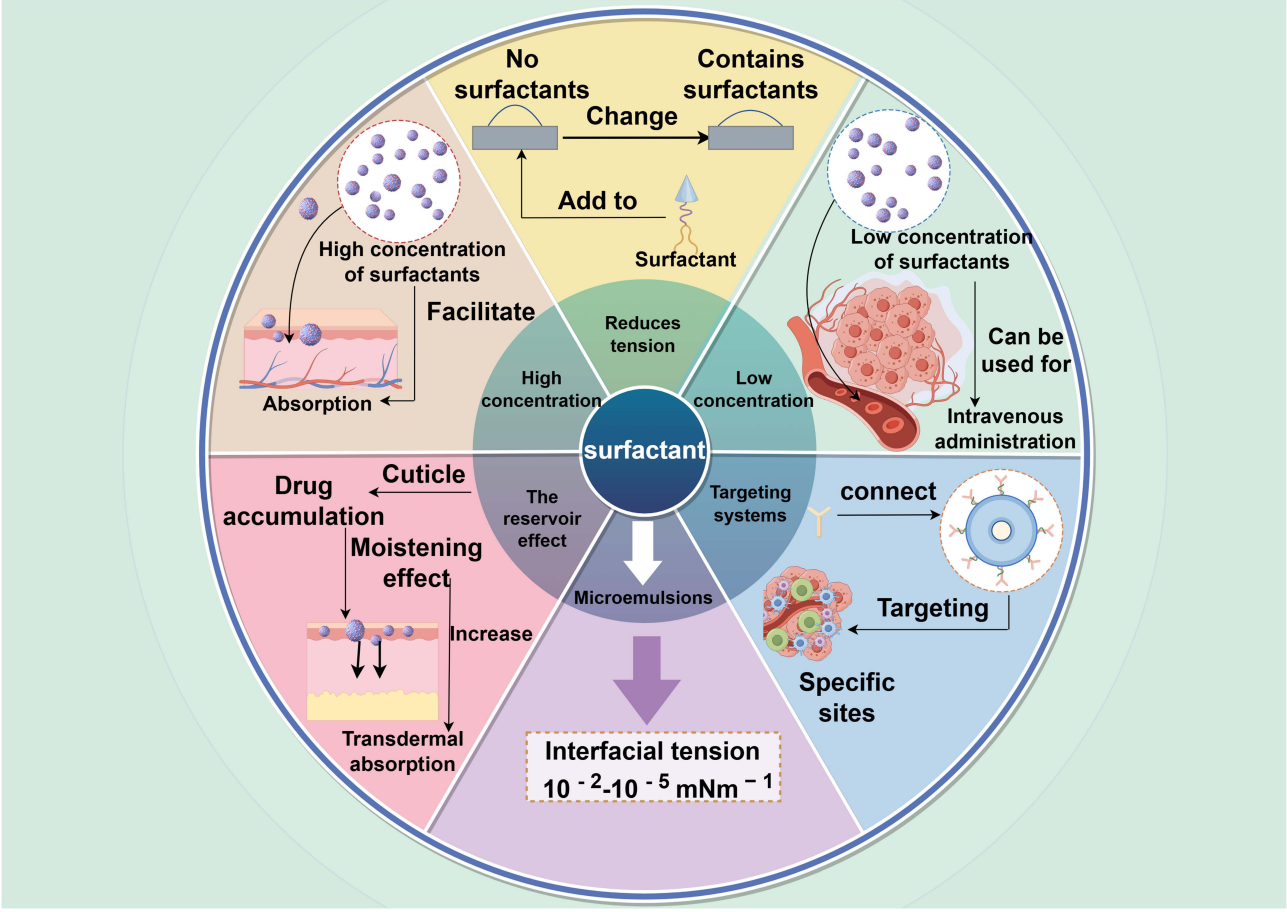

Figure 2 Effect of Surfactants on Microemulsions. (Drawn by Figdraw).

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Components

Surfactants

Surfactants are key compounds in the formation of microemulsions, and their chemical properties play a decisive role in stabilizing the system.[14] The primary function of surfactants is to reduce interfacial tension, and microemulsions are formed when ultra-low tension is achieved. Typically, the interfacial tension required for microemulsion formation is in the range of 10^{-2} to 10^{-5} mNm^{-1}. Temperature, salinity, and surfactant characteristics all influence their formation.[34] The high concentration of surfactants in microemulsions can temporarily destabilize the skin cell matrix, thus enhancing the permeation of drugs through the skin.[35,36] At the same time, microemulsions can also be produced with lower surfactant concentrations, maintaining thermodynamic stability without significantly disrupting the stability of the skin cell matrix, which is sufficient for intravenous administration.[37,38] On the other hand, the surfactant layer can also allow the microemulsion to act as a reservoir/storage effect.[39] By binding with specific components, surfactants can design microemulsions as drug-targeting systems, enabling targeted drug delivery to specific sites and reducing drug side effects.[40]

Solvents

The solvents in microemulsions are divided into aqueous phase solvents and oil phase solvents. The selection of oil phase solvents and surfactant components in microemulsions is a critical factor for drug release and improving skin penetration.[41] Common oil phase solvents include both saturated and unsaturated fatty acids, which also act as penetration enhancers in transdermal delivery.[42] Natural oils, such as cottonseed oil,[43] coconut oil,[44] and flaxseed oil,[45] are used as non-aqueous carriers and permeation enhancers in skin and transdermal formulations due to their good biocompatibility, low irritation, and safety.[46]

In recent years, there have been numerous reports on the use of ionic liquids to replace water or oil (hydrocarbon solvents) in the formulation of ionic liquid microemulsions.[47–58] The microemulsification of ionic liquids with surfactants favors the formation of microenvironments with controlled microstructures and promotes different polarities. Furthermore, it can significantly reduce the consumption of expensive ionic liquids, improving their viscosity and conductivity.[59] Microemulsions stabilized by ionic surfactants typically have higher electrical conductivity than those stabilized by nonionic surfactants, and the aggregation of anionic surfactants catalyzes electropolymerization. Studies have demonstrated that the HIL-based microemulsion stabilized by the anionic surfactant bis(2-ethylhexyl) sulfosuccinate AOT is more suitable for electropolymerization.[60] Additionally, research has shown that the anionic surfactant [C_2 mim][AOT]-stabilized HIL microemulsion serves as an excellent medium for electropolymerization of EDOT, achieving better electropolymerization performance compared to traditional systems.[59]

Other Additives

Cosurfactants are typically short- and medium-chain alcohols or polyols. In addition to stabilizing the system and reducing the surfactant concentration, cosurfactants are also used to enhance solubilization capacity and expand the region of microemulsion (ME) existence on phase diagrams.[61,62]

To improve the water solubility and skin permeation of Panax Notoginseng Saponins (PNS),[63,64] a study designed an oil-in-water microemulsion (PNS ME) using jojoba oil, fractionated coconut oil, RH 40 + Span 80, and the cosurfactant D-panthenol as ingredients to enhance the skin permeation of PNS. The cosurfactant D-panthenol not only expanded the microemulsion area, reduced the surfactant usage, and alleviated skin irritation, but also stimulated dermal papilla cell (DPC) migration, exhibiting a synergistic effect in promoting hair growth.[65]

Physical and Chemical Properties

Transparency

Microemulsions differ significantly from conventional emulsions. Conventional emulsions are not thermodynamically stable, are heterogeneous, and appear opaque. In contrast, microemulsions are thermodynamically stable systems that form spontaneously, with a uniform texture. The droplet size of microemulsions is typically less than 150 nm, and their

appearance is transparent or translucent because their droplets are much smaller than the wavelength of visible light. They exhibit excellent centrifugal stability and are less prone to phase separation.[66–68]

Viscosity

Microemulsions are generally low-viscosity systems,[42] and their viscosity is related to the viscosity of the surfactants used. The low viscosity of microemulsions provides a significant advantage in drug delivery systems, as they can effectively promote drug absorption and transport within the body. However, due to their low viscosity and high flowability, microemulsions tend to have a shorter retention time on the skin, making them less suitable for transdermal drug delivery.[23] To address this issue, studies have utilized gels to modify the viscosity, thus better utilizing the advantages of microemulsions.[69]

Droplet Size Distribution

A typical characteristic of microemulsions is that the droplet size is smaller than 150 nm. Static and dynamic light scattering (SLS, DLS) techniques can be used to infer droplet sizes from molecular weight (Mw) measurements (SLS) and hydrodynamic radius (Rh) measurements (DLS), providing insight into the droplet structure.[70]

Stability Challenges of Biopharmaceuticals

Biopharmaceuticals, particularly protein and nucleic acid-based drugs, face numerous stability challenges due to their complex molecular structures and functional characteristics. Stability is a key consideration in biopharmaceutical development, as it directly determines the drug's shelf life, clinical efficacy, and patient safety. Physicochemical instability and aggregation tendencies may trigger immunogenic responses and significantly reduce therapeutic effectiveness. Understanding these challenges is critical for ensuring the efficacy and safety of these drugs.

Characteristics of Biopharmaceuticals

Protein-Based Therapeutics

Protein-based therapeutics are composed of 20 different amino acids linked by peptide bonds, with the sequence of these amino acids (ie, the primary structure) determining the protein's overall structure. These drugs typically exhibit complex tertiary or quaternary structures, and their function depends on correct folding and a stable spatial conformation. Proteins, due to their large molecular size, complex higher-order structures, poor stability, and susceptibility to physical and chemical degradation, are prone to losing activity or generating degradation products once their structure is compromised. This not only results in the loss of therapeutic effects but may also lead to unpredictable side effects, such as tissue damage, toxicity, or immunogenicity.[71] Polymer Based Protein Therapeutics.

Nucleic Acid Drugs

Nucleic acid drugs can directly interfere with the genetic material of pathogens or regulate gene expression within cells, thereby achieving therapeutic effects. The basic components of nucleic acids include the phosphodiester backbone and sugar rings, and the chemical properties of these components directly influence the drug's chemical stability. For example, the sugar rings (such as deoxyribose or ribose) and phosphate groups in nucleic acids are prone to hydrolysis in acidic or basic environments, which can lead to chain cleavage. Furthermore, the sequence and structure of nucleic acids (eg, single-stranded vs double-stranded, the formation of secondary structures) also affect their susceptibility to nucleases and, consequently, their biological stability.

Factors Affecting Stability of Protein Drugs

External Environment

Temperature

Proper control of processing, storage, and transportation temperatures for protein-based therapeutics is crucial to ensure their efficacy and safety. High temperatures can disturb the native protein conformation, causing aggregation at temperatures far below the protein's melting temperature (Tm). Heat-induced denaturation typically leads to irreversible

conformational changes,[72] and elevated temperatures can also accelerate chemical degradation reactions, such as deamidation and oxidation.[73]

pH

pH mainly affects protein stability by altering the charge state and conformation of the protein. The ionization state of amino acid residues changes at different pH levels, which can alter the overall charge of the protein, causing aggregation or precipitation through electrostatic interactions.[74] Extreme acidic or basic conditions can lead to protein unfolding, resulting in irreversible structural changes.

Light Exposure

Aromatic residues in proteins are highly sensitive to light, mainly undergoing photooxidation or forming oxygen free radicals (eg, superoxide anion and hydroxyl radicals), which can induce photodegradation. Tryptophan, in particular, is more sensitive than other amino acids, with ultraviolet (UV) light having a more pronounced effect on protein photodegradation than visible light. This is primarily because UV radiation, with its higher energy, can excite aromatic residues, leading to oxidation and free radical formation.[75] Luis et al[76] tested several IgG1 monoclonal antibodies (mAbs 1–5) under various environmental light conditions and compared them with ICH light exposure conditions. The recommended ICH light conditions contain high UV components, which may not be effective in ranking photosensitivity under normal protein drug product (DP) processing conditions. Furthermore, direct exposure to environmental light affects the quality of protein DPs, with the impact being determined by the amount of light exposure rather than light intensity.[77]

Oxygen

Protein oxidation may occur in the presence of oxidizing agents (such as peroxides, light, or metals) or even in the absence of such agents, a process known as autoxidation. Oxygen can facilitate photochemical oxidation reactions in proteins, leading to the oxidation of amino acid residues (such as tryptophan and tyrosine). Additionally, oxygen can induce the formation of free radicals, which then attack protein molecules, causing chain cleavage, crosslinking, or other chemical modifications.[78] The degradation, crosslinking, and aggregation of proteins in the presence of oxygen can drive these reactions forward, thereby reducing protein activity.

Internal Environment

Aggregation

Protein molecules may interact with each other in solution, leading to aggregation. This aggregation can be either reversible (eg, forming temporary dimers or multimers) or irreversible (eg, precipitates or fibrillar aggregates). Based on the types of intermolecular interactions, protein aggregation can be classified into covalent aggregation and non-covalent aggregation.[79] Covalent aggregation involves chemical bonds or partial unfolding between two or more monomers. A common mechanism for covalent aggregation is the formation of disulfide bonds between previously unpaired thiol groups, or oxidation of tyrosine residues leading to the formation of covalent crosslinks. Non-covalent aggregation occurs when proteins bind based on their charge or polarity, forming reversible aggregates through weaker interactions, such as hydrophobic-hydrophilic interactions.[80] Various external factors, such as changes in protein concentration or pH, can affect the equilibrium between monomers and non-covalent aggregates. Reversible protein aggregation can increase the viscosity of protein solutions.[81] It is noteworthy that protein aggregation not only markedly affects the physical stability and formulation feasibility of biopharmaceuticals but may also enhance the immunogenicity of the drug, stimulating the human immune system to produce antibodies. This, in turn, reduces therapeutic efficacy and poses serious challenges to the safety and effectiveness of the medication.

Degradation

Autoxidation and deamidation are two major chemical degradation processes in proteins. Under conditions of endogenous reactant accumulation or intramolecular interactions, certain amino acid residues (such as methionine, histidine, and cysteine) can undergo autoxidation without external oxidizing agents, forming disulfide bridges. In basic environments, high pH values can increase the deprotonation of amino acids, promoting oxidative reactions and strengthening disulfide

bond formation. In the presence of water, certain amino acids (such as asparagine and glutamine) can lose their amide group (-CONH2), forming cyclic imide intermediates that lead to structural distortion of the polypeptide. This reaction can occur in both acidic and basic conditions, where hydrogen ions in acidic environments can promote the reaction, while hydroxide ions in basic conditions act as catalysts.

Simply put, auto-oxidation refers to a process in which certain amino acids (such as methionine and cysteine) undergo oxidation without the involvement of external oxidizing agents. This occurs through intra- or intermolecular interactions, leading to the formation of disulfide bonds that alter the protein's structure; an alkaline environment can accelerate this process. Deamidation, on the other hand, involves the loss of an amide group from specific amino acids (such as asparagine and glutamine) in the presence of water. This reaction forms a transient cyclic intermediate, resulting in conformational distortion of the overall protein structure, and can be accelerated under both acidic and basic conditions.

Factors Affecting the Stability of Nucleic Acid Drugs

Nucleic acid drugs, due to their chemical composition and structural features, are highly sensitive to environmental conditions, which can drastically affect their therapeutic efficacy.

Hydrolysis

Hydrolysis is a primary mode of degradation for nucleic acid drugs.[82] Self-cleaving nucleases and protein-nucleic acid enzymes can break down nucleic acid drugs through hydrolysis. The phosphodiester bond, which connects nucleotide units in nucleic acids, is particularly vulnerable. In the case of mRNA, ester exchange reactions begin when the 2′-OH group attacks the phosphodiester bond, leading to cleavage of the P-O5′ bond. Research indicates that the base sequence and secondary structure of mRNA influence the rate of hydrolysis.[83,84] Specifically, base stacking stabilizes the nucleic acid structure, reduces enzyme contact, and affects enzyme recognition, thereby decreasing the cleavage rate of the phosphodiester bonds. This strategy is often used to improve the stability of nucleic acid drugs. For mRNA vaccines or antisense oligonucleotides, hydrolysis often occurs during transport, storage, or use. To enhance the stability of nucleic acid drugs, various strategies are employed, such as chemical modifications to the nucleic acid (eg, adding modification groups to the phosphodiester bonds) or using lipid nanoparticles (LNPs) to protect the drugs from hydrolysis, thereby extending their half-life in vivo.

Temperature

High temperatures can lead to the degradation of nucleic acid drugs, particularly heat-sensitive RNA drugs. Due to their unstable single-stranded structure, RNA molecules are highly prone to secondary structure changes or hydrolysis, resulting in the loss of biological activity. Packer et al[85] investigated the impact of different environmental temperatures (−20°C, 5°C, 25°C, and 40°C) on the stability of mRNA-LNP formulations. RP-IP HPLC analysis revealed that degradation occurred in all mRNA drugs over time, with higher temperatures leading to more significant degradation. While much research has focused on the effects of high-temperature environments on nucleic acid drug potency, exposure to freezing temperatures can also harm the quality of many nucleic acid drugs, particularly those in lipid-based formulations. Some adjuvants in nucleic acid drugs can aggregate, leading to phase separation or structural changes, negatively affecting the drug's immunogenic properties.[86]

pH

pH sensitivity has been shown to be a key factor in mRNA delivery and the subsequent release of mRNA into the cytosol after endocytosis. pH also plays a critical role in the stability of nucleic acid molecules, as it directly influences the hydrolysis rate of these molecules. Typically, nucleic acid molecules are more stable in neutral to mildly alkaline environments (pH 7–8.5). Bauer et al found that the hydrolysis rate of DNA fragments significantly accelerated when the pH dropped from 7.0 to 5.8.[87] Under highly acidic conditions, nucleic acid molecules are prone to deamination reactions, leading to chain cleavage. In highly alkaline conditions, the 2′-hydroxyl group in RNA is particularly susceptible to hydrolysis, and the double-stranded structure of DNA may unwind (denature). Extreme alkaline conditions can also break the phosphodiester bonds in DNA, causing degradation. To maintain stability, appropriate buffers are typically included in drug formulations to ensure the drug remains within a suitable pH range. For example, the original

formulation of the Comirnaty vaccine used phosphate-buffered saline, but due to significant pH fluctuations after freezing, it was replaced with Tris buffer, which is more stable at low temperatures and helps maintain pH through absorption or release of hydrogen ions.[88,89]

Ion Concentration

Ion concentration impacts the stability of nucleic acid drugs (eg, mRNA, DNA) in multiple ways, including their structural stability, drug delivery efficiency, immune response, and degradation rate. For instance, in the presence of Mg^{2+} or Ca^{2+}, the phosphodiester bonds in RNA molecules are more prone to hydrolytic cleavage.[90,91] Manon Ripoll et al[92] described a novel ionizable lipid DOG-IM4, which consists of an ionizable headgroup (composed of imidazole and dioleoyl lipids) and a flexible polyoxyethylene spacer between the head and tail. This headgroup is neutral at pH 7.4 in the extracellular space but becomes cationic after endocytosis, facilitating nucleic acid delivery and release in the cytosol (pH < 5.5), a key factor for the potency of nucleic acid drugs in vivo.

Mechanisms of Microemulsion in Enhancing the Stability of Biopharmaceuticals

Due to the impact of drug stability, there is often a significant discrepancy between the potent pharmacological effects of many drugs and their low bioavailability after administration, which limits their clinical application. Microemulsions and related formulations (such as self-microemulsifying drug delivery systems) are thermodynamically stable, isotropic, and transparent dispersion systems composed of water, oil, and surfactants—or formulations capable of spontaneously forming such systems. They possess notable advantages, including small droplet size, low interfacial tension, and strong solubilization capacity. By leveraging the physical and chemical stability of materials and controlling drug release properties, microemulsions can enhance the stability of biopharmaceuticals through mechanisms such as inhibiting P-glycoprotein activity and intestinal metabolism, increasing lymphatic absorption, and reducing food effects.[93]

Physical Stability

A microemulsion is a liquid system characterized by isotropy, low viscosity, and thermodynamic stability.[94] This structural feature enables preformed microemulsions to maintain long-term physical stability during storage and use, effectively preventing instability phenomena such as phase separation and precipitation. For example, microemulsions containing eutectic NRG/HPT, produced via melt quenching technology, can prevent the precipitation of naringin (NRG) and hesperidin (HPT) by creating a supersaturated state, thus enhancing the skin permeability of both compounds. In an in vitro study by Singer et al, Poloxamer 188 was shown to effectively inhibit the precipitation of CFZ (caffeine) by blocking the action of P-glycoprotein and promoting the formation of chylomicrons.[95]

At the same time, microemulsions and self-microemulsifying systems can form emulsions both in vitro and in vivo, allowing the drug to be uniformly dispersed in water in an ultrafine state, resulting in a transparent or semi-transparent homogeneous system (Figure 3). This highly dispersed state makes it easier for drug molecules to be absorbed and utilized by the body, reduces drug aggregation and precipitation, and enhances the physical stability of the drug.[96–98] Microemulsions also improve the solubility of both lipophilic and hydrophilic drugs, often achieving solubilization levels higher than the sum of their solubility in water and oil.[99,100] This improves the uniform distribution of the drug within the microemulsion, reducing the likelihood of aggregation and precipitation, thereby enhancing drug stability (Figure 4).

The solubility and dispersion of drug particles in microemulsions are enhanced due to their nano-sized droplets, which provide a larger specific surface area.[101,102] The rapid release of FK506 relies on the large interfacial area provided by the nanosized droplets formed in the SMEDDS. According to a study by Abeer Khattab et al,[103] after administration, the self-nanoemulsifying system (a subtype of self-microemulsifying system) comes into contact with gastrointestinal fluids and, with the aid of gastrointestinal motility, forms an oil-in-water (o/w) nanoemulsion. When this nanoemulsion is generated in the gastrointestinal tract, the drug is presented in a dissolved form within nanosized droplets, which provide a large surface area for enhanced drug release and absorption. This mechanism increases the solubility of lipophilic drugs with poor water solubility, such as CoQ, thereby improving their oral absorption and more effectively alleviating liver injury (Figure 5). Additionally, the small droplet size in microemulsions resists gravity-induced separation, further enhancing the system's stability.[104,105]

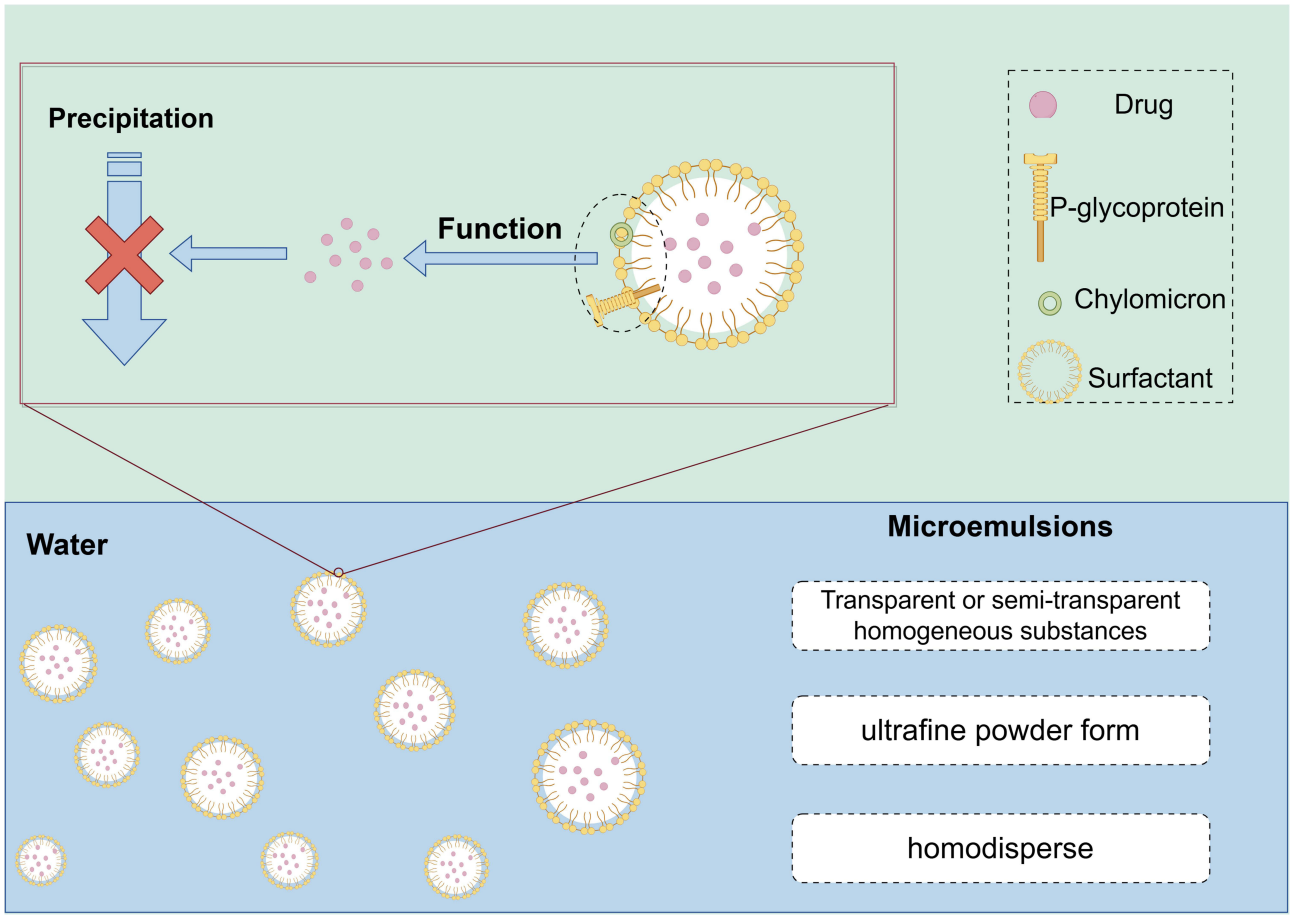

Figure 3 Inhibition of dispersion by chylomicrons and P-glycoprotein: Microemulsions can prevent the precipitation of drugs like CFZ by inhibiting the action of P-glycoprotein and promoting the formation of chylomicrons (Drawn by Figdraw).

These small droplet sizes also enable drug delivery via multiple routes[106] (Figure 6). For microemulsions containing both hydrophilic and hydrophobic phases, the incorporation and delivery of both hydrophilic and hydrophobic active pharmaceutical ingredients (APIs) are possible. Water-in-oil microemulsions are particularly suitable for lipophilic drug delivery, while oil-in-water microemulsions are ideal for hydrophilic drugs. Both hydrophilic and hydrophobic drugs can also be delivered through microemulsion gel systems.

Drug precipitation involves a complex sequence of processes, including the formation of supersaturated systems, nucleation, and crystal growth. Polymer precipitation inhibitors can stabilize the supersaturated system, preventing the formation and growth of crystals, thus avoiding drug precipitation (Figure 7). For example, Yeom et al[107] used Poloxamer 407 as a precipitation inhibitor to prepare a supersaturated self-microemulsion delivery system (VST Su-SMEDDS) loaded with valsartan, which prevented drug precipitation while increasing the drug loading capacity. Jaisamut et al[108] used Eudragit EP as a polymer precipitation inhibitor in a low-surfactant Su-SMEDDS formulation for curcumin, showing superior prevention of curcumin precipitation compared to standard curcumin self-microemulsions and suspensions.

By controlling particle size, microemulsions can reduce the risk of drug particles breaking apart or agglomerating under external forces such as shear or impact. This helps maintain the integrity and stability of the drug particles, extending the shelf life and usability of the drug (Figure 8). SMEDDS formulations can encapsulate both lipophilic and poorly water-soluble drugs, improving their solubility. Examples include cyclosporine, tacrolimus, atorvastatin, silymarin, itraconazole, carvedilol, fenofibrate, paclitaxel, ibuprofen, and simvastatin. The improvement in solubility is attributed to the small droplet size (less than 100 nm) and low interfacial tension.[109–114]

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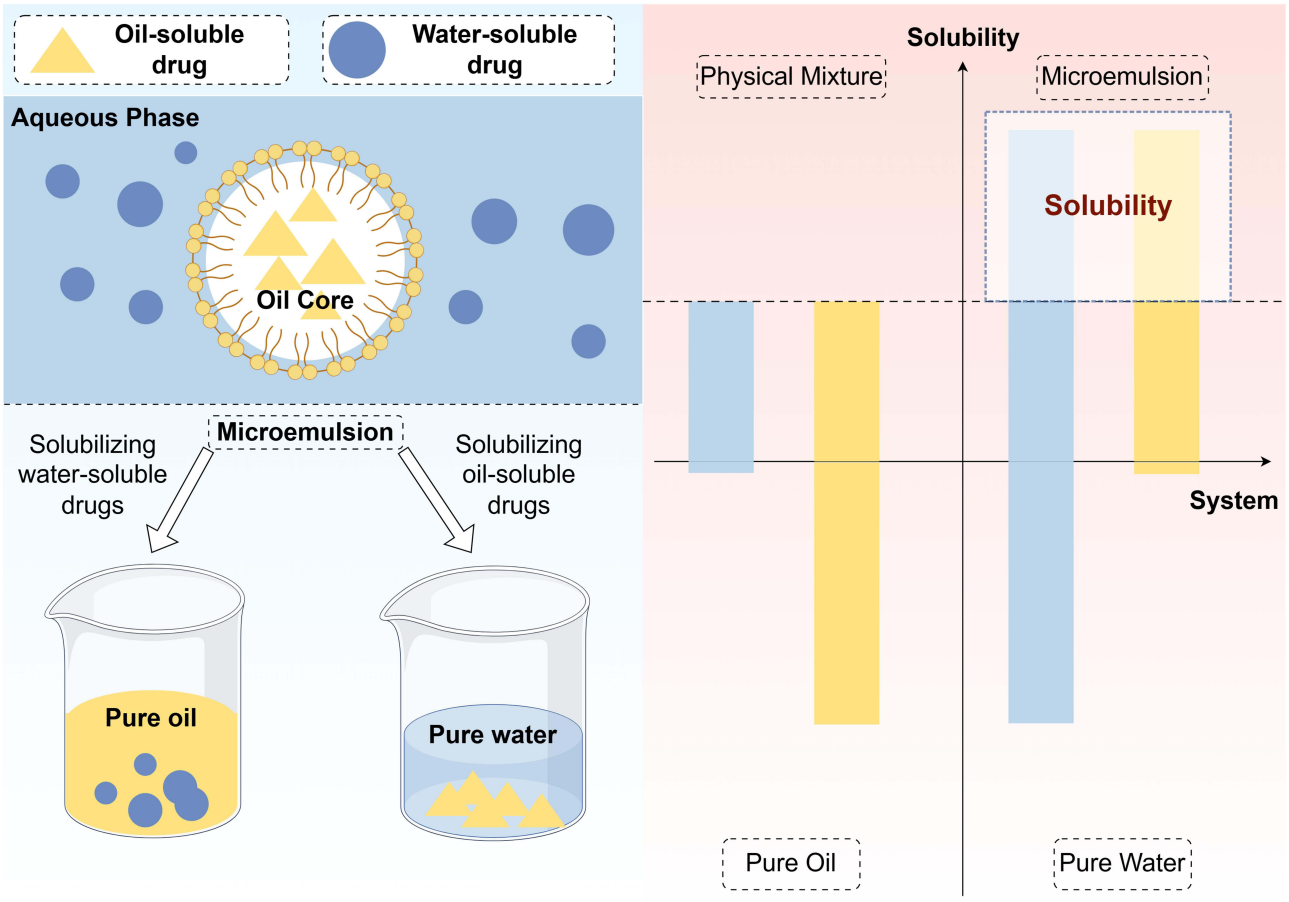

Figure 4 Solubilization of both oil-soluble and water-soluble drugs: Microemulsions enhance the solubility of both hydrophilic and lipophilic drugs, achieving a solubilization greater than the sum of their individual solubility in water and oil (Drawn by Figdraw).

Chemical Stability

Microemulsions can provide a relatively stable microenvironment that maintains the conformation and activity of drug molecules under specific conditions. This stable environment helps reduce oxidation and degradation reactions caused by environmental changes such as temperature and pH variations (Figure 9A). The chemical stability of microemulsions benefits a wide range of drugs. For example, microemulsions prepared using surfactant concentration methods and encapsulating beet juice pigment in W/O type microemulsion systems (pH 3–7) can enhance the light and heat stability of the pigment, preventing oxidation and degradation.[115] Likewise, lycopene encapsulated in microemulsions shows improved solubility and stability while effectively delaying its light-induced and thermal degradation, thus offering protection against degradation.[116] Studies have shown that the lycopene microemulsion (LME) group exhibited significantly greater cognitive improvement in rats compared with the traditional lycopene olive oil solution (LOO) group. The LME-treated rats had a markedly shorter escape latency ($p < 0.05$) and a number of platform crossings comparable to the normal control group. At the molecular level, LME induced a significantly stronger upregulation of neurogenesis-related genes (Pax6 and Nestin) than the LOO group ($p < 0.05$). Immunofluorescence analysis further revealed that the number of newly generated neurons ($BrdU^+/Dcx^+$) in the hippocampal region was substantially higher in the LME group, while the number of activated microglial cells ($Iba1^+$) was significantly lower.[117] Cristina Skoromoroshenko et al[118] found that curcumin encapsulated in plant oil-based microemulsions and gel microemulsions could utilize synergistic effects to prevent the influence of external degradation factors, thereby enhancing antioxidant activity and stability.[119] Furthermore, plant sterols incorporated into microemulsions, micelles, microcapsules, microparticles, nanoparticles, and liposomes can prevent or at least minimize the formation of oxidation products (POP).

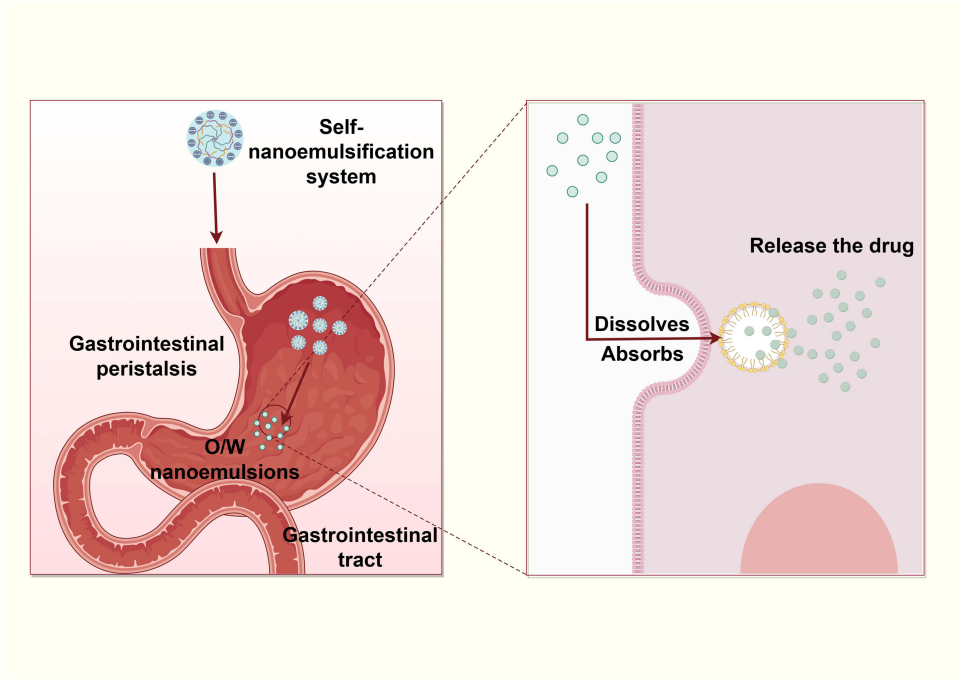

Figure 5 Drugs delivered in nano-sized droplets: Drugs are delivered in the form of nano-sized droplets, improving their solubility and absorption by increasing the surface area available for interaction with biological membranes (Drawn by Figdraw).

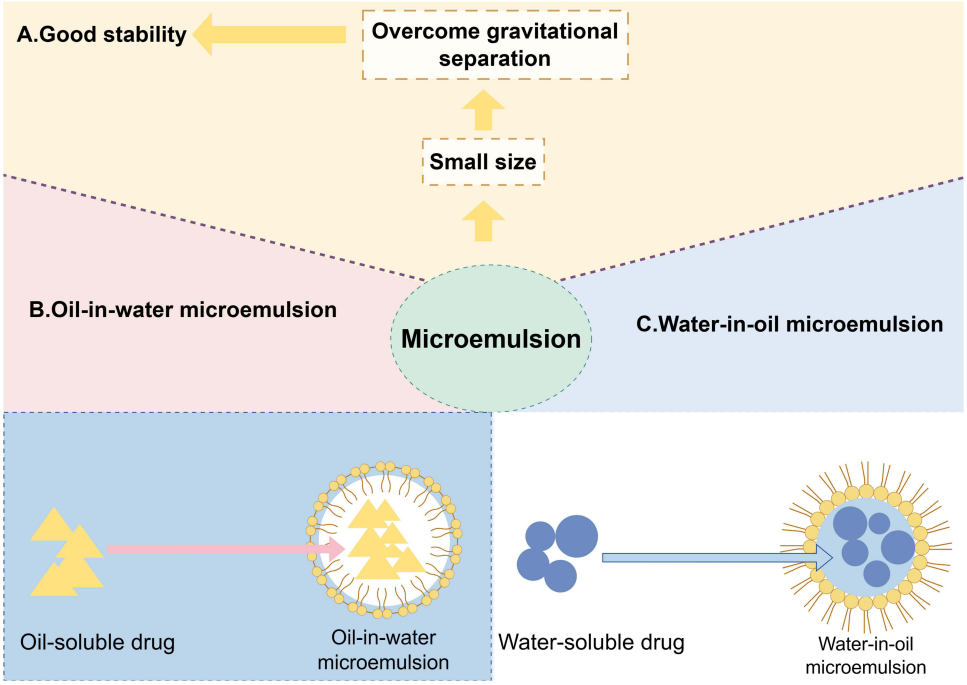

Figure 6 Resistance to gravity-induced separation and delivery via multiple routes: The small droplet size helps the microemulsion resist gravitational separation, ensuring long-term stability and enabling drug delivery through various routes (Drawn by Figdraw).

Microemulsions also reduce enzymatic hydrolysis and metabolic degradation in the body, extending the drug's action duration, thereby improving both stability and therapeutic efficacy[120,121] (Figure 9B). Salawi[122] demonstrated that liquid microemulsion drug delivery forms are advantageous in terms of gastrointestinal (GI) stability. Drugs pass through the digestive system within 20–30 minutes, with a shorter residence time in the stomach, thereby reducing exposure to GI

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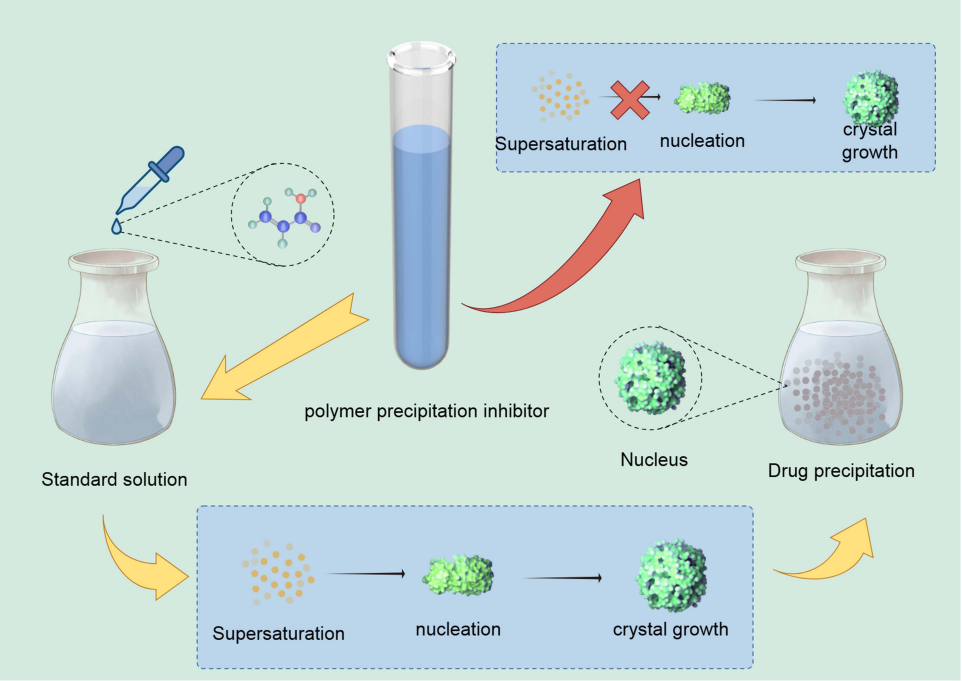

Figure 7 Inhibition of crystal nucleation and growth: Polymer precipitation inhibitors maintain the stability of supersaturated systems, preventing the formation and growth of drug crystals, thus avoiding drug precipitation (Drawn by Figdraw).

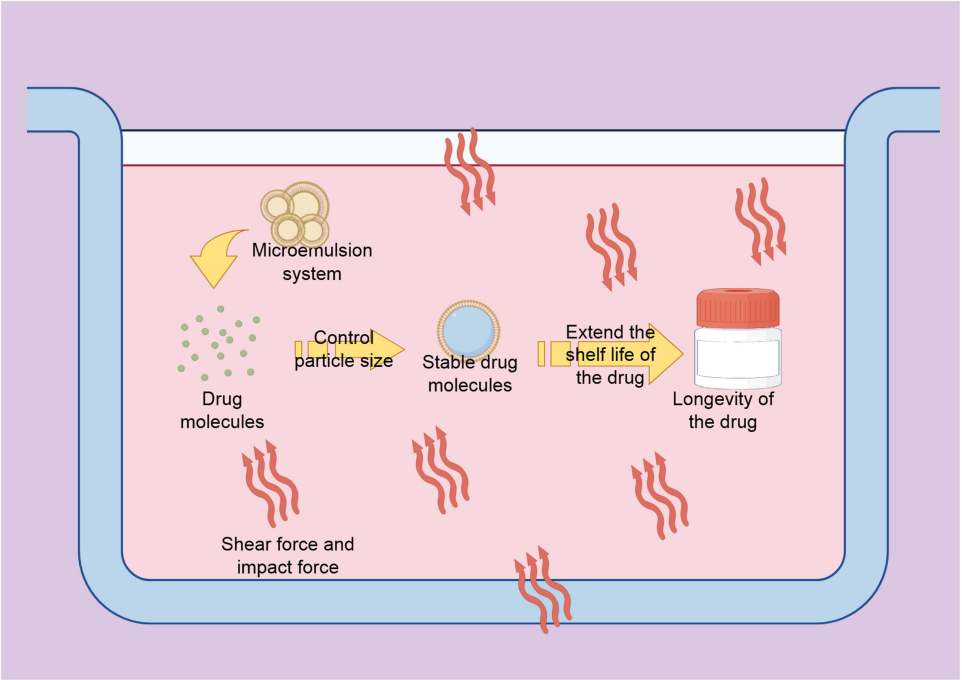

Figure 8 Control of drug particle size: By controlling the particle size of the microemulsion, the system can prevent drug particles from breaking or aggregating under shear or impact, maintaining the stability and integrity of the drug (Drawn by Figdraw).

enzymatic degradation and preventing premature drug breakdown, ensuring drug stability in the GI tract. Furqan A. Maulvi et al[123] showed that lidocaine, formulated as a microemulsion containing a lidocaine-tPP (tri-potassium phosphate) complex, exhibits depot effects in the skin, prolonging anesthetic effects. Compared to lidocaine

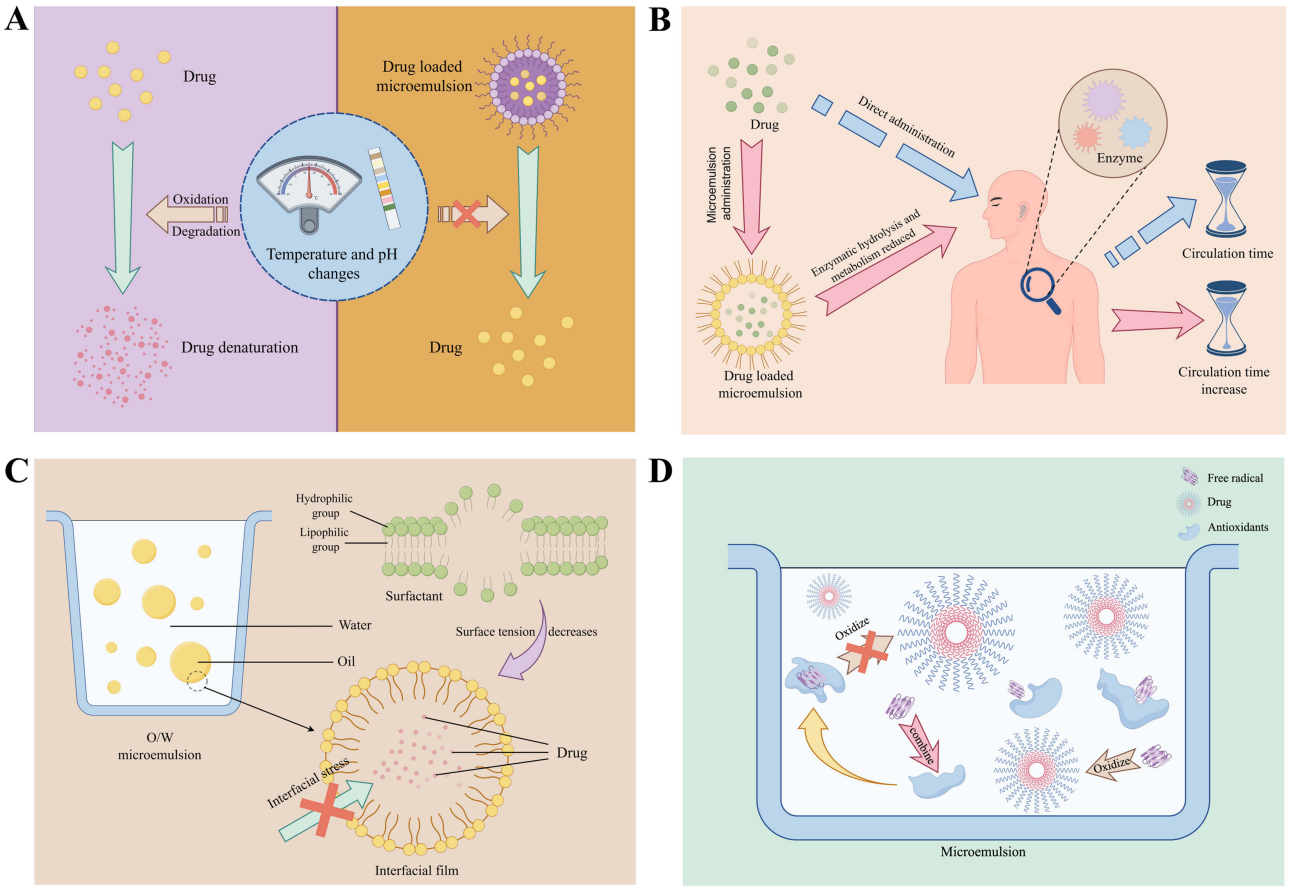

Figure 9 (**A**) Providing a stable microenvironment. (**B**) Reducing enzymatic hydrolysis and metabolism. (**C**) Reducing interfacial tension between oil and water. (**D**) Scavenging free radicals in the system (Drawn by Figdraw).

hydrochloride (4 hours) and ointment-based formulations (7 hours), the microemulsion offers sustained release for up to 12 hours.

Additionally, surfactants in microemulsions significantly reduce the interfacial tension between oil and water, forming stable interfacial films. This reduction in tension helps prevent aggregation and stress concentration of bioactive compounds at the interface, thus lowering the risk of drug degradation caused by interfacial stress[124–126] (Figure 9C). Self-microemulsifying drug delivery systems (SMEDDS) can enhance the solubility and oral absorption of BCS Class II drugs. Antioxidants in microemulsions can scavenge free radicals in the system, preventing oxidative damage to bioactive components (Figure 9D). Zhang et al[18] discovered that redox conversion of PSeP enabled efficient switching of ODD/HCO40/DGME/PSeP/water microemulsions. These microemulsions significantly improve the solubility (23 times), stability, antioxidant capacity (91.74% DPPH· free radical scavenging rate), and skin permeability of curcumin, demonstrating strong potential for encapsulating and delivering curcumin and other bioactive substances. New microemulsions composed of co-solvents (DES), Tween 80, and water exhibit stronger hydrogen bonds and van der Waals interactions compared to ethanol, methanol, and acetone, improving the solubility, stability, and antioxidant activity of carotenoids, which show higher DPPH free radical scavenging activity. Moreover, the stable microenvironment of microemulsions helps reduce stress responses caused by environmental changes, thereby protecting bioactive components from damage.[127,128] The surfactant coating on nano-droplets can also protect unstable biological molecules from the effects of chemically active silver ions.

Drug Release Properties

The drug concentration gradient exists between the inside and outside of the microemulsion droplets, and the permeability of the drug through the droplet interface can be modulated. This allows microemulsions to achieve sustained or

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controlled release of drugs, reducing fluctuations in drug levels within the body, and improving both drug stability and bioavailability. As a drug carrier, microemulsions can enhance the solubility and permeability of drugs, facilitating their absorption and utilization by the body (Figure 10A). For example, an O/W microemulsion prepared with a 2:1 ratio of soybean lecithin and alkyl glycoside hydroxypropyl sulfonate has shown excellent permeation enhancement for insoluble polyphenolic compounds.[129] When chloramphenicol is encapsulated in a water-in-oil (W/O) microemulsion without alcohol, the phenyl ring of the chloramphenicol molecule is positioned close to the α2-CH2 group and the oxyethylene group of the surfactant molecules. This facilitates the selective release of chloramphenicol from bulk water, significantly improving its stability. The nanodroplets in the microemulsion, with their large surface area, enhance interactions between polyphenolic compounds and biological membranes or intestinal enzymes, facilitating effective transfer through intestinal mucosa and improving dissolution and dissolution rate.[130]

Drugs encapsulated in microemulsions are contained within tiny droplets that function as "miniature reservoirs" for the drug. By adjusting the composition and structure of the droplets, the drug release rate can be controlled, enabling sustained or controlled release (Figure 10B).[131–133] Self-microemulsifying drug delivery systems (SMEDDS) enhance the oral bioavailability of docetaxel by inhibiting P-glycoprotein and cytochrome P450 metabolism, limiting first-pass metabolism in the liver. Studies have shown that curcumin, encapsulated in an oil-based microemulsion with butyl acetate as the oil phase and stabilized with Pluronic F127 and sodium decanoate, exhibits over 88% encapsulation efficiency (EE), extended release time, and high anticancer activity. These release properties help maintain a stable drug concentration in the body, preventing sharp fluctuations in drug levels and improving drug stability and efficacy.[134] The unique structure of microemulsions facilitates better absorption and utilization of drugs by the body.[135]

The dispersion state of drugs in microemulsions improves their solubility and permeability, aiding in the passage of the drug across biological membranes into cells (Figure 10C). A study by CO-S-SME demonstrated changes in the gut microbiota composition, reducing the ratio of Firmicutes to Bacteroidetes, lowering the relative abundance of lactic acid bacteria, and modulating both alpha and beta diversity, thus promoting drug absorption[136] (Figure 10D). This improved bioavailability not only enhances the drug's efficacy but also reduces drug wastage in the body, indirectly improving drug stability. Microemulsions also exhibit lymphatic targeting, enabling direct drug delivery to the lymphatic system. This targeting property helps reduce drug loss in systemic circulation, increasing drug concentration in target tissues and thereby enhancing both the drug's efficacy and stability. SME promotes the secretion of endogenous bile salts and phospholipids, facilitates transmembrane absorption of drugs after gastrointestinal digestion, enhances the formation of lipoproteins/chylomicrons, and inhibits P-glycoprotein and other efflux pumps, thus promoting drug absorption[137] (Figure 10E). Additionally, by altering drug distribution in tissues, microemulsions can reduce drug clearance and elimination, further enhancing bioavailability.[138,139]

SMEDDS significantly improve the oral bioavailability of poorly soluble drugs through mechanisms such as enhancing drug solubility, increasing cellular permeability, and triggering lymphatic transport. By modifying the composition and structure of the microemulsion, it is possible to adjust the kinetic parameters of drug release, such as release rate and duration. This adjustment capability allows microemulsions to be designed with specific release characteristics to optimize drug efficacy and stability according to different therapeutic needs (Figure 10F). A new SMEDDS formulation using BHL as the oil phase exhibited approximately sixfold higher bioavailability in vivo compared to a standard EFA suspension.[140] Curcumin-SMEDDS developed using BHL as the oil phase and a novel semi-synthetic oleic acid derivative (E1E) showed a 14-fold and 2.6-fold increase in curcumin solubility compared to oleic acid and oleic acid ethyl ester, respectively.[136]

Organic gels formed from oil-in-water microemulsions, using natural polymers such as gelatin, agar, or cellulose derivatives, can maintain enzyme activity encapsulated in the aqueous core of the microemulsion and enhance its stability within the gel matrix. A study by Surajit Das et al[141] demonstrated that microemulsion-gel formulations exhibited superior stability compared to microemulsions alone and significantly improved the in vitro membrane permeation (release) rate of ivermectin. Chen Huabing et al[142] reported that a microemulsion hydrogel composed of 3% ibuprofen, 6% EO, 30% Tween 80/PG (2:1), and water had a permeation rate of up to 38.06 μg cm^-2 h^-1, significantly enhancing ibuprofen permeation compared to its saturated solution.

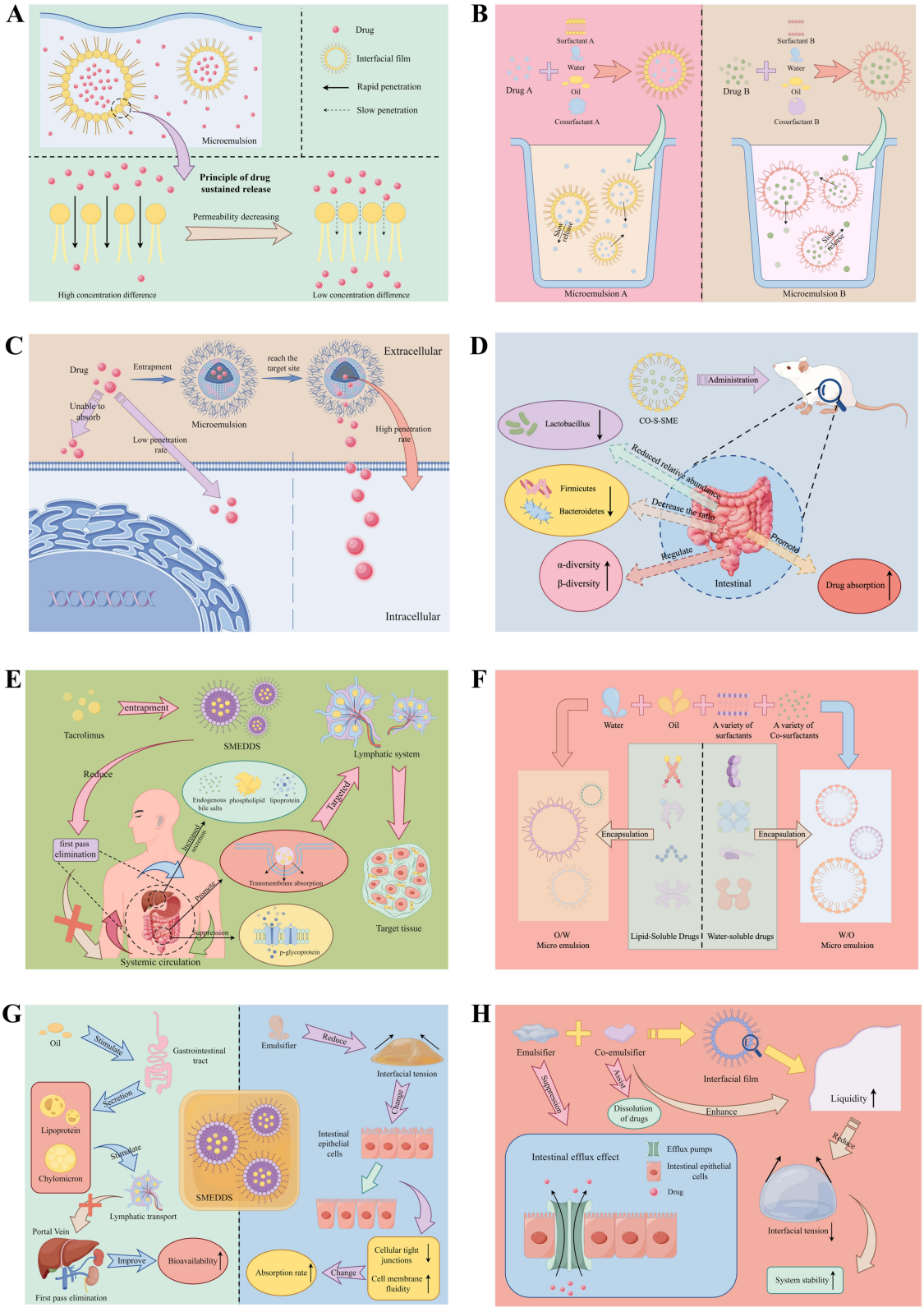

Figure 10 (**A**) Control of drug sustained and controlled release. (**B**) Regulation of drug release rate. (**C**) Improvement of drug solubility and permeability. (**D**) Alteration of gut microbiota composition. (**E**) Lymphatic targeting. (**F**) Regulation of drug release kinetics. (**G**) Prevention of first-pass effect. (**H**) Reduction of interfacial tension (Drawn by figdraw).

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In SMEDDS, the oil phase stimulates the gastrointestinal tract to produce lipoproteins and chylomicrons, facilitating lymphatic transport and enhancing bypass transport, thereby avoiding the first-pass effect in the hepatic portal system and indirectly improving drug bioavailability.[143] Surfactants reduce interfacial tension, alter the fluidity of small intestinal epithelial cell membranes and tight junctions between cells, increasing drug membrane permeability and further improving drug absorption (Figure 10G). Some surfactants can also increase drug absorption by inhibiting intestinal efflux. Cosurfactants assist in dissolving drugs and, in conjunction with surfactants, form the interface membrane of the microemulsion, increasing its flexibility, reducing interfacial tension, and enhancing the system's stability (Figure 10H). Some microemulsions may undergo lipolysis under the action of pancreatic enzymes and bile, forming smaller droplets and bile salt micelles, which further enhance transmembrane absorption of drugs.[144]

Specific Applications of Microemulsions in Biopharmaceuticals

Protection and Delivery of Protein Drugs

Insulin is the core protein drug for diabetes treatment and is traditionally administered by subcutaneous injection, which often leads to poor patient compliance. Oral delivery is the most desirable alternative route; however, it faces several barriers, including degradation by gastric acid, enzymatic hydrolysis, and low intestinal permeability.[145] A study constructed a W/O/W-type insulin microemulsion stabilized with albumin (Alb) and incorporated piperine (PIP) as a permeation enhancer. This system remained stable in simulated gastrointestinal environments, showing no significant changes in particle size or PDI ($P > 0.05$). Albumin markedly enhanced insulin protection—after 1 hour in trypsin solution, only about 40% of insulin degraded in the ME(INS)-PIP-Alb group, significantly lower than the 65% observed in the non-Alb group ($P < 0.05$). In vivo, the cumulative hypoglycemic effect of ME(INS)-PIP-Alb (38.84%) was 3.2 times that of the non-Alb group, achieving a relative bioavailability of 25.67% and an apparent permeability coefficient four times higher than that of free insulin.[146] This study convincingly demonstrated that microemulsions can effectively enhance the oral stability and delivery efficiency of insulin through dual mechanisms of interfacial stabilization and enzymatic inhibition.

Stabilization of Peptide Drugs

Cyclosporine A (CsA) is a highly lipophilic cyclic peptide with poor and variable oral absorption, representing a classic case of a biotechnologically derived poorly soluble drug. Its marketed microemulsion formulation is a landmark example of microemulsion technology in the biopharmaceutical field. The commercial product Neoral®, a self-microemulsifying preconcentrate system, was developed as an improved version of Sandimmune®. Upon oral administration, Neoral® spontaneously forms a microemulsion with droplet sizes below 0.15 μm in the gastrointestinal tract, significantly enhancing CsA bioavailability (relative bioavailability 174–239%) and improving dose linearity. Clinical studies showed that Neoral® achieved faster and more consistent absorption (shorter time to peak concentration, reduced interindividual variability) and was less affected by food. In renal transplant patients, the required dose to achieve equivalent trough concentrations was reduced by approximately 16%, with a lower incidence of acute rejection and comparable safety. This case exemplifies how microemulsion technology can improve the oral stability, absorption efficiency, and clinical efficacy of peptide drugs.[147]

Encapsulation and Delivery of Nucleic Acid Drugs

Nucleic acid drugs (eg, siRNA, mRNA) are highly negatively charged, hydrophilic, and easily degraded by nucleases, posing major delivery challenges. Cationic microemulsions and liposomes can encapsulate nucleic acids through electrostatic interactions while providing strong enzymatic protection.[148] RNA interference (RNAi) is a naturally occurring defense mechanism, with small interfering RNA (siRNA) identified as the mediator of RNAi in mammalian cells.[149,150] Delivery of exogenous siRNA can harness this endogenous mechanism to achieve gene silencing, offering new therapeutic opportunities. However, its clinical application remains limited by key challenges such as delivery efficiency, stability, off-target effects, and immunogenicity.[151]

To address these challenges, microemulsions offer promising solutions. One research team developed a thermosensitive gel system based on W1/O/W2 multiple microemulsions (MMEs) for vaginal siRNA delivery. The stable MMEs, prepared via a two-step emulsification process, exhibited particle sizes of 166–279 nm in various media, effectively encapsulated and protected siRNA, and provided sustained release for up to 13 hours. In vitro and in vivo studies demonstrated excellent transfection efficiency and gene silencing capability, along with good biocompatibility, minimal cytotoxicity, and no mucosal irritation. This MMEs-gel system shows great potential as a vaginal siRNA delivery platform, particularly for the prevention and treatment of reproductive tract infections such as HPV.[152]

Another study utilized a water-in-oil microemulsion system to deliver PrP-siRNA via rectal administration, successfully crossing the blood–brain barrier and significantly reducing prion protein expression in mouse brains (PrP^c protein decreased by 28%, mRNA by 17.6%). In a prion infection model, the formulation alleviated neuronal vacuolation and gliosis and promoted neuronal survival, confirming that microemulsions can exert neuroprotective effects by stabilizing siRNA and enhancing delivery efficiency.[153]

For mRNA delivery, researchers employed a microemulsion-based method to synthesize stimuli-responsive dendritic nanogels (DNGs). These DNGs exhibited uniform particle sizes (100–300 nm) and excellent colloidal stability for up to 90 days in various media. Among them, DNGs-pH showed the strongest mRNA condensation ability (complete condensation at a mass ratio of 8:1), and after loading, the complex particle size decreased by 30–40%. In dendritic cells, DNGs-pH/mEGFP complexes achieved the highest EGFP expression efficiency—3.6-fold and 1.2-fold higher than DNGs-GSH and DNGs-ROS, respectively—comparable to commercial transfection reagents. Moreover, at a concentration of 400 μg/mL, over 80% cell viability was retained.[154] This work highlights the great potential of microemulsion-derived nanogels for significantly enhancing mRNA stability and delivery efficiency.

Case Analysis

Jojoba oil is a promising transdermal drug delivery carrier, offering better oil phase properties for microemulsion formation and stability than other vegetable oils, with the added benefits of low skin irritancy and anti-inflammatory properties.[155] Previous experiments with microemulsions have highlighted potential skin irritation due to the use of high concentrations of surfactants or combinations thereof.[156] Studies[157,158] have shown that the surface tension of jojoba oil is similar to that of human skin, which facilitates diffusion between the oil and skin and enhances drug permeation through the skin. Ketorolac, with a short half-life and severe gastrointestinal side effects when administered orally, and lidocaine, a local anesthetic requiring frequent dosing to maintain its effect, both benefit from transdermal delivery, which can modify their limitations and extend drug action. S.M. Assaf's team studied jojoba oil as a potential carrier with enhanced permeation capabilities in microemulsions and its effects on the stratum corneum. They selected Brij 97, Tween 80, and Cremophore as surfactants and hexanol as a co-surfactant for microemulsion preparation. Five different formulations of jojoba oil microemulsions were set up, followed by selection of surfactants, characterization of jojoba oil, characterization of the jojoba oil microemulsions, stability studies, and skin irritation tests.[159] Results confirmed the physical stability of jojoba oil microemulsions at higher temperatures and showed no skin irritation;[156,157] however, microscopic observations after 24 hours revealed some disruption in the stratum corneum. Jojoba oil microemulsions demonstrated excellent capability in improving drug permeation and duration of action.

Redox reactions occur in every organism,[160] and pathological studies indicate that inflammatory or cancer cells contain more reactive oxygen species than normal cells.[161] Redox-responsive microemulsions (ME) may represent a promising nanoplatform for encapsulating and releasing drugs at specific cellular sites. Polyphenols are common plant-derived natural products with antioxidant properties.[162] Curcumin, extracted from turmeric rhizomes, is an inexpensive and beneficial polyphenol hindered by low water solubility, bioavailability, and poor thermal and photostability for practical applications.[163] Zhang's team evaluated whether redox-responsive microemulsions (ME) could enhance the antioxidant properties of curcumin, using PSeP and diethylene glycol monohexyl ether (DGME) as cosurfactants, ethoxylated hydrogenated castor oil (HCO 40) as a surfactant, and 2-octyl-1-dodecanol (ODD) as the oil phase. They studied the redox-responsive behavior of PSeP-ME under the influence of oxidants (H2O2) and reductants (N2H4·H2O), analyzing through NMR, phase diagrams of PSeP-ME, macroscopic phase behaviors, dynamic light scattering (DLS) characterization, interfacial tension, and the potential mechanisms of PSeP-ME's redox reactions. PSeP-ME was also

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tested as a carrier for encapsulating curcumin, improving its storage, thermal stability, photostability, antioxidant capacity, and transdermal absorption. Essentially, the redox responsiveness of PSeP-ME depends on the reversible transition between amphiphilic PSeP and hydrophilic PSePOx, with PSeP-ME showing high sensitivity to redox agents, particularly in the reduction phase.[164] This redox-responsive ME could be an ideal candidate for encapsulating and transdermally delivering curcumin and other low water-soluble bioactive substances.

Resveratrol, insoluble in water and unstable, has limited applications.[165,166] Microemulsions, with low viscosity and strong flowability, have short skin retention times, making them unsuitable for direct transdermal administration.[167] Li's team improved the deficiencies of resveratrol and microemulsions by dispersing resveratrol microemulsion in a gel, creating a resveratrol microemulsion gel to utilize its advantages. Through in vitro and in vivo skin retention tests, they confirmed that the resveratrol microemulsion gel enhances drug retention in the skin, with its in vitro transdermal release following a zero-order release model, thus extending the duration of drug action. Cell tests and zebrafish embryo tests validated that the microemulsion enhances the inhibition of tyrosinase activity and melanin production by resveratrol. The resveratrol microemulsion gel inhibited tyrosinase activity in A375 human melanoma cells and reduced melanin content in cells and zebrafish, demonstrating its efficacy and safety through human skin patch tests.

Periodontitis is a multifactorial inflammatory disease characterized by severe alveolar bone damage and attachment loss.[168] Alveolar bone damage is caused by an imbalance between T helper 17 (Th 17) and regulatory T cells (Treg), inducing overexpression of interleukin (IL) 17, exacerbating the progression of periodontitis.[169] Based on this mechanism, Li's team[170] aimed to regulate the ROS-macrophage polarization cascade, reshape the Th 17/Treg homeostasis, and construct a new system for promoting alveolar bone regeneration in periodontitis treatment. Quercetin (Qu) has excellent antioxidant and anti-inflammatory activities and can clear ROS while protecting bone tissue involved in SMAD, Nrf 2, and Wnt-dependent pathways.[171] Peppermint oil (PO), extracted from peppermint, has analgesic and anti-inflammatory effects on the gums.[172] Therefore, the team prepared folate-modified curcumin microemulsions (FA-Qu-MEs) with peppermint oil as part of the mixed oil phase to increase quercetin solubility and formulated a thermosensitive hydrogel system (FA-Qu-MEs@Gel) (as shown in Figure 11). They injected FA-Qu-MEs@Gel into the periodontal pocket, forming an in situ solution-gel transition to extend drug retention time and achieve sustained release. FA-Qu-MEs actively target macrophages via folate receptors, effectively clearing intracellular ROS, promoting the transition from M1

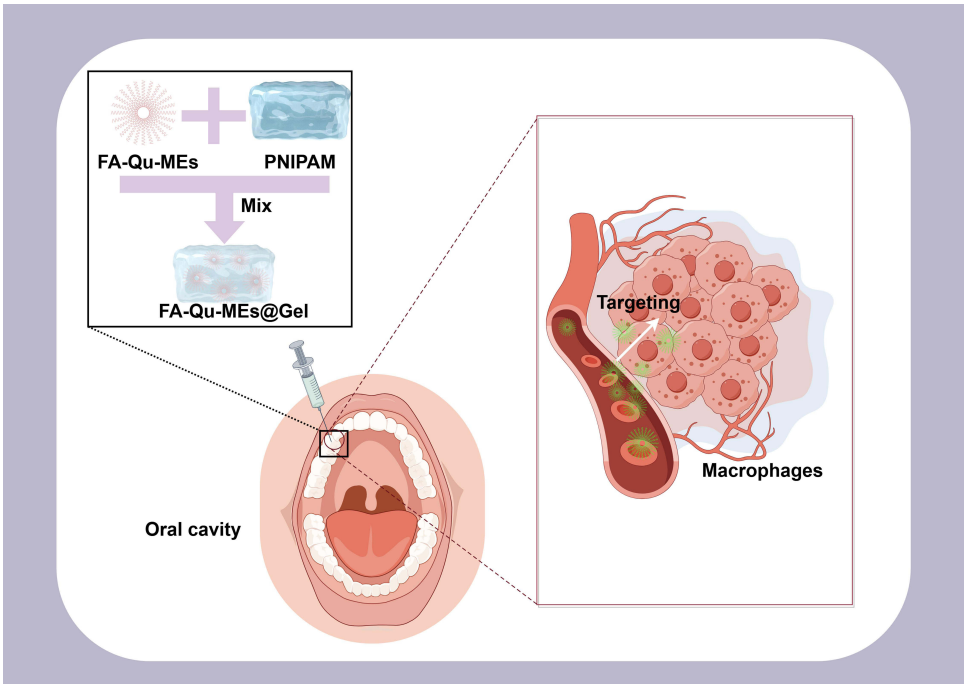

Figure 11 Preparation of Thermosensitive Hydrogel System and Targeted Drug Delivery (Drawn by FigDraw).

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to M2 macrophage phenotypes, thereby alleviating the inflammatory environment, restoring Th 17/Treg homeostasis, and repairing damaged alveolar bone.[170]

Transarterial Chemoembolization (TACE) has demonstrated significant clinical efficacy and is widely recognized as the standard first-line treatment for patients with intermediate and advanced hepatocellular carcinoma (HCC).[173,174] Current TACE therapies, combined with free doxorubicin (DOX) – lipiodol emulsions (DOX/L), offer a promising clinical approach for the curative treatment of advanced HCC. However, these formulations suffer from poor colloidal stability, which not only greatly reduces tumor retention but also accelerates the release of the drug into the bloodstream, leading to suboptimal clinical outcomes.[175] Liu et al[175] developed doxorubicin (DOX) – disulfide-crosslinked polymer vesicles (Ps-DOX) combined with lipiodol (Ps-DOX/L) to form ultra-stable and uniform microemulsions, aimed at improving stability and prolonging drug release. In vitro studies on the anti-HCC activity of Ps-DOX and Ps-DOX/L emulsions, as well as in vivo investigations on systemic exposure, tumor retention, and therapeutic efficacy in an N1S1 orthotopic liver cancer rat model, demonstrated that Ps-DOX not only serves as an oxidation-reduction responsive agent to enhance intracellular release of DOX into liver cancer cells but also stabilizes the lipiodol emulsion. Ps-DOX/L microemulsions exhibited excellent emulsification properties, including enhanced stability, optimal particle size, good injectability, prolonged tumor retention, sustained and controlled drug release, reduced plasma exposure, and minimal systemic toxicity.[176–180] The doxorubicin-lipiodol microemulsion thus provides a novel and potentially translatable strategy for TACE in treating advanced liver tumors.

Future Directions of Microemulsion Technology

Technological Innovations

Surfactants play a crucial role in the formation of microemulsions by lowering surface tension and enhancing emulsification speed. Common surfactants used in microemulsions include anionic, nonionic, zwitterionic, cationic, and mixed surfactants. These surfactants offer various advantages depending on the type of product and the application in the reaction process.

As shown in Table 1, recent studies have highlighted the remarkable potential of commonly used surfactants in enhancing drug stability, improving bioavailability, and reducing irritation. Among them, nonionic surfactants (such as Tween 80 and Poloxamer) are widely used in protein drug delivery owing to their excellent biocompatibility and ability

Table 1 Advantages, Types, and Common Applications of Surfactants in Microemulsions

Surfactant Name	Type	Advantages	Typical Applications	References
Tween 80	Nonionic	Excellent emulsifying capacity, strong solubilization ability, high biocompatibility, low irritation	Used in protein and peptide microemulsions to prevent aggregation and enhance physical stability	[9,181–184]
Tween 20	Nonionic	Mild, minimal effect on protein denaturation	Suitable for microemulsion systems of sensitive therapeutic antibodies and enzyme preparations	[182–185]
Poloxamer (P188, P407)	Nonionic block copolymer	Amphiphilic block structure effectively inhibits protein aggregation; thermoreversible gelation suitable for local delivery	Applied in thermosensitive in situ gel microemulsions to prolong local drug retention and enhance therapeutic protein stability	[186–188]
Lecithin	Zwitterionic	Excellent biodegradability and biocompatibility, high safety, capable of forming stable bilayer structures	Primary emulsifier in lipid-based microemulsions for lipophilic vitamins and nucleic acid delivery, providing strong encapsulation and protection	[189]
Labrasol	Nonionic	Outstanding self-microemulsifying ability, significantly enhances oral bioavailability of poorly soluble drugs	Used in self-microemulsifying drug delivery systems (SMEDDS) to improve absorption of orally administered peptide drugs	[190,191]
Cremophor RH 40	Nonionic	Strong solubilizing capacity, forms stable microemulsions, suitable for multiple administration routes	Applied in microemulsion formulations of poorly soluble chemical drugs to increase drug loading and formulation stability	[192–194]

(*Continued*)

Table 1 (Continued).

Surfactant Name	Type	Advantages	Typical Applications	References
Sucrose Esters	Nonionic	Biodegradable, extremely low irritation, high safety	Suitable for oral and transdermal microemulsions, improving drug solubility and absorption	[195]
Alkyl Polyglucosides(APG)	Nonionic	Minimal skin and mucosal irritation, excellent biodegradability	Used in transdermal and mucosal microemulsion delivery systems (eg, nasal, oral), enhancing drug permeability and stability	[196,197]
Cocamidopropyl Betaine	Zwitterionic	Mild, non-irritating, broad pH applicability, good compatibility with other surfactants	Commonly used as a co-emulsifier or stabilizer to reduce potential irritation and enhance formulation safety	[198]
Quaternary Ammonium Salt	Cationic	Positively charged, easily modifiable, suitable for gene delivery	Used in nucleic acid microemulsions (eg, siRNA, mRNA) to improve encapsulation efficiency and cellular uptake	[199–201]

to inhibit protein aggregation. In contrast, cationic surfactants (such as quaternary ammonium salts) possess easily modifiable structures and efficient gene delivery capabilities, giving them distinct advantages in the design of nucleic acid drug carriers. In the last five years, newly emerging surfactants in microemulsions have shown distinct benefits, classified by their types and applications, as summarized in Table 1.

However, recent research by Jonas Blahnik et al suggests that surfactants may not always play a positive role in polymerization reactions mediated by microemulsions. Surfactant residues can, to some extent, affect the properties of the final products. The use of polymerizable aqueous and oil co-solvents may emerge as a promising approach to enhance the stability of related materials in the future.[17] Table 1 summarizes the advantages, types, and common applications of frequently used surfactants in microemulsions.

Intelligent Microreactors in Microemulsion-Based Drug Delivery Systems

Intelligent microreactors have been widely applied in microemulsion-based drug delivery systems to control the physicochemical properties of the microemulsions and improve therapeutic efficacy. Traditional intelligent microreactors often suffer from low mixing efficiency, and most are single-phase emulsions, which exhibit high homogeneity and complete isotropy in droplet size. These limitations hinder their application in multiphase reactions.[202–204] However, in recent research by Wei et al, the differences in solubility of reactants across different phases were utilized to achieve spatial separation and selective distribution of reactants. The complex droplet microreactor successfully enabled a three-phase cascade reaction model under mild temperature and no stirring conditions, with esterification conversions reaching 100%. By precisely controlling the structure and morphology of the droplet microreactors, the efficiency and selectivity of multiphase reactions can be significantly improved, offering new strategies for green chemistry and sustainable synthesis.[204]

In contrast to Wei D's approach, Zhang et al employed a biomimetic microreactor to simulate intracellular reaction environments, utilizing a Pickering emulsion microreactor to achieve high-efficiency continuous flow cascade reactions.[205]

Future Applications

Microemulsions, as fine, transparent oil-in-water or water-in-oil dispersion systems, are considered promising for targeted gene therapy and viral vaccines due to their long-term stability, self-emulsifying properties, extended shelf life, photostability, and high drug solubility.

In a study by Lamaisakul et al, a novel vaccine prepared with a cationic microemulsion as an adjuvant was shown to elicit stronger humoral and cellular immune responses, making it a potential candidate for rapidly mutating influenza vaccine production.[206] Additionally, Peng et al developed a microemulsion loaded with ultra-small iron oxide nanoparticles and transforming growth factor-β1 (TGF-β1) siRNA. This microemulsion precisely delivered TGF-β1 siRNA to

tumor cells, significantly inhibiting tumor growth and metastasis, thus providing an effective gene therapy strategy for cancer treatment. Moreover, the microemulsion-enhanced magnetic resonance (MR) imaging performance offers high-resolution imaging for early tumor detection and monitoring.[207]

Future designs of microemulsions could expand to the delivery of other drugs or genes, offering new possibilities for diagnostics and therapeutic interventions across various biological systems.

The latest exploration of microemulsion technology includes the development of self-microemulsifying drug delivery systems (SMEDDS), which play a significant role in improving bioavailability, targeted delivery, and the physicochemical properties of drugs. In research by Xia F and Liu Y, SMEDDS was utilized as an effective oral delivery system for macromolecular drugs. This system's ability to survive in the gastrointestinal tract, undergo lipid digestion, penetrate the epithelium, and be transported via lymphatics to accumulate in the liver was demonstrated for the delivery of chlorambucil, a promising drug for hepatocellular carcinoma treatment.[208,209] This supports the extensive application potential of cancer and gene therapy via these pathways and other emerging targets.

Conclusion

This review systematically discusses the core mechanisms, current formulation challenges, and corresponding strategies of microemulsions in enhancing the stability of biopharmaceuticals, while emphasizing their promising applications in advanced biologics such as gene therapy, oral peptide formulations, and tumor-targeted delivery. As an advanced drug delivery system, microemulsions have been widely utilized in the biopharmaceutical field to improve the stability and delivery efficiency of protein-, peptide-, and nucleic acid-based drugs. These therapeutics commonly face challenges such as aggregation, chemical degradation, and physical instability. Through their unique oil–water–surfactant system, microemulsions can form a thermodynamically stable nanoscale microenvironment that effectively encapsulates and protects drug molecules, shielding them from external stressors such as light, oxygen, and pH fluctuations. Consequently, they help suppress hydrolysis, oxidation, and conformational inactivation. Moreover, their nanosized droplets and high specific surface area significantly enhance drug solubility and membrane permeability, while self-microemulsifying systems enable controlled release, targeted delivery, and lymphatic transport to achieve precise therapeutic outcomes.[210]

Beyond the pharmaceutical field, microemulsion technology also demonstrates great potential and application value in environmental engineering due to its efficiency, multifunctionality, recyclability, and eco-friendliness. It has been explored for soil remediation, industrial wastewater treatment, and groundwater decontamination, suggesting a broader role in resource recycling and environmental protection.[211]

However, further development of microemulsion technology still faces several formulation and biological challenges, such as the biocompatibility and potential toxicity of surfactants and co-surfactants, limited encapsulation efficiency for complex biomolecules (eg, mRNA and monoclonal antibodies), and difficulties in ensuring physicochemical consistency during large-scale production. These limitations may be addressed through the development of novel functional lipids and surfactants, the incorporation of stimuli-responsive components for spatiotemporal controlled release, and the application of Quality by Design (QbD) principles to optimize formulation and manufacturing processes.

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Disclosure

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