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REVIEW

Solubilization techniques used for poorly water-soluble drugs

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Inorganic carriers

Abstract About 40% of approved drugs and nearly 90% of drug candidates are poorly water-soluble drugs. Low solubility reduces the drugability. Effectively improving the solubility and bioavailability of poorly water-soluble drugs is a critical issue that needs to be urgently addressed in drug development and application. This review briefly introduces the conventional solubilization techniques such as solubilizers, hydrotropes, cosolvents, prodrugs, salt modification, micronization, cyclodextrin inclusion, solid dispersions, and details the crystallization strategies, ionic liquids, and polymer-based, lipid-based, and inorganic-based carriers in improving solubility and bioavailability. Some of the most commonly used approved carrier materials for solubilization techniques are presented. Several approved poorly water-soluble drugs using solubilization techniques are summarized. Furthermore, this review summarizes the solubilization mechanism of each solubilization technique, reviews the latest research advances and challenges, and evaluates the potential for clinical translation. This review could guide the selection of a solubilization approach, dosage form, and administration route for poorly water-soluble drugs. Moreover, we discuss several promising solubilization techniques attracting increasing attention worldwide.

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1. Introduction

About 40% of approved drugs and nearly 90% of drug candidates are poorly water-soluble drugs (PWSDs)[1]. Low solubility affects the drug dissolution rate, failing to achieve adequate blood concentrations. Clinically, it is often solved by increasing the dosage, which also brings new problems such as adverse effects, high treatment costs and poor patient compliance[2]. In addition, studies *in vitro* cannot fully simulate the human body environment. PWSDs have poor *in vitro*−*in vivo* correlation, and studies are often terminated in the clinical trial stage.

The formulation design is more significant in accelerating the launch of investigational drugs and promoting the redevelopment of marketed refractory drugs. Conventional solubilization techniques include adding solubilizers, hydrotropes, cosolvents, prodrugs, pH modulation and salt modification, micronization, cyclodextrin (CD) inclusion, and solid dispersions (SDs). Long-term use of surfactants is potentially toxic, cosolvents are diluted with the risk of vascular occlusion, and salt modification requires that drugs have ionizable groups[3]. In response to the above limitations, several new strategies have been developed, including crystallization strategies, ionic liquids (ILs), and drug delivery systems (DDSs). The crystallization strategy focuses on nanocrystals and cocrystals, both are carrier-free DDSs. Nanocrystals have high drug loading and high safety, are easy to produce industrially, and are suitable for almost all PWSDs[4]. Drug-drug cocrystals (DDCs) improve dissolution rate and bioavailability without changing drugs' molecular structure. DDCs show significant advantages in co-delivery and synergistic therapy. ILs are considered "green alternatives" to organic reagents, increasing solubility and permeability. Conversion of the active pharmaceutical ingredient (API) into ILs can effectively address solid drug polymorphisms[5].

DDSs mainly include polymer-based carriers (*e.g.*, micelles, dendrimers, and gels), lipid-based carriers (*e.g.*, nanoemulsions, self-emulsifying drug delivery systems (SEDDSs), liposomes, transferosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanocapsules (LNCs)), and inorganic carriers (*e.g.*, mesoporous silica nanoparticles (MSNs), mesoporous carbon nanoparticles (MCNs), layered double hydroxides (LDHs), and metal nanoparticles (MNPs)). Polymer-based carriers are widely available and can be readily synthesized for delivery with specific properties. Environmentally sensitive blocks in polymers can further control drug release[6]. Lipid-based carriers have high biocompatibility, biodegradability, and low immunogenicity. They are powerful delivery carriers for grease balls and the Biopharmaceutical Classification System (BCS) IV drugs[7]. The size, structure and geometry of inorganic carriers can be easily adjusted to jointly diagnose and treat diseases[8,9]. Notably, nanocarriers with small particle sizes and large specific surface areas are significant in drug delivery[10,11]. Nanocarriers' modification enables targeted delivery and environmentally responsive release, reducing toxicity and improving therapeutic efficacy[12-15].

Several reviews summarized some specific techniques to solubilize PWSDs for improving the oral bioavailability[16,17], including CD inclusion, crystallization strategy, and SDs[18-22]. However, many new solubilization techniques, such as ILs and DDCs, are emerging and have promoted the PWSD development in the last 5 years. Herein, we provide a comprehensive overview of traditional and novel solubilization techniques for PWSDs. We reviewed the solubilization mechanisms, potential advantages, challenges faced, and pclinical translational potential of each solubilization technique. We highlight the ILs for PWSD delivery. ILs are used as solvents and penetration enhancers for transdermal delivery, and they can also be formed into nanocarriers (microemulsions, nanoemulsions, and micelles, etc.) for controlled release or targeted delivery. In addition, we have summarized the clinical application of solubilization techniques. We hope that this review could guide the scientist to select solubilization techniques according to the drug types, administration route, treatment purpose, etc.

2. Conventional solubilization techniques

2.1. *Solubilizers, hydrotropes, and cosolvents*

Solubilizers are amphiphilic surfactants that form micelles in aqueous phase when surfactant concentration exceeds the critical micelle concentration (CMC). PWSDs enter micelles' hydrophobic region or are adsorbed on micelles' surface[23]. Surfactants can be categorized into cationic[24-27], anionic[28,29], and nonionic surfactants[30-34]. Temperature is one factor influencing the solubilizing capacity of surfactants. When the temperature exceeds the critical micelle temperature, its solubilizing ability can be enhanced[35]. Therefore, the risk of drug precipitation increases with decreasing temperature. The type and amount of solubilizer are also responsible for solubilizing ability[32]. Surfactants' toxicity is related to their properties, with cationic surfactants being the most toxic while nonionic surfactants are the least. Excess surfactants have the potential to cause local or systemic adverse reactions and induce membrane reorganization and morphological changes to alter cellular integrity, leading to cellular hemolysis[36,37].

Hydrotropes are usually low molecular compounds that combine with PWSDs through chemical bonds (such as ligand bonds) to form soluble complexes, complex salts, or aggregates. Common hydrotropes include organic acids and their sodium salts, amides, and amines[38-40]. Hydrotropes reduce the risk of solvent residues due to using organic solvents[41]. Unlike colloidal solutions formed by solubilizers, solutions formed by hydrotropes are true solutions. When hydrotropes exceed the minimum hydrotrope concentration (MHC) in aqueous solution, complexes are formed by intermolecular binding through non-covalent interactions[42,43]. Unlike CMC, MHC is not hydrophobic enough to support aggregate formation with micelle-like organization[44]. In addition, MHC is typically applied at higher concentrations than CMC, and the molar content of MHC is in the molar range, whereas the molar content of CMC is typically in the millimolar range or even lower[43].

Cosolvency is a phenomenon in which the drug solubility is significantly increased in mixed solvents at specific ratios[45]. Cosolvents are usually water-soluble organic solvents that effectively increase nonpolar drug solubility by reducing the solvent polarity and approaching the nonpolar solutes' polarity[46]. Common cosolvents include ethanol, methanol, propylene glycol, and others[47-53]. In general, cosolvents' solubilization is positively related to solute polarity[54]. Cosolvents are commonly used in combination with other solubilization strategies. The combination of surfactants and cosolvents is effective in avoiding drug precipitation when diluting cosolvent preparations before intravenous administration[3,55]. When combining CDs with cosolvents, cosolvents increase free drug concentration, which increases the CDs'

complexation drive[3]. CDs can complex both small molecule cosolvents and drugs, forming highly soluble drug-cosolvent-CDs ternary complex[56].

2.2. Synthesis of water-soluble drug prodrugs

Prodrugs are compounds that are transformed *in vivo* to have pharmacological activity[57]. Prodrugs can be categorized into carrier linked prodrugs and bioprecursors[57]. Carrier linked prodrugs improve drug solubility by adding polar functional groups[57,58]. Bioprecursors are inactive compounds, and their metabolites are active compounds[59]. Currently, approximately 10% of approved drugs are considered prodrugs, and at least 30 prodrugs are approved by the U.S. Food and Drug Administration (FDA)[58]. Fostemsavir, a phosphonomethyl prodrug made by introducing a phosphate group into Temsavir, is more than 500-fold more water-soluble and has been approved for the treatment of HIV-infected patients who cannot be treated with other therapies[60]. Polymer prodrugs are formed by the covalent linkage of the drug to polymer and self-assemble into nanocarriers[61,62]. Polymer prodrug nanocarriers can avoid burst release effect, increase drug loading, control drug release, and realize drug co-delivery[63-66]. Luo et al.[67] attached doxorubicin (DOX) to poly [*N*-(2-hydroxypropyl) methacrylamide] *via* disulfide bonds to form a glutathione (GSH)-sensitive polymer prodrug. This prodrug was self-assembled to form nanoparticles (NPs) and encapsulated with a Ce6 photosensitizer for chemotherapy and photodynamic therapy.

2.3. pH regulation and formation of soluble salts

Adjusting pH and forming soluble salts from weakly acidic or weakly alkaline drugs are preferred methods for optimizing ionizable[3]. Approximately 40% of approved drugs are pharmaceutical salts by the FDA[68]. The most commonly used salt-forming counterions in FDA-approved drugs are hydrochloride, sodium salt, and toluene sulfonate salts[68,69]. Numerous antibiotic and anticancer drugs are solubilized with hydrochloride, successful launches including moxifloxacin, clindamycin, fidaxomicinib and so on. Salt formation improves the solubility and bioavailability of ionizable drugs by increasing the dissociation degree, altering crystalline lattice and intrinsic properties[70]. According to the Henderson-Hasselbalch equation, adjusting pH also leads to exponential changes in ionizable drug solubility[3]. Salt-forming counterions may themselves have toxicity. For example, oral fumarate is prone to gastrointestinal complications[71]. In addition, the homoionic effect predisposes to drug precipitation[72].

2.4. CD inclusion

CDs are cyclic oligosaccharides consisting of multiple D-(+)-glucopyranose units linked by α-1,4 glycosidic bonds[73]. CDs have hydrophilic external surface and hydrophobic internal cavities[74,75]. Drugs are combined with internal hydrophobic cavities by non-covalent bonding to form inclusion complexes[76]. β-CD is the most commonly used natural CD, however, low solubility and severe nephrotoxicity limit its application[77]. Hydrophilic CD derivatives, such as hydroxypropyl-β-CD, hydroxypropyl-γ-CD and sulfobutylether-β-CD, have high stability and low toxicity[78-81]. Zulresso® solubilizes brexanolone with sulfobutylether-β-CD, which has been approved to treat postpartum depression[82]. CD-based polymers are materials that combine CDs with polymers, including CD-based poly rotaxanes, grafted CD, cross-linked CD, and star/multi-arm CD polymers[83]. CD-based polymers can form micelles, NPs, nanogels, nanofibers, and hydrogels, and have potential applications in drug delivery[84-87]. Drugs can be formed as CD inclusions, coupled to polymers, or encapsulated in DDSs[88]. The involment of stimuli-responsive bonds and ligands allows these DDSs to have stimuli-responsive release and targeted delivery[89].

2.5. SDs

SDs uniformly disperse PWSDs in microcrystalline, amorphous, or molecular states in carriers, which allow for the solidification of liquid drugs[90,91]. SDs can significantly reduce particle size and improve drug wettability compared to micronization. Marketed SDs are available in tablet and capsule dosage forms[16]. SDs can be categorized into four generations according to carrier materials (Fig. 1). The first-generation SDs have excellent thermodynamic stability but slower drug release[92]. The second-generation SDs use polymers to prepare amorphous SDs (ASDs), which exhibit higher solubility and dissolution rate[93-95]. However, ASDs are in a high-energy state and belong to thermodynamically unstable systems, which are susceptible to crystallization when stored at high temperature and high humidity[96]. Although adding surfactants or polymer materials to formulations avoids recrystallization and improves drug wettability and stability, long-term storage stability remains not optimistic[97,98]. Therefore, marketed solid dispersing formulations have a short validity period.

The third-generation SDs use surfactants as carriers, avoiding drug recrystallization[99]. Poloxamer and Soluplus are commonly used surfactant carriers[100,101]. Łyszczarz et al.[102] prepared SDs of aripiprazole using poloxamer 407 (P407), which increased drug solubility more than 100-fold. The fourth-generation SDs use enteric-soluble or water-insoluble carriers to achieve sustained and controlled release of PWSDs[92,103-109]. Drug properties, polymers' types, and preparation technology are crucial to the development of SDs. Braftovi®, Oriahnn™, Tukysa™, and others are successful cases that can be referenced[110,111].

The conventional solubilization techniques used to solubilize PWSDs, including solubilization mechanisms, solubilization components, technical benefits, and challenges are summarized in Table 1. Conventional solubilization techniques can be used for solubilization of BCS II drugs, but for BCS IV drugs with poor permeability, they usually need to be combined with some emerging solubilization techniques.

3. Crystallization strategy

3.1. Nanocrystals

Micronization reduces the drug particle size to the micron scale, which improves the dissolution rate and oral bioavailability by increasing the wettability and decreasing lattice energy[112-115]. Nanosized drugs have a larger specific surface area, and their dissolution rate will be further increased.

Nanocrystals are submicron drug particles (10−1000 nm) stabilized by stabilizers (surfactants, polymers or proteins)[116]. Compared with DDSs, nanocrystals do not need carrier materials and have a simple prescription composition, resulting in high drug-loading capacity and easy industrial production. Currently, twenty nanocrystal products have been approved (Table 2).

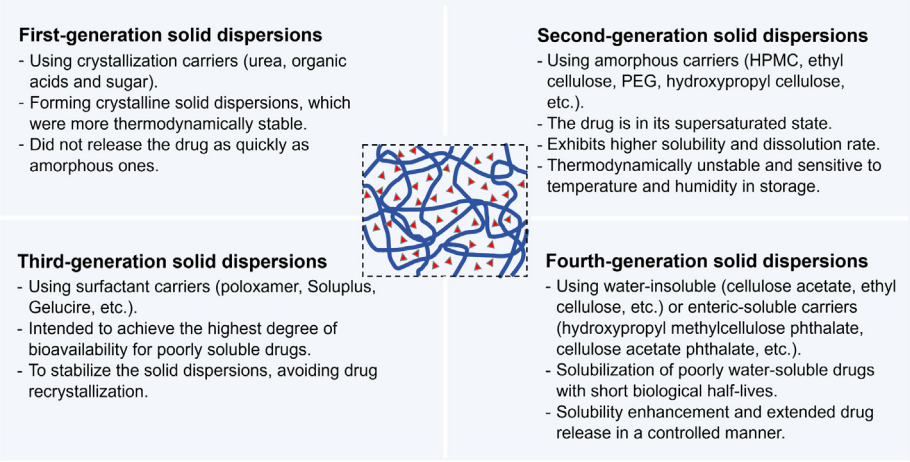

Figure 1 Four generations of solid dispersions classified by carrier materials.

Nanocrystals are manufactured by top-down approaches (media milling, high-pressure homogenization), bottom-up approaches (antisolvent precipitation, supercritical fluid technology, spray drying) and combined approaches (Fig. 2A)[117-119]. He et al.[120] used machine learning techniques to accurately predict nanocrystals' particle size and polymer dispersity index (PDI) prepared by high-pressure homogenization and ball-wet milling. The application of machine learning approaches can accelerate the development of nanocrystals.

According to the Noyes−Whitney equation, nanocrystals with large specific surface areas can significantly improve dissolution rate. Nanocrystals administered orally are partly dissolved into drug molecules for passive diffusion and partly enter the blood or lymphatic circulation[121]. Furthermore, nanocrystals can reduce the absorption fluctuation caused by feeding/fasting[122]. In addition to preventing aggregation and precipitation, stabilizers can also affect drug dissolution rate and pharmacokinetic (PK)[123-127]. Zhang et al.[125] used polyvinylpyrrolidone (PVP), poloxamer 188 (P188), P407, and hydroxypropyl methyl cellulose (HPMC) as stabilizers to prepare naringenin nanocrystals. The nanocrystals prepared by the four stabilizers had similar particle size, potential, morphology and crystallinity. The most decisive interaction between PVP and naringenin inhibited naringenin dimer formation and maintained the supersaturation, showing a high dissolution rate, oral bioavailability, and excellent anti-inflammatory effects. Qin et al.[124] prepared celecoxib (CXB) nanocrystals using PVP K17, d-α-tocopherol polyethylene glycol (PEG) 1000 succinate and P188 as stabilizers. CXB nanocrystals *via* intramuscular injection with PVP K17 as stabilizers showed long-acting release, while the other nanocrystals showed rapid release.

Nanocrystals administered intravenously show similar *in vivo* behavior to NPs, which are phagocytosed by macrophages and accumulated in the mononuclear phagocyte system (MPS) organs[128]. Wang et al.[129] doped trace environmentally responsive fluorescent dyes into curcumin (CUR) nanocrystals and visually demonstrated the nanocrystals' fate *via* real-time imaging. Fluorescent dyes were quenched immediately in the aqueous environment, ensuring that only the fluorescence emitted by the nanocrystals was detected. CUR nanocrystals injected intravenously accumulate in the MPS organs, such as the liver and lungs. Maintaining nanocrystals' integrity in blood circulation facilitates surface modification for targeting ligands. Luo et al.[130] prepared self-assembled cabazitaxel nanocrystals *in vivo* for the targeted treatment of metastatic triple-negative breast cancer. Cabazitaxel nanocrystals absorbed albumin, transferrin, apolipoprotein A-IV and apolipoprotein E in plasma. Transferrin, apolipoprotein A-IV and apolipoprotein E made cabazitaxel nanocrystals target tumor cells *in situ*, blood−brain barrier (BBB)/blood-tumor barrier and activated platelets supporting tumor metastasis, respectively. Self-assembled cabazitaxel nanocrystals showed excellent therapeutic effects in tumor, brain, and lung metastasis models. Cell membrane-coated NPs have extended systemic circulation and natural targeting ability because of surface-specific protein and immune recognition escape ability[131]. Furthermore, cell membrane-coated nanocrystals have high drug loading and high stability. Lin et al.[132] prepared platelet membrane-coated paclitaxel (PTX) nanocrystals (PPNCs) for postoperative tumor chemotherapy. Compared with PTX nanocrystals, the particle size of PPNCs showed no noticeable increase during storage at 4 °C for 2 months. Due to the selective adhesion of platelet membranes to damaged blood vessels, PPNCs actively targeted and accumulated in postoperative residual lesions and tumor hemorrhage sites. Chai et al.[133] prepared red blood cell (RBC) membrane-coated docetaxel nanocrystals and then modified targeting ligands on the cell membrane to treat glioma.

Nanocrystals administered intramuscularly provide sustained release, improve patient compliance, and have been widely used in treating acquired immunodeficiency syndrome and schizophrenia (Fig. 2B)[134-137]. For example, Aristada®, developed by Alkermes, is injected every 1 to 2 months for adult schizophrenia therapy. Limited tissue fluid in the muscle or subcutaneous site allows for slow dissolution and sustained release. Further, prodrug nanocrystals show longer extended releases due to the slow prodrug conversion *in vivo*. Deodhar et al.[138] linked 18-carbon fatty acids with dolutegravir through ester bonds and prepared them into nanocrystals for antiretroviral therapy. Prodrug nanocrystals injected intramuscularly with a single dose of 45 mg/kg dolutegravir achieved ultra-long-lasting release in mice and rats for up to one year. In rhesus monkeys, a second booster dose was injected on day 217. Cabotegravir's fatty acid ester nanocrystals also allowed injecting once a year[139]. Nanocrystals for intramuscular injection may cause inflammatory responses, granulomas, and fibrosis. This leads nanocrystals to be phagocytosed by macrophages and forms a secondary reservoir, which delays the drug's dissolution and absorption[140]. Ho et al.[141] found that small-sized crystals (d_{50} = 0.8 or 2.3 μm) were widely distributed in

Table 1 Conventional solubilization strategies for solubilizing insoluble drugs.

Solubilization technology	Solubilization mechanism	Solubilizing component	Benefit	Challenge
Solubilizers	Forming micelles in the aqueous phase using surfactants.	Cationic surfactants (DTAB, DDAB, CTAB), anionic surfactants (SDS, NaC), and nonionic surfactants (poloxamer and polyol-based surfactants).	Intravenous administration. Reduces surface tension.	Toxicity of excessive use of surfactants.
Hydrotropes	Forming soluble complexes, complex salts, or aggregates.	Organic acids and their sodium salts (*e.g.*, amino acids, citric acid, sodium salicylate), amides, and amines (*e.g.*, nicotinamide, *N*-methylglucamine, urea).	Avoidance of surfactants and organic solvents. Increase the solubility of drugs by several or even dozens of times.	Requires a high concentration of hydrotrope.
Cosolvents	Reducing the polarity of the solvent mixture closely reflects nonpolar solutes' polarity.	Ethanol, methanol, propylene glycol, glycerol, DMSO, and PEG.	Suitable for drugs that lack ionizable functionality and show low affinity for solubilization by surfactants or lipids.	Reduced solubilization power on dilution. Pain on administration. Cell-based toxicity.
Synthesis of water-soluble drug prodrugs	Modifying the chemical structure of drugs.	Adding polar functional groups (*e.g.*, phosphates, esters, carbamates, amides, carbonates, *N*-mannich bases, ethers, among others).	Improvement of aqueous solubility and pharmacokinetic profile of parent drug. Enable parenteral administration. Improved metabolic stability and targeting. Prolonged duration of action. Fewer side effects.	Complex and time-consuming development of prodrugs. While solubility may increase, the prodrug may be less permeable. Difficulty in initial screening of prodrugs in a single animal model.
pH regulation and formation of soluble salts	Increasing the dissociation degree and altering crystalline lattice and intrinsic properties of ionizable drugs.	Hydrochloride, sodium salt, and toluene sulfonate salts, etc.	Suitable for ionizable drugs. Significantly enhance dissolution rate/solubility (often $> 10^3$ fold).	Pharmaceutical salt and intrinsic toxicity of counterions.
CD inclusion	CDs form non-covalent dynamic inclusion complexes in solution.	α-CD, β-CD, γ-CD, methyl-β-CD, hydroxypropyl-β-CD, sulfobutylether-β-CD and hydroxypropyl-γ-CD, etc.	Convert drugs into microcrystalline or amorphous powders. Eliminate unpleasant smells or tastes. Prevent drug−drug or drug−additive interactions.	Ototoxicity and nephrotoxicity associated with large CD applications.
Solid dispersions	Reduced particle size. Drug in an amorphous state. High porosity particles. Improved particle wettability.	Urea, organic acids, sugars, polymer materials, surfactants and enteric-soluble carriers.	Solidification of liquid drugs. Highly dispersed drug in the carrier. More effective than particle size reduction methods.	Low drug loading capacity due to carrier dosage limitation. Thermodynamic instability of drug in the amorphous form. Aging easily after prolonged storage. Difficult to manufacture and scale up.

DTAB, dodecyltrimethylammonium bromide; DDAB, dodecylethyldimethylammonium bromide; CTAB, cetyltrimethylammonium bromide; SDS, sodium dodecyl sulfate; NaC, sodium cholate; DMSO, dimethyl sulfoxide; PEG, polyethylene glycol; CD, cyclodextrin.

Table 2 Drug-nanocrystal products in the clinic.

Brand name	API	Indication	Route of administration	Company	Approval year
Gris-PEG	Griseofulvin	Fungal infection	Oral	Novartis	1995
Ritalin LA	Methylphenidate hydrochloride	Attention deficit hyperactivity disorder	Oral	Novartis	1995
Verelan PM	Verapamil	Essential hypertension	Oral	Schwarz Pharma	1998
Celebrex	Celecoxib	Anti-inflammation	Oral	Pfizer	1998
Focalin XR	Dexmethylphenidate hydrochloride	Attention deficit hyperactivity disorder	Oral	Novartis	2001
Avinza	Morphine sulfate	Moderate to severe pain	Oral	King Pharm	2002
Zanaflex	Tizanidine hydrochloride	Muscle spasticity	Oral	Acorda	2002
Emend	Aprepitant	Nausea and vomiting	Oral	Merck	2003
Tricor	Fenofibrate	Hypercholesterolemia	Oral	Abbott	2004
Megace ES	Megestrol acetate	Loss of appetite and wasting syndrome with acquired immunodeficiency syndrome	Oral	Par Pharm	2005
Tridlide	Fenofibrate	Hypercholesterolemia	Oral	Skye Pharma	2005
Naprelan	Naproxen sodium	Analgesia and anti-inflammation	Oral	Wyeth	2006
Invega Sustenna	Paliperidone palmitate	Schizophrenia	IM	Janssen	2009
Ryanodex	Dantrolene sodium	Malignant hyperthermia	IV	Eagle	2014
Invega Trinza	Paliperidone palmitate	Schizophrenia	IM	Janssen	2015
Rapamune	Sirolimus	Prophylaxis of organ rejection and lymphangioleiomyomatosis	Oral	Pfizer	2015
Aristada	Aripiprazole lauroxil	Schizophrenia	IM	Alkermes	2018
Invega Hafyera	Paliperidone palmitate	Schizophrenia	IM	Janssen	2021
Cabenuva	Cabotegravir	HIV-1 infection	IM	Viiv	2021
Apretude	Cabotegravir	HIV-1 pre-exposure prophylaxis	IM	Viiv	2021

IM, intramuscular injection; IV, intravenous injection.

muscle tissues, resulting in mild inflammatory reactions. After 4 weeks, the inflammatory reaction and secondary reservoir almost disappeared, and the drugs were dissolved entirely and distributed in the blood. However, large-sized crystals showed concentrated inflammatory lesions. After 4 weeks, a circular single-focus drug library remained, hindering drug dissolution and systemic exposure. Therefore, small-sized crystals may have good local tolerance and bioaccessibility and are more clinically relevant.

Nanocrystals can increase the solubility of almost all PWSDs. Gamma irradiation, filtration sterilization, and thermal sterilization have been used to sterilize nanosuspensions, laying the groundwork for marketing parenterally administered nanocrystals[142].

3.2. *Cocrystals*

Cocrystals are crystalline and composed of two or more components in a stoichiometric ratio through non-covalent bonds. One component is an API, and the other components are cocrystal coformers (CCFs) or APIs[143,144]. Cocrystals improve drugs' physicochemical or mechanical properties (solubility, stability, fluidity, and compressibility) without changing chemical structure[145]. The selection of CCFs is crucial to designing cocrystals. Experimental screening methods (differential scanning calorimetry and phase diagrams) are time-consuming and labor-intensive. Virtual screening methods (hydrogen bond synthons, Hansen solubility parameter, crystal structure prediction, and machine learning models based on artificial neural networks) can improve the effectiveness and accuracy[145-147]. Eight cocrystal products have been approved for clinical application (Table 3)[148-155].

Cocrystals have been widely used to improve solubility and bioavailability. For example, the solubility of ketoconazole (KCZ)-glutaric acid cocrystal was 1800-fold increased compared to the pure drug in water[156]. The AUC_{0-32h} of miconazole-succinic acid cocrystal was 2.4 times enhanced compared to the pure drug[157]. Cocrystal solubility is related to the intermolecular interaction in the lattice and the solvation of components[19]. CCFs with high solubility can effectively improve cocrystal solubility. Ren et al.[158] prepared myricetin cocrystals with nicotinamide, isonicotinamide, caffeine, and proline. The solubility of CCFs from large to small is proline, nicotinamide, isonicotinamide, and caffeine, consistent with the apparent solubility order of the four cocrystals. In addition, cocrystal solubility also depends on the pH, ionic strength, surfactant concentration and type[158-160]. The rapid dissolution of cocrystals may cause insoluble drug precipitation. Extending drug supersaturation by adding suitable polymers can solve this problem[161-163].

DDCs are composed of APIs (Fig. 2C). DDCs are expected to solve the problems of differences in solubility and stability between APIs in combinations to exert synergistic or dual pharmacotherapeutic effects[164]. For example, Seglentis®, a cocrystal of tramadol hydrochloride and CXB in a 1:1 molecular ratio, has four different and complementary analgesic mechanisms for acute pain in adults[165]. DDCs have strict requirements for composition structure. Strong hydrogen bonding or interaction forces between the two components are necessary to form DDCs. Nonsteroidal anti-inflammatory, antitubercular, and diuretic drugs are the three main classes of drugs that form DDCs, possibly due to the high number of hydrogen bond donors and acceptors in the drug

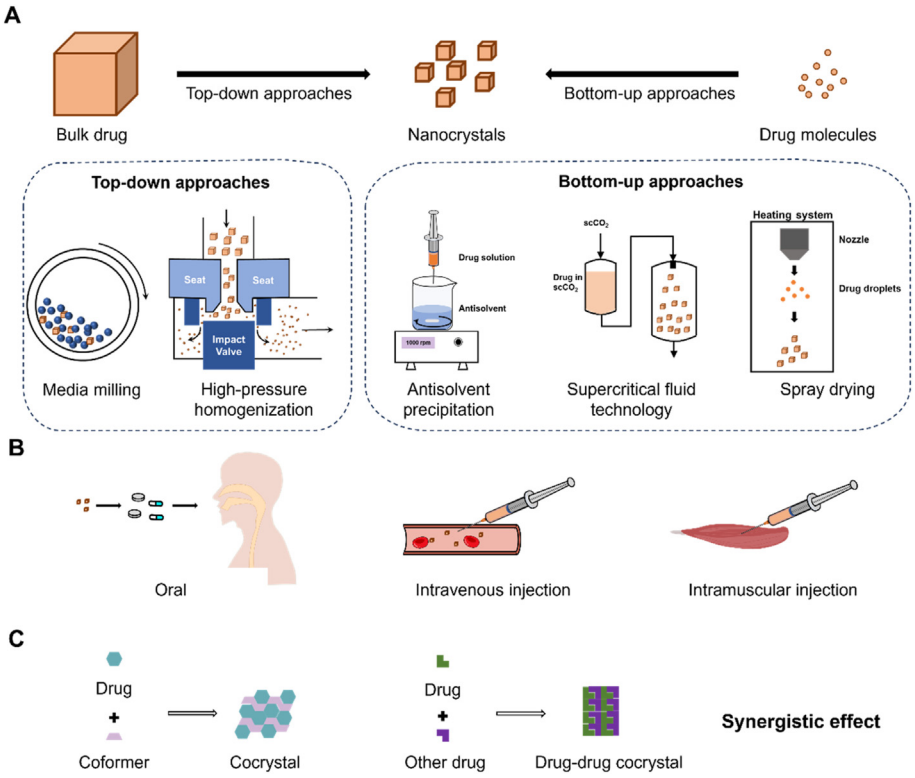

Figure 2 (A) The production methods of nanocrystals. Top-down approaches include media milling and high-pressure homogenization. Bottom-up approaches include antisolvent precipitation, supercritical fluid technology and spray drying. (B) Nanocrystals are used for oral, intravenous, and intramuscular administration. (C) Composition of cocrystal and drug−drug cocrystal. Drug−drug cocrystals often have a synergistic effect.

molecules[166]. In addition, DDCs alter the components' PK. For example, the intrinsic dissolution rate of tramadol hydrochloride in Seglentis® was reduced 7-fold, while that of CXB was increased 3-fold[167]. In human PK experiments, the absorption of tramadol hydrochloride decreased ($P < 0.001$), while the absorption of CXB increased ($P < 0.01$). The results corresponded to *in vitro* dissolution data and indicated that DDCs alter the PK behavior of tramadol and CXB.

Cocrystal preparation methods mainly include grinding and solution crystallization, which are only suitable for small-scale screening and preparation. New technologies, such as hot melt extrusion, supercritical fluid technology and resonant acoustic mixing, make it possible for industrial production and continuous manufacturing[168,169]. The advantages and disadvantages of cocrystal preparation methods are summarized in Table 4[170-177]. In addition, the Regulatory Classification of Pharmaceutical Co-Crystals published by the FDA considers that cocrystals are equivalent to the polymorphism of API[178]. Therefore, cocrystals can be approved through the 505 (b) (2) pathway[179], which allows applicants to submit data from published safety and efficacy studies. This significantly reduces development costs and facilitates commercialization.

Table 3 Cocrystal products in the clinic.

Brand name	Combination	Indication	Route of administration	Company	Approval year	Ref.
Lexapro	Escitalopram oxalate and oxalic acid	Anxiety disorders and major depression	Oral	Forest	2002	148
Abilify	Aripiprazole and fumaric acid	Schizophrenia	Oral	Otsuka	2002	149
Suglat	Ipragliflozin and L-proline	Type 2 diabetes	Oral	Kotobuki and Astellas	2014	150
Entresto	Valsartan and sacubitril	Chronic heart failure	Oral	Novartis	2015	151
Odomzo	Sonidegib and phosphoric acid	Locally advanced basal cell carcinoma	Oral	Novartis	2015	152
Steglatro	Ertugliflozin and L-pyroglutamic acid	Type 2 diabetes	Oral	Merck and Pfizer	2017	153
Mayzent	Siponimod and fumaric acid	Active secondary progressive multiple sclerosis	Oral	Novartis	2019	154
Seglentis	Celecoxib and racemic tramadol hydrochloride	Acute pain in adults	Oral	Esteve	2021	155

Table 4 Advantages and disadvantages of cocrystal preparation methods.

Method	Advantage	Disadvantage	Ref.
Milling (liquid-assisted grinding)	Controlling polymorphism Higher yields Broader range of synthesized cocrystals	Not easy to scale up Use of solvents	170,171
Solution crystallization (solvent evaporation method)	Simple operation	Not easy to scale up Large amounts of solvents Time-consuming	172
Hot melt extrusion	No organic solvents Real-time monitoring Continuous production Polymer matrix-assisted crystallization improves cocrystal production efficiency	Energy consuming Not applicable to thermally unstable drugs	173,174
Supercritical fluid technology	High-quality cocrystal No organic solvents Continuous production	High investment	175
Resonance acoustic mixing	Scale-up production High-throughput screening	–	176,177

–, not applicable.

4. ILs

ILs are liquid compounds composed of asymmetric organic cations and anions (Fig. 3A) with a melting point below 100 °C[180]. Deep eutectic solvents (DESs) are eutectic mixtures formed primarily by hydrogen bonding, with melting points significantly lower than any individual component[181]. DESs are also considered as ILs analogs[182]. ILs and DESs have low volatility, thermal stability, chemical stability, and high adjustability and are considered green solvents that replace organic solvents[183]. In biomedicine, ILs improve drug solubility, enhance permeation drug delivery, and eliminate solid-state drug polymorphism.

The apparent solubility of PWSDs has been significantly improved through ILs[184-186]. For example, Propylene glycol increased the solubility of ibuprofen (IBU) by 193-fold[187]. ILs synthesized from salicylic acid and choline (Ch) increased the solubility of IBU by 6000-fold[188]. The solubilizing ability of ILs is mainly related to anion's type and the interaction between drug molecules. Hu et al.[189] synthesized six ILs with acetate anion and six heterocyclic imidazole cations and investigated the solubilizing ability of six ILs on arabinoxylan. Cations' chemical structure directly affected the acetate anion's ability to form hydrogen bonding. Strong hydrogen bonding acceptance led to greater solubilization of ILs. However, the acetate anion formed more extensive hydrogen bonds with the hydroxyl groups in arabinoxylan. Therefore, anions played a significant role in increasing solubility. Wu et al.[190] studied the solubility of KCZ in ILs composed of Ch and different anions. In carboxylic acid anion ILs, hydroxyl groups limited the dissolution of KCZ, while carboxyl groups and double bonds increased the dissolution of KCZ. However, in the amino acid ILs, hydroxyl groups increased the dissolution of KCZ. Therefore, the interaction between ILs and KCZ also significantly affected solubility. Hu et al.[191] found that isoliquiritigenin solubility in DESs composed of Ch and different organic acids (oxalic acid, malic acid, and gallic acid) was significantly improved. Molecular dynamics simulation proved that the hydrogen bonding formed between drug molecules and ILs was the main reason for improving solubility.

ILs, as permeation enhancers, are used for transdermal delivery of small molecule drugs, biomolecules, and rigid NPs. ILs enhance penetration by extracting lipids in the skin, disrupting the tight arrangement of the stratum corneum (SC), and altering the surface properties of the SC[192-195]. In addition, compared with chemical penetration enhancers, ILs/DESs have more substantial skin permeability and lower skin irritation and are a robust functional material for local administration[196]. The permeability-promoting ability of ILs is related to the ions' type and stoichiometric ratio. Tanner et al.[197] investigated the transdermal delivery of hydrophilic acarbose and lipophilic rucotinib by ILs composed of choline and geranic acid (CAGE) in different stoichiometric ratios (2:1, 1:1, 1:2, 1:4). CAGE in a 1:2 stoichiometric ratio had the best transdermal effect, consistent with the results of CAGE transdermal insulin delivery[198]. Subsequently, they used anions similar to vanillin and cations with a similar structure to Ch to synthesize new ILs. They found that the inter-ionic interactions of ILs were negatively correlated with drug transport by 2D NMR spectroscopy. The hydrophobic portion of the anion entered the skin and disrupted lipids to enhance transdermal drug delivery. Strong inter-ionic interactions reduced the contact between anions and SC lipids and strongly interacted with solvated drugs, resulting in low skin penetration[197]. Zhao et al.[199] bonded citric acid to mesoporous silica and then heated it with lysine to obtain DES-MSN. DESs reversibly changed the microstructure of SC and delivered DES-MSN to deep skin and blood circulation. Similarly, Li et al.[200] used DES-MSN to deliver nanoceria and methotrexate to the dermis to synergistically treat rheumatoid arthritis. Therefore, DESs provide a new strategy for non-invasive transdermal drug delivery of rigid particles.

ILs can form micelles, micro-emulsions and nanoemulsions in the medium[201]. Ali et al.[202] encapsulated PTX in micelles formed by ILs and Span 20 to achieve transdermal delivery. Only the combination of ILs and Span 20 could form stable micelles. In addition, ILs improved drug encapsulation capability and enhanced skin penetration. ILs' content in the surfactant mixture increased, and the skin permeability of PTX was more vital. Esson et al.[203] prepared amphotericin B nanoemulsions with ILs and medium-chain triglycerides as oil phases, which prevented the self-aggregation of amphotericin B and reduced toxicity. Lin et al.[204] prepared oil-in-IL nanoemulsions by replacing the aqueous phase with ILs, which served as an intranasal mucosal delivery system for the vaccine. ILs significantly improved the stability of the nanoemulsions, enhanced the permeability of

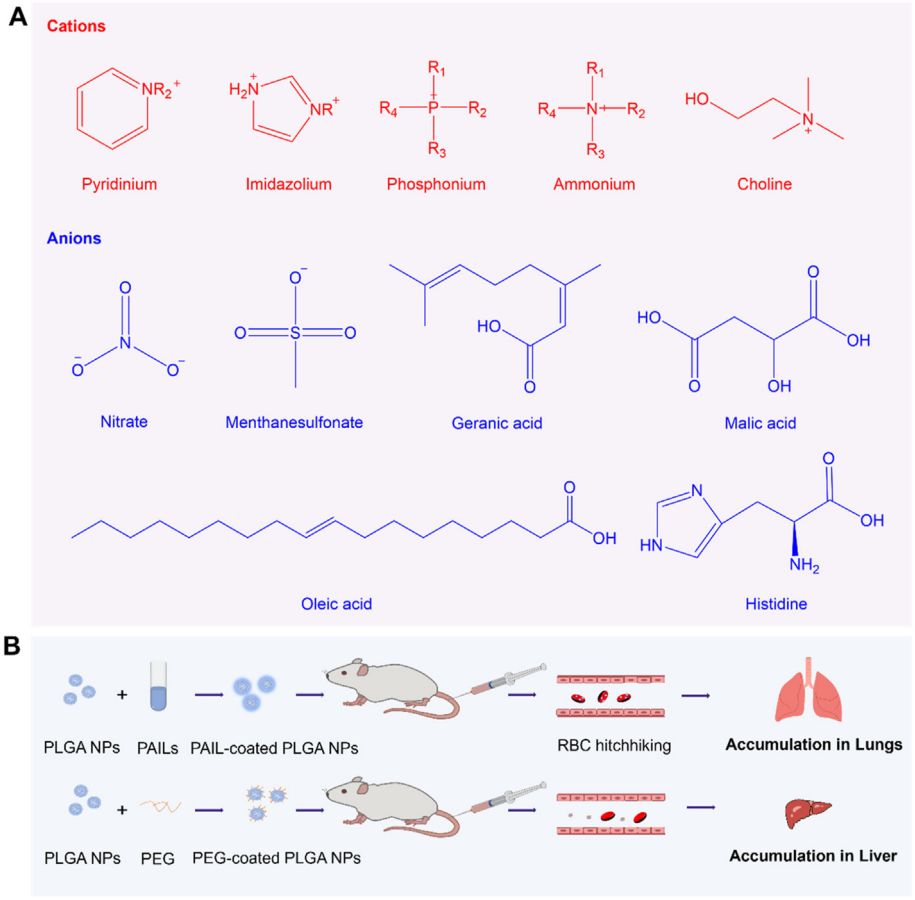

Figure 3 (A) Cations and anions commonly used in ionic liquids. Choline, geranic acid, malic acid, oleic acid and histidine are ions from natural sources. (B) Protein-avoidant ionic liquid (PAIL)-coated NPs drive biodistribution. PEG-coated NPs mainly accumulated in the liver, whereas PAIL-coated NPs accumulated in the lungs due to RBC hitchhiking.

antigens in the nasal mucosa, and induced more robust immune responses. Poly(ionic liquid)s (PILs) consist of a polymer backbone and repeating units of ILs[205]. Lu et al.[206] synthesized amphiphilic block copolymers containing PILs, light, and pH-responsive blocks. The amphiphilic block copolymers self-assembled in water to form spherical NPs. NPs were stimulated to release drugs by pH and ultraviolet irradiation, which significantly inhibited tumor growth *in vivo* and *in vitro*.

ILs can extend circulation half-life and change the biological distribution. Hamadani et al.[207,208] used Ch and hexenoic acid to synthesize protein-avoidant ionic liquid (PAIL). PAIL-coated PLGA NPs significantly reduced opsonization and prolonged circulation time *in vivo*. PEG-coated PLGA NPs mainly accumulated in the liver, whereas PAIL-coated PLGA NPs mainly accumulated in the lungs (Fig. 3B). The spontaneous RBC hitchhiking of PAIL-coated PLGA NPs caused this. PAIL-coated PLGA NPs were transferred to vascular endothelial cells under the shear force of the dense capillary bed of lung tissue after tail vein injection.

API-ILs are ILs converted from drug molecules with pharmacological activity[209]. API-ILs can improve solubility, enhance permeability, and even inhibit polymorphic conversion and crystallization of solid APIs[210]. Drug polymorphs differ in solubility, stability, dissolution rate, and hardness, directly affecting PK and pharmacodynamics. Drug polymorphs are challenging to detect and differentiate, which brings hidden dangers to drug marketing and application[211]. API-ILs transform solid drugs into liquid forms and are an effective strategy to solve the polymorphism. For example, IBU with imidazolium, ammonium, or pyridinium formed API-ILs to eliminate polymorphism[212]. In addition, API-ILs formed by dual APIs can co-delivery and have synergistic therapeutic effects. A clinical combination of diphenhydramine, IBU, or naproxen provides better analgesic and sleeping effects. Wang et al.[213] prepared API-ILs of diphenhydramine with IBU and naproxen and dispersed the API-ILs into mesoporous materials to improve powder fluidity and manufacturability, laying the groundwork for the manufacture of tablets and capsules. Etodolac-lidocaine ILs in a 1:1 stoichiometric ratio significantly improved solubility and increased etodolac but decreased lidocaine permeability. This may be due to etodolac-lidocaine ILs existed as ion pairs or clusters in the skin[214]. In addition, etodolac-lidocaine ILs are used to treat ankle sprains, and phase III clinical trials have been completed[215].

The potential toxicity and biodegradability of ILs have been widely discussed. Computer simulation methods, such as constructing quantitative structure−activity relationship models and molecular dynamics simulations, can be used to predict the potential toxicity and explore the toxicity mechanism of ILs, laying the foundation for designing low-toxicity ILs[216,217]. ILs formed by natural ions (amino acids, Ch, polysaccharides and organic acids) have better biocompatibility and occupy an essential position in the biomedical field[218-220]. Currently, CAGE Bio

Inc. focuses on the transdermal delivery of CAGE, and has four products in clinical trials. MEDRx is committed to commercializing API-ILs and has developed 10 kinds of API-ILs[210].

5. Drug delivery systems

5.1. Polymer-based carriers

Increasing polymer-based carriers are being used to improve drug adsorption and hemodynamic characteristics due to good biocompatibility, low toxicity, cleared bloodstream, and biodegradability[221]. They have shown their potential for drug delivery in various administration routes. Commonly used polymer-based carriers include polymer micelles (PMs), dendrimers, and gels[22]. Polymer-based carriers can be coupled to drugs, embedded in a polymer matrix to form a host-guest complex, or loaded into reservoirs formed by polymer-based carriers[222]. Surface modification alllows the polymer-based carriers to have the targeted delivery ability. In addition, applying pH, light, heat, enzyme, or redox-sensitive copolymer blocks to dissociate and release drugs at controlled sites could improve the precise drug delivery.

Encapsulation of PWSDs by polymer-based carriers can improve drug solubility, *in vivo* stability, and affinity to intestinal membranes[223]. PMs' nanostructures can facilitate drug absorption in intestinal epithelial cells *via* transcytosis or endocytosis and in the systemic circulation *via* lymphatic transport[224,225]. Bile salts can also induce micellar transition morphology, or form hybrid micelles and novel hybrid aggregates, enhancing the transcellular channeling of drugs[226,227]. Dendritic polymers are carriers for facilitating intestinal permeation and drug transepithelial transport. They allow the drug to bypass p-glycoprotein (P-gp) efflux and be absorbed *via* endocytosis[228].

5.1.1. PMs

PMs are nanocore-shell structures formed by the self-assembly of amphiphilic block copolymers in aqueous media (Fig. 4A)[229]. Insoluble drug molecules are encapsulated in hydrophobic micelle cores through non-covalent interactions or chemically coupled to nucleated blocks of block copolymers through covalent bonding[230-232]. Compared to micelles formed by traditional small molecule surfactants, PMs have lower apparent CMC, lower toxicity, higher drug-loading capacity, higher kinetic stability, and avoid leakage in blood circulation[226]. Genexol® PM is the first marketed PTX PM formulation with methoxy poly(ethylene glycol)-poly(D,L-lactide) as the polymeric material[233-235]. Cremophor EL in Taxol® is the main component causing serious side effects. However, Genexol® PM could give higher doses of PTX without additional toxicity in clinical trials[236,237]. Except for Genexol® PM, other PM products launched on the market include Nanoxel®, Nanoxel® M, Paclical® and Zisheng® (Table 5)[236,238-241].

Micellar materials mainly include diblock, triblock (Fig. 4B), tetra block, graft, and ionic copolymers[242-245]. PEG and its derivatives are the most widely used hydrophilic blocks in marketed products. Hydrophobic blocks are usually polylactic acid (PLA)[242], racemic PLA[246], glycolic acid, lactic acid copolymer[247], polycaprolactone (PCL)[248], polypropylene oxide[249], etc. Rasoulianboroujeni et al.[250] used PEG as a non-selective solvent for PEG-*b*-PLA to prepare PMs with over 95% encapsulation efficiency. There were no significant changes in PTX encapsulation, average particle size, and PDI after scaling up the batch size to 25 times. In addition, this method eliminates PEG's safety and regulatory issues and simplifies the scale-up production process. Natural amphiphilic polymers are also used as carriers due to low toxicity. Liu et al.[251] prepared an amphiphilic acetylated debranched starch by inserting hydrophobic acetyl groups into debranched starch, forming self-assembly micelles to solubilize CUR. Encapsulation and controlled release of CUR was achieved by hydrophobic interaction between the CUR aromatic group and the acetyl group of acetylated debranched starch.

PMs are rich in morphology, with spherical, vesicular, rod-shaped, hollow, tubular, worm-like, fibrous, and other forms (Fig. 4C)[226,252]. Spherical PMs are the most classical and are categorized into star and flathead micelles. Star micelles have thicker shell layer structures, and the length of shell-forming embedded segments is much larger than that of nucleating embedded segments[253]. PM morphology can be modulated by varying structure and relative chain length of block polymers, pH and composition of solvents, and drug capacity[254,255]. In addition, changing PM morphology, in turn, improves their toxicity and cellular endocytosis[256].

PMs are now widely used as targeted delivery systems for antitumor drugs and non-viral genes[257]. Surface modification of PMs with targeting ligands enables active tumor-targeting. The introduction of stimulus-sensitive fragments or chemical bonds into the polymer materials realizes stimulated release at the tumor, significantly reducing side effects caused by off-target effects[258]. To deliver the hydrophobic anticancer drug DOX, Zhang et al.[259] formed self-assembled PMs by triphenylphosphonium (TPP)-grafted PEG-ss-PLA copolymers using disulfide bonds as intermediate linkers, followed by coating with a chondroitin sulfate (CS) layer. Dual cell membrane/mitochondrial targeting and pH/redox responsive PMs were prepared with 70% encapsulation. The CS layer extends blood circulation while empowering cell membranes with active targeting capabilities. In acidic lysosomes, the CS layer was initially deshielded by pH response, TPP-mediated anchoring to the outer membrane of mitochondria. Then, the disulfide bond was cleaved by GSH response to release DOX.

5.1.2. Dendrimers

Dendrimers are permanently branched polymers consisting of three parts: a core, a branched chain inner shell, and a functional surface group-modified outer shell and have a highly branched three-dimensional structure and abundant terminal functional groups[260]. Dendrimers have been widely used in the central nervous system[261], cancer[262], and anti-inflammation fields[263]. Dendrimers are primarily spherical, and their core initiators can be monatomic, organic, or inorganic molecules, cyclic compounds, amino acids, esters, and polymers like polystyrene[264]. Repeated branching units connected to the core form an inner shell and easily modified functionalized surface exponential growth with increasing generations of inner shells[260]. The inner shell has abundant internal cavities that can encapsulate or trap drug molecules through hydrogen bonding, van der Waals forces, electrostatic interactions, hydrophobic interactions, and spatial site resistance[265]. It can encapsulate hydrophobic drugs to form stable host-guest complexes and improve drug stability *in vivo*. Hydrophobic drug molecules can also be chemically coupled to dendrimer terminal functional groups *via* esters, amides, imines, disulfide bonds, and other groups[266]. The core, inner shell and functionalized surface of dendrimers together determine size, solubility, biocompatibility, PK and other properties, and the *in vivo* fate of payloads[260].

Polyamidoamine (PAMAM)[267] and poly(propylene imine) are widely used and studied dendrimers in the market[268]. In addition,

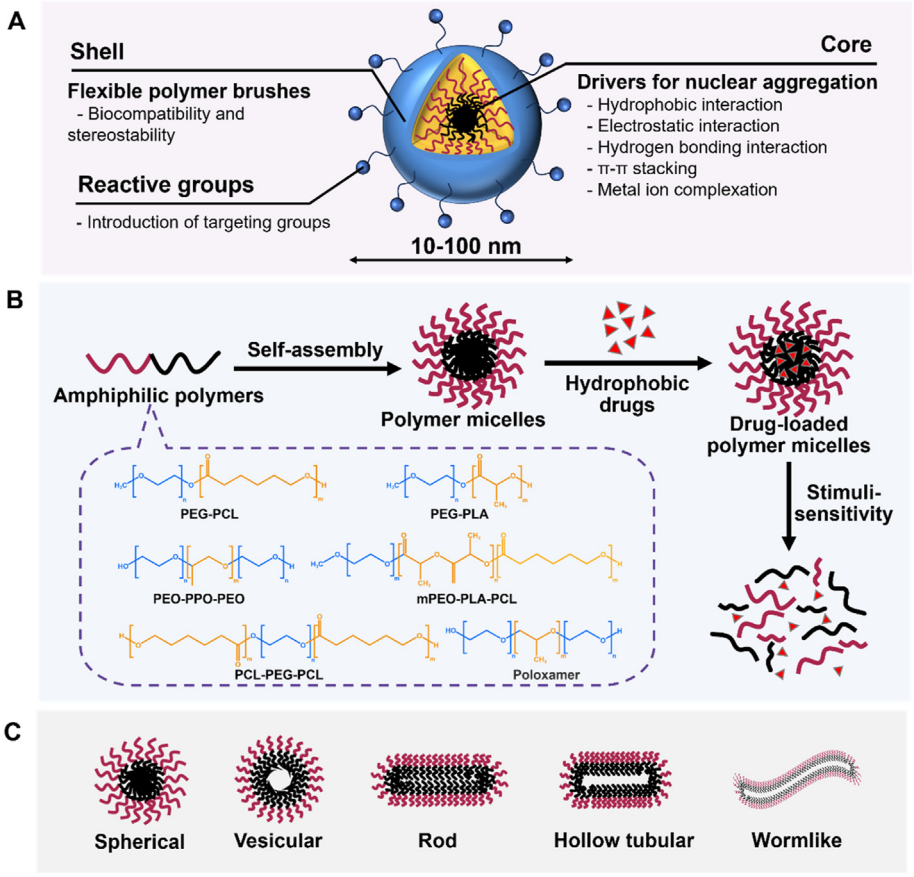

Figure 4 Structure, assembly, and disassembly schematic and different morphologies of polymer micelles. (A) Structure of typical polymer micelles. Genexol® PM is the first polymer micelle product, a PTX-loaded mPEG-*b*-PDLLA micellar formulation (20−50 nm, mPEG: 2000 g/mol and PDLLA: 1750 g/mol). (B) Polymer micelles: polymer-material assembly, drug loading and disassembly. (C) Polymer-micelle morphology.

dendrimers include dendritic polyglycerol[269], carbosilane dendrimers[270], poly L-lysine[271,272], amphiphilic Janus dendrimers and glycopeptide dendrimers[273], etc. The first dendrimer to be synthesized and commercialized was PAMAM, with a complete G1−G10 polymer family, of which the 4th generation PAMAM (G4) is the most widely studied. VivaGel® is the only marketed dendrimer product[274]. VivaGel® consists of 3% (*w*/*w*) SPL7013 and Carbopol® hydrogel to treat bacterial vaginosis. SPL7013 is a dendrimer developed by Starpharma and serves as the active ingredient in VivaGel®. SPL7013 with a polyanionic surface binds to viral targets, preventing the virus from attaching or adsorbing to cells[275]. Vivagel® was found little adverse effects in phase I clinical trials, but one study showed mild inflammation and epithelial irritation[276]. Dendrimer OP-101 nano therapy for severe COVID-19 has entered phase II clinical trials[277]. OP-101 is a covalent conjugate of the fourth-generation hydroxyl-terminated PAMAM (G4-PAMAM-OH) to *N*-acetylcysteine, significantly improves survival and reduces inflammatory and neurological injury markers in critically ill patients with COVID-19. To increase the solubility of glutaminase inhibitor JHU29,

Table 5 Overview of PM-products in market.

Brand name	API	Block copolymer	Administration route	Development stage	Company	Approval year	Ref.
Genexol PM	Paclitaxel	mPEG-*b*-PDLLA	IV	South Korea, Philippines, India, Vietnam and Indonesia	Samyang	2007	236,238
Nanoxel	Paclitaxel	PVP-*b*-PNIPAM	IV	India	Dabur	2007	239
Nanoxel M	Docetaxel	mPEG-*b*-PDLLA	IV	South Korea	Samyang	2012	240
Paclical	Paclitaxel	Micellar retinoid-derived XR-17	IV	Russia	Oasmia	2015	241
Zisheng	Paclitaxel	mPEG-PDLLA	IV	China	Shanghai Yizhong	2021	–

mPEG-*b*-PDLLA, methoxy poly(ethylene glycol)-*block*-poly(D,L-lactide); PVP-*b*-PNIPAM, poly(vinylpyrrolidone)-*block*-poly(*N*-isopropyl acrylamide); XR-17, isoforms of *N*-retinoyl-cysteic acid methyl esters; IV, intravenous injection; –, not applicable.

Khoury et al.[278] coupled JHU29 to G4-PAMAM-OH dendrimer with an average of 5 JHU29 molecules attached to each dendrimer, which resulted in an approximately 100-fold increase in solubility compared to free JHU29. The structural core of dendritic biopolymer octenylsuccinate hydroxypropyl phytoglycogen is plant glycogen, which is a dendritic α-D-glucan. Xie et al.[279] used it as a solubilizer to increase the solubility of CXB, docetaxel, and fenofibrate by 1755, 1137, and 1066 times, respectively.

Compared with traditional polymer carriers, dendrimers have precisely controllable nanoscale dimensions (typically 1−20 nm), defined molecular weights, low PDI, and radially symmetric structures, which can promote cell permeation and increase cellular uptake[280]. Dendrimers are highly potential nanocarriers due to the abundant internal cavities characterized by high drug-loading capacity[260,281]. Dendrimers with terminal primary amines such as PAMAM and poly (propylene imine) have significant *in vitro* cytotoxicity due to cationic groups presenting on surfaces[282]. Modifying the surfaces using negatively charged or neutral groups (*e.g.*, PEGylation, acetylation, glycosylation, or fluorination) can reduce immunogenicity and systemic toxicity[283] and provide targeted delivery and long-lasting sustained-release effects[284]. Dendrimer toxicity is related to their high stability and non-degradability under physiological conditions, and bioaccumulation in the body can lead to severe toxic reactions[285]. Therefore, developing biodegradable dendrimers is crucial for clinical applications.

5.1.3. *Polymer gels*

Polymer gels refer to a semi-solid formulation of solution, suspension, or emulsion with a polymer matrix capable of forming gel, which can be administered locally or systematically[286-292]. Compared with other polymer-based carriers, gel formulations have unique advantages, such as a three-dimensional structure resembling the extracellular matrix, good biodegradability, low toxicity, and a simple preparation process[293]. Polymer gels can also act directly on lesions, mitigate systemic adverse effects with sustained and controlled drug release, and serve as reservoirs for PWSDs[293]. According to different formation principles, gels can be divided into temperature-sensitive, pH, magnetic, electric, and light-responsive gels[294,295]. Temperature-sensitive gels are more widely used because of their faster sol-gel transition rate. When the temperature changes, the spatial structure of temperature-sensitive gels changes, and intermolecular hydrogen bonding is destroyed. The temperature-sensitive polymer molecules are transformed from dispersed micelles to dense three-dimensional network structures, thus causing sol-gel transition[293,296]. Commonly used temperature-sensitive materials include PEG-PCL copolymer[297], poloxamer[298], poly(*N*-isopropyl acrylamide)[299], hydroxypropyl chitin[300], chitosan[301], etc. Lee et al.[302] designed a degradable PEG-PCL-PEG thermosensitive gel by introducing reactive oxygen species (ROS) -responsive oxalate functional groups into polymer main chain during the coupling reaction of PEG-PCL diblock copolymers. The thermosensitive gel was degraded into PEG-PCL diblock copolymer in response to high ROS concentration, so the hydrophobic peptide cyclosporine A was released for more than 21 days *in vitro* and *in vivo*, with favorable sustained release.

Polymer gels are usually aqueous. Therefore, insoluble drug solubility in gels is a crucial issue that should be considered in gel formulation preparation. Most drugs currently approved for marketing by the FDA are dissolved in ethanol to increase insoluble drug solubility[303]. Specifically, Differin® commercially available topical gel increases adapalene solubility using propylene glycol[304]. Carrier technologies such as NPs[305], SDs[306], liposomes[307], and microemulsions[308,309] have also been used to improve solubility and transdermal penetration of PWSDs in gels. Permana et al.[290] prepared *in situ* vaginal gels containing gel sheets of itraconazole SDs to improve the solubility of itraconazole. Using P407 and P188 as gelling agents and incorporating HPMC as mucosal adhesion polymer. SDs prepared by water-soluble polymers increased the itraconazole solubility to 4 mg/mL. Additionally, gel sheets and *in situ* gel systems could improve gel adhesion and spread on the surface of the vaginal epithelium, prolong contact time with vaginal mucus, and achieve drugs' local targeting[290]. Shu et al.[310] developed a thermally responsive hydrogel loaded with IL microemulsion prepared with water, Tween 20, and CAGE as a drug reservoir for transdermal delivery of methotrexate. Microemulsion increased the solubility of methotrexate by 9 times. The gel increased the permeability of methotrexate by 27.6%.

Gels are not able to maintain a stable structure under physiological conditions for the required time due to low mechanical strength and stability, leading to drug sudden releaseand severe adverse reactions[311]. To improve the long-term stability of the hydrogel and control the release of drugs, Lee et al.[312] successfully introduced adamantane (Ad) units at the termini of Pluronic F127 to synthesize F127-Ad. Subsequent host-guest interactions between F127-Ad and polymerized β-CDs (CDPs) resulted in a physically cross-linked micellar stacking structure. The critical gelation concentration of F127-Ad/CDPs was significantly reduced compared to unmodified F127. And increased stability of gels with an increasing number of Ad molecules. In addition, complexation between CDPs and insulin loaded in gels further enhances drugs' sustained release characteristics[312].

5.2. *Lipid-based carriers*

The main components of lipid carriers are lipids and surfactants. Hydrophobic drugs are dissolved in lipids or encapsulated in the phospholipid bilayer. Lipid-based carriers include emulsions, SEDDS, liposomes, transferosomes, SLNs, NLCs, and LNCs, which have biodegradability, high biocompatibility and low immunogenicity[313-315]. In addition, lipid-based carriers can also be modified to prolong systemic circulation time, target specific sites and stimulate response release[316].

Lipids stimulate the secretion of lipases and bile from the gastrointestinal tract. Then, bile salts, lipids, and lipid digestion products form micelles or vesicles in the intestinal[317]. Insoluble drugs are dissolved in the colloidal structures and enter the hepatic portal vein *via* the paracellular and transcellular pathways[318]. Oral lipid nanoparticles (LNs) first need to penetrate the mucus barrier, which the ones with small particle size, neutrally charge or PEG-modification demonstrate higher penetration ability[319]. Subsequently, LNs penetrate the epithelial barrier through paracellular, transcellular, and lymphatic transports[320]. Chitosan reversibly opens tight junctions and facilitates paracellular transport[321]. Receptor-modified LNs such as transferrin can enhance cellular uptake[322]. In addition, LNs are rapidly transported to lymphocytes after uptake by microfold cells, entering the lymphatic pathway[323]. Thus, lipid-based carriers deliver the drugs into the systemic circulation *via* the hepatic portal vein and lymphatic circulation.

5.2.1. Emulsions

Emulsions are heterogeneous systems formed by two immiscible components in the presence of surfactant and cosurfactant (Fig. 5A). Nanoemulsions are thermodynamic stability systems with 20 to 200 nm particle sizes[324,325]. Nanoemulsions can encapsulate lipophilic drugs in the oil phase to protect them from the external environment, penetrate physiological barriers, and improve solubility and bioavailability. Nanoemulsions can be further formulated into conventional dosage forms (aerosol, injection, gel, cream, etc.) suitable for oral, parenteral, topical, nasal cavity and lung administration[326-329].

Oral nanoemulsions improve bioavailability by enhancing drug stability and initiating lymphatic transport to avoid first-pass elimination[330,331]. Guo et al.[332] encapsulated CUR and 5-fluorouracil in nanoemulsions. The AUC_{0-t} of CUR and 5-fluorouracil in nanoemulsions was 8.85 and 8.59 times higher than that of pure drugs, respectively. To improve patient compliance, nanoemulsions are often converted into semisolid dosage forms such as hydrogel, cream or ointment[333]. Hydrogel has high water content, excellent ductility, low skin irritation and high stabilization, and is the most commonly used semisolid dosage form[334-336]. Hussain et al.[337] loaded rifampicin nanoemulsions into carbomer gel to treat tuberculosis. Rifampicin nanoemulsion gel showed a 4.34-fold increase in $AUC_{0-\infty}$ compared to nanoemulsions for oral administration.

Intravenous lipid emulsions, with phospholipids as emulsifiers, include parenteral nutritional emulsions and drug-containing emulsions[338,339]. Injectable emulsion products for delivering drugs in the clinic have been summarized in Table 6[340-347]. Diprivan® is an injectable emulsion consisting of soybean oil, egg phospholipids, propofol, and glycerol. It is widely used for general anesthesia and sedation due to its rapid onset of action and rapid systemic clearance[348]. PEGylated nanoemulsions prolong circulation time, but repeated injections can cause the accelerated blood clearance (ABC) phenomenon. PEG derivatives and branched PEG instead of linear PEG, can attenuate or even avoid the ABC phenomenon[349-351]. Li et al.[352] encapsulated PTX and docosahexaenoic acid in folic acid-modified nanoemulsions for breast cancer therapy. Docosahexaenoic acid, as an adjuvant, enhanced the drug cytotoxicity. Synergism and active targeting combined to enhance the anti-tumor effects. Hydrophobic contrast agents or dyes encapsulated in nanoemulsions are used for imaging diagnosis[353]. Perfluorocarbons are highly hydrophobic, and their nanoemulsions are widely used as diagnostic agents[354,355]. Yang et al.[356] prepared nanoemulsions encapsulating PTX and sulforhodamine B, which had therapeutic and diagnostic functions. PTX and sulforhodamine B were covalently coupled through vitamin E and then realized the simultaneous release. In addition, the theranostic nanoemulsions had a long circulation ability and showed excellent therapeutic imaging effects.

Conventional emulsions have unstable phenomena such as coalescence, demulsification and Ostwald ripening[357]. Compared with conventional emulsions, pickering emulsions are stabilized by solid particles with high physical stability and drug loading[358-360]

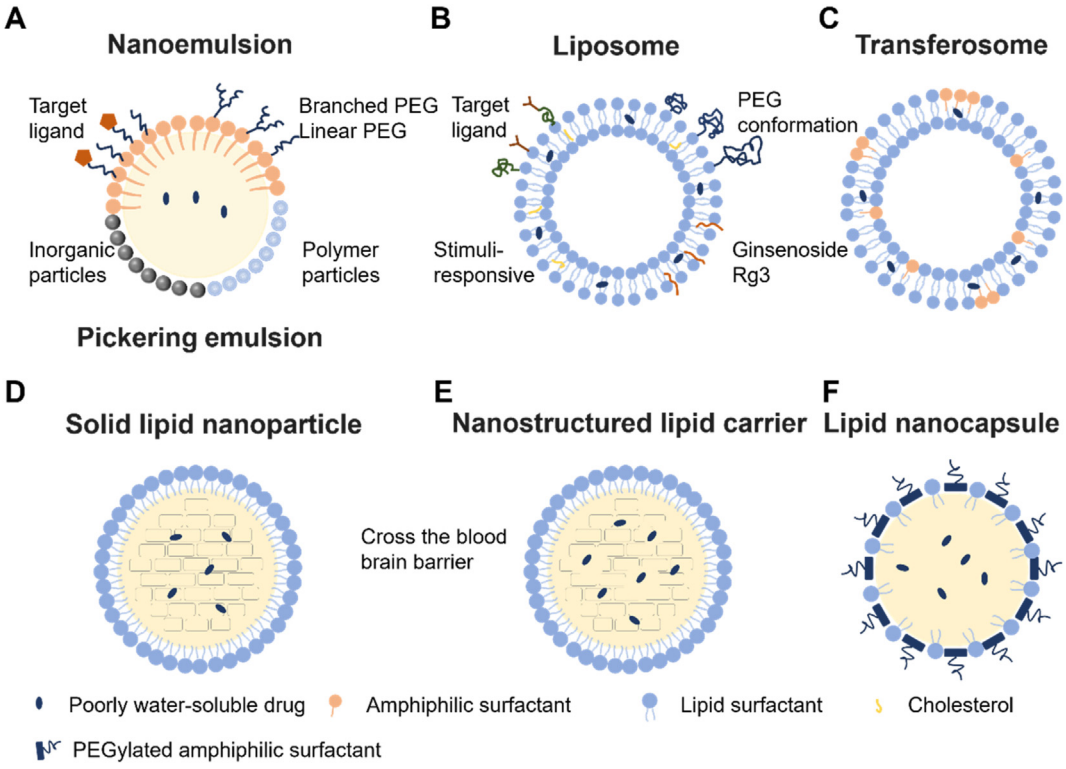

Figure 5 Lipid-based carriers for solubilization. (A) Nanoemulsions and picking emulsions. Diprivan® is a typically commercialized emulsion consisting of soybean oil, egg phospholipids, propofol and glycerol. Picking emulsions are stabilized by inorganic and polymer particles with high physical stability. (B) Liposomes. AmBisome®, a typical commercialized product, comprises hydrogenated soy phosphatidylcholine, cholesterol, distearoylphosphatidylglycerol and amphotericin B. (C) Transfersomes. Diractin®, an approved formulation of ketoprofen transfersomes, was withdrawn from the market due to its similar therapeutic effect to ketoprofen gel. (D) Solid lipid nanoparticles. (E) Nanostructured lipid carriers. Solid lipid nanoparticles and nanostructured lipid carriers have an inherent ability to cross the BBB. (F) Lipid nanocapsules.

Table 6 Injection emulsion for delivering drugs in the clinic.

Brand name	API	Indication	Lipid excipient	Company	Approval year	Ref.
Diazepam-Lipuro	Diazepam	Preoperative sedation	SO, MCT, EL	B. Braun	1985	340
Diprivan	Propofol	General anesthesia	SO, EL	AstraZeneca	1989	341
Vitalipid	Vitamins A, D_2, E and K_1	Intravenous nutrition	SO, EL	Fresenius Kabi	1991	342
Liple	Alprostadil	Chronic arterial occlusive disease	SO, EP, OA	Mitsubishi Tanabe	1998	343
Limethason	Dexamethasone p almitate	Rheumatoid arthritis	SO, EL	Mitsubishi Tanabe	1998	344
Etomidate-Lipuro	Etomidate	General anesthesia	SO, MCT, EL	B. Braun	2001	345
Cleviprex	Clevidipine	Hypertension	SO, EP	AstraZeneca	2008	346
Cinvanti	Aprepitant	Emesis	SO, EL	Heron	2017	347

SO, soybean oil; MCT, medium-chain triglycerides; EL, egg lecithin; EP, egg phospholipid; OA, oleic acid.

(Fig. 5A). Particle stabilizers can be inorganic particles, polymer-based particles, and nanocrystals[361-363]. Modifying particle stabilizers allows light, heat, and pH-responsive release of drugs. Zhao et al.[364] used an azobenzene-PEG adduct as the guest and β-CD-grafted alginate as the host. Self-assembled NPs of the two materials were used as particle stabilizers. Under ultraviolet irradiation, trans-azobenzene-PEG was converted into cis-isomer, resulting in the disassembly of NPs and light-responsive release of CUR. The pH response involves materials' charge transformation and degradation at different pH. Lignin and chitosan oligosaccharide were self-assembled into NPs encapsulating cytarabine by electrostatic interaction. Under acidic conditions, the amino protonation of chitosan oligosaccharide made the NPs loose and released CUR and cytarabine[365]. Eudragit RL100 can control drug release under alkaline conditions[366]. Temperature response involves the rapid transition of waxy materials from solid to molten. The molten waxy material is dissolved in the oil phase, realizing emulsions coalescence and drug release[367,368].

5.2.2. *SEDDSs*

SEDDSs are anhydrous homogeneous liquid mixtures composed of drugs, oils, surfactants, and cosolvents and can spontaneously emulsify in the gastrointestinal tract. Oils can solubilize the lipophilic drugs and affect the extent of lymphatic transport. Long-chain fatty acids, unsaturated fatty acids, or long-chain triglycerides enhance lymphatic transport[369,370]. Long-chain fatty acids in SEDDS formulations are reconverted to triglycerides, which further form chymotrypsins[371]. Chylomicrons are transported by lymphatic circulation, avoiding the first-pass effect and significantly improving oral bioavailability[372]. SEDDSs can also open the cellular epithelial tight junctions, inhibit the efflux of P-gp, enhance mucus penetration and adhesion[373-376]. SEDDS products in the clinic were summarized in Table 7[20,377-382].

Cyclosporin A belongs to BCS IV drugs and is used as an immunosuppressant for solid organ transplantation[383,384]. Sandimmune® and Neoral® are SEDDSs formulations. Sandimmune® is first brought into the market. Neoral® consists of cyclosporin A, alcohol, corn oil-mono-di-triglycerides, and polyoxyl 40 hydrogenated castor oil, which forms small droplets in the gastrointestinal tract, further enhancing drug absorption[378]. Liporaxel® is the world's first oral PTX solution based on lipid self-emulsifying drug delivery technology[385]. Liporaxel® consists of PTX, monoolein, tricaprylin, and Tween 80, and is indicated for advanced or metastatic gastric cancer therapy[386]. Compared with Taxol®, Liporaxel® reduces adverse effects such as neurotoxicity and hypersensitivity reactions[387]. The safety and efficacy of Liporaxel® for recurrent/metastatic breast cancer therapy are currently being evaluated, but results have not been reported[388].

Conventional SEDDSs have low drug loading and high surfactant content, and cosolvents' volatilization leads to precipitation of lipophilic drugs. Drugs in a supersaturated state also tend to form precipitates or crystals. Precipitation inhibitors (PIs) are added to SEDDSs to form supersaturated SEDDSs (super-SEDDSs), which increase intestinal absorption by increasing drug loading and maintaining drug supersaturation[20]. PIs include HPMC, PVP, Soluplus[389-391]. Bannow et al.[392] prepared super-SEDDSs loaded with simvastatin. Super-SEDDSs containing 20% (*w*/*w*) PIs showed a 2.4-fold increase in drug loading compared to SEDDSs. In addition, super-SEDDSs did not show crystallization within 6 months at room temperature, whereas SEDDSs showed crystallization within 1 day. Nora et al.[393] combined amorphous SD with super-SEDDSs (super-SEDDSs + ASD) for oral ritonavir delivery. The drug loading of conventional SEDDSs was 90% saturation solubility, whereas super-SEDDSs + ASD was 275% saturation solubility. In addition, the AUC_{0-7h} and AUC_{0-23h} of super-SEDDSs + ASD was 3- and 1.5-fold increase compared to the conventional ones, respectively.

Liquid SEDDSs are encapsulated in hard or soft gelatine capsules, and drugs are easily precipitated during storage. Solid SEDDSs (S-SEDDSs) can improve drug stability, and commonly used techniques include spray drying, freeze drying, hot melt extrusion and solid carriers adsorption[380]. Solid carrier adsorption is a promising technology with more controllable drug release. Solid carriers include mainly porous materials such as silica magnesium aluminosilicate[394,395]. Yan et al.[396] linked poly (acrylic acid) with mesoporous silica through amide bonds to realize the acid-sensitive release of β-elemene self-micro-emulsifying. The drug release under acidic conditions was 1.8 times higher than under neutral conditions. Sirolimus SEDDSs were adsorbed on methyl, amino, and carboxyl-modified mesoporous silica[397]. The properties of modified groups and the interactions between drug molecules and carrier groups significantly impacted drug release. Methyl-modified mesoporous silica was hydrophobic, and the drugs were difficult to release in water, but they were released rapidly in surfactant-containing solutions. Carboxy-modified mesoporous silica was hydrophilic, and the drugs were released rapidly in water and surfactant-containing solutions. Hydrogen bonding formed between sirolimus and amino groups significantly delayed sirolimus release.

Table 7 SEDDSs products in the clinic.

Brand name	API	Indication	Lipid excipient	Company	Approval year	Ref.
Depakene	Valproic acid	Epilepsy	Corn oil	AbbVie	1978	20
Rocaltrol	Calcitriol	Calcium regulator	Medium-chain triglycerides	Roche	1978	377
Accutane	Isotretinoin	Severe recalcitrant nodular acne	Hydrogenated soybean oil flakes Hydrogenated vegetable oil Soyabean oil	Roche	1982	377
Sandimmun	Cyclosporine	Organ transplantation	Corn oil Linoleoyl macrogolglycerides	Novartis	1990	378
Neoral	Cyclosporine	Organ transplantation	Corn oil-mono-di-triglycerides Polyoxyl 40 hydrogenated castor oil	Novartis	1995	378
Vesanoid	Tretinoin	Acute promyelocytic leukemia	Hydrogenated soyabean oil Partially hydrogenated soyabean oil Soyabean oil	Roche	1995	20
Norvir	Ritonavir	HIV infection	Oleic acid Polyoxyl 35 castor oil	AbbVie	1996	379
Fortovase	Saquinavir	HIV infection	Medium chain mono- and diglycerides	Roche	1997	380
Agenerase	Amprenavir	HIV infection	TPGS	Glaxosmithkline	1999	380
Targretin	Bexarotene	Cutaneous manifestations of cutaneous T-cell lymphoma	Polysorbate 20	Valeant Luxembourg	1999	380
Kaletra	Ritonavir Lopinavir	HIV infection	Polyoxyl 40 hydrogenated castor oil	AbbVie	2000	381
Aptivus	Tipranavir	Acquired immune deficiency syndrome	Mono/diglycerides of caprylic/capric acid Polyoxyl 35 castor oil	Boehringer Ingelheim	2005	379
Liporaxel	Paclitaxel	Advanced or metastatic gastric cancer	Monoolein Tricaprylin Tween 80	Daehwa and KIST	2016	382

TPGS, D-alpha tocopheryl polyethylene glycol 1000 succinate; KIST, Korea Institute of Science and Technology.

High concentrations of surfactants in SEDDSs cause gastrointestinal irritation by disrupting the intestinal mucosal barrier[398]. Recent studies have shown that SEDDSs disrupt the intestinal microbiota and cause intestinal inflammation in rats[399]. S-SEDDSs improve the stability of liquid SEDDSs, but the surface modification and porous structure of solid carriers could affect the dissolution and PK[400,401]. Therefore, further exploration of *in vitro−in vivo* correlation and PK in humans is necessary[402].

5.2.3. *Liposomes*

Liposomes are vesicular structures composed of phospholipids and cholesterol, with a hydrophilic core and hydrophobic lipid bilayer (Fig. 5B)[403-406]. Phospholipids and cholesterol are the main components of the cell membrane. Therefore, liposomes have biodegradability, outstanding biocompatibility and low toxicity. Altering the composition and surface modification produce functionalized liposomes such as long-circulation, ligand-targeted, and stimuli-responsive liposomes[315,407-411]. Approved liposomes have been summarized in Table 8. For example, AmBisome®, a liposomal formulation of amphotericin B, consists of hydrogenated soy phosphatidylcholine, distearoylphosphatidylglycerol, and cholesterol[412]. Compared with amphotericin B deoxycholate, AmBisome® significantly reduces nephrotoxicity and infusion adverse effects. However, AmBisome® has potential hepatotoxicity. The mechanism remains unknown[413].

The phospholipid bilayer of liposomes provides space for hydrophobic drugs. Conventional liposomes undergo partial degradation under gastrointestinal lipase and pH conditions, leading to premature drug leakage[414]. Polymer-modified liposomes have high gastrointestinal stability, long intestinal retention time and increased intestinal permeability[415]. Wu et al.[416] prepared PEG-coated liposomes with different densities expressing Lip, 2%, 5%, and 10% PEG-Lip. The particle size and PDI of 5% PEG-Lip and 10% PEG-Lip remained almost unchanged in gastric fluid during the 150 min. In addition, the penetration thicknesses in the mucus layer of Lip, 2%, 5%, and 10% PEG-Lip were about 30, 40, 70, and 60 μm, respectively. The density of 2% PEG-Lip had mushroom conformation, and the diffusivity was limited by mucus. The density of 10% PEG-Lip had brush conformation, and the interaction between the longer PEG chains and the mucus network hindered the penetration. The density of 5% PEG-Lip had mushroom-brush conformation with moderate length and the highest mucus permeability.

PEGylated liposomes are well-known as passive, long-circulating liposomes. Doxil®, the first approved PEGylated liposome with a terminal half-life of 20 to 45 h, is used to treat ovarian cancer and breast cancer[417]. Functionalized liposomes improve PK and biological distribution, reduce systemic toxicity, and enhance therapeutic effect, which have attracted wide attention[418]. Zhu et al.[419] prepared PTX liposomes targeting glioma. Ginsenoside Rg3 replaced cholesterol to improve the stability and fluidity of liposomes. The glucose residue in ginsenoside Rg3 had

Table 8 Liposomal products in the clinic.

Brand name	API	Indication	Route of administration	Company	Approval year
Epaxal	Inactivated hepatitis A virus	Hepatitis A infection	IM	Crucell Berna	1993
Doxil	Doxorubicin	Ovarian cancer	IV	Sequus	1995
DaunoXome	Daunorubicin	Advanced HIV-associated Kaposi's sarcoma	IV	Galen	1996
AmBisome	Amphotericin B	Systemic fungal infection	IV	Gilead	1997
Inflexal V	Haemagglutinins	Flu (influenza)	IM	Crucell Berna	1997
Depocyt	Cytarabine	Lymphomatous meningitis	IT	Pacira	1999
Visudyne	Verteporfin	Subfoveal choroidal neovascularization	IV	Novartis	2000
Myocet	Doxorubicin	Breast neoplasms	IV	Elan	2001
Lipusu	Paclitaxel	Ovarian cancer	IV	Luye	2003
DepoDur	Morphine	Postoperative analgesia	Epidural	Pacira	2004
Mepact	Mifamurtide	Osteosarcoma	IV	Takeda	2009
Exparel	Bupivacaine	Postoperative analgesia	Local infiltration	Pacira	2011
Marqibo	Vincristine	Acute lymphoblastic leukemia	IV	Acrotech	2012
Lipo-Dox	Doxorubicin	Metastatic ovarian cancer Metastatic breast cancer	IV	Sun	2013
Onivyde	Irinotecan	Metastatic pancreatic cancer	IV	Ipsen	2015
Vyxeos	Cytarabine Daunorubicin	Acute myeloid leukemia	IV	Jazz	2017
Shingrix	Recombinant varicella-Zoster virus glycoprotein E	Herpes zoster	IM	GlaxoSmithKline	2018
Arikayce	Amikacin	Mycobacterium avium complex lung disease	Inhalation	Insmed	2018

IM, intramuscular injection; IV, intravenous injection; IT, intrathecal injection. Depocyt®, Exparel® and DepoDur® are multivesicular liposomes.

a high affinity for glucose transporters highly expressed in glioma cells, which promoted liposomes to target brain tumors. The liposomes were eliminated slowly in mice, and the accumulated amount in the brain was 3-fold increased compared to conventional liposomes.

Most approved liposomes are conventional ones, but preclinical research mainly focuses on developing and applying functional liposomes. Functionalized liposomes have shown more excellent therapeutic effects in animal models. Several actively targeted liposomes have entered clinical trials, however, some demonstrated unsatisfactory outcomes[420]. The clinical application of functionalized liposomes may be promoted by exploring the fate *in vivo*, predicting the potential therapeutic effects, and developing methods for large-scale production[421,422]. Microfluidic vortex focusing enabled high-throughput production of liposomes with precisely controlled particle size, high stability, and high reproducibility, which brings the promise of simplifying liposome production steps[423].

5.2.4. *Transferosomes*

Transferosomes are composed of phospholipids, edge activators, ethanol, and water and have good permeability and high deformability (Fig. 5C)[424]. Surfactants are the leading edge activators, improving the membrane's deformability[425]. The high deformability allows transferosomes to pass through the SC intactly[426]. Zhang et al.[427] found that the penetration depth of transferosomes was 280 μm after application to human cadaveric skin for 24 h. The SC is the main penetration barrier with a 10−15 μm thickness[428]. Therefore, transferosomes are potent vehicles for topical and systemic drug delivery.

Sahu et al.[429] summarized that transferosomes were used to enhance the skin penetration of insoluble plant bioactives. Zhang et al.[430] prepared meloxicam transferosomes using cetyl pyridine chloride as an edge activator. Compared with conventional liposomes, the deformability index of transferosomes was much more significant. The permeability coefficient of transferosomes hydrogel in human cadaver skin was 1.71-fold increased compared to meloxicam-loaded hydrogel. Transferosomes are loaded in hydrogels to prolong retention on the skin and improve patient compliance[430-432]. Jiang et al.[433] prepared cell penetrating peptide (CPP)-modified PTX transfersomes for melanoma therapy. CPP allowed PTX transfersomes to penetrate deep into the tumor spheroid model. Subsequently, CPP-modified PTX transfersomes were loaded into oligopeptide hydrogel, which prolonged the retention time on the skin. The combination minimized tumor size and weight and treated melanoma more efficiently. Currently, there are no transfersomes on the market[434]. Diractin®, a gel containing ketoprofen transferosomes, was withdrawn from the market because of its therapeutic effect, similar to ketoprofen gel[435].

5.2.5. *SLNs and NLCs*

SLNs are colloidal particles composed of solid lipids and surfactants, which are solid at room and body temperatures (Fig. 5D)[436]. NLCs are colloidal particles composed of liquid lipids, solid lipids and surfactants, the second generation of SLNs (Fig. 5E)[437]. Compared with liposomes and emulsions, SLNs can reduce the degradation of API and improve physical stability[438]. However, the crystal transition of solid lipids in SLNs leads to drug leakage. Liquid lipids in NLCs can reduce the crystallinity of solid lipids and inhibit drug efflux, improving drug loading and storage stability[439,440]. In addition, SLNs and NLCs are highly biocompatible, biodegradable, and highly attractive in drug delivery, especially brain delivery.

SLNs and NLCs have an inherent ability to cross the BBB[441,442]. Pawar et al.[443] quantified drug concentrations in the brain to visualize the ability of SLNs to cross the BBB. Oral and brain bioavailability of SLNs were 1.6 and 5.8 times higher than that of the pure drug, respectively. SLNs and NLCs are modified with ligands or peptides to enhance brain targeting[442,444-446]. For example, Farshbaf et al.[447] prepared bortezomib NLCs with dual

modifications of D8 and RI-VAP. D8 showed a high affinity for nicotine acetylcholine receptors on brain capillary endothelial cells, which benefited NLCs to cross the BBB. RI-VAP showed a high affinity for the receptors on cancer cells, which urged NLCs to actively target cancer cells. Compared with unmodified NLCs, dual-modified NLCs in BBB and blood−brain tumor barrier models showed a 5.1- and 2.4-fold increase in transcytosis efficiency, respectively. SLNs and NLCs for nasal administration can directly enter the brain parenchyma through the trigeminal and olfactory regions, circumventing the BBB and achieving non-invasive delivery[448,449]. Sabry et al.[450] labeled valsartan-loaded SLNs with rhodamine B, and found that SLNs administered nasally accumulated in the brain by photon imaging.

Based on Quality by Design, researchers screened lipids, surfactants, preparation methods and process parameters to determine the optimal prescriptions for SLNs and NLCs[451-453]. Recently, Kovačević et al.[454] established a new lipid screening method based on the Hansen solubility parameter. This method significantly reduced the scope of lipid screening and developed NLCs efficiently and quickly. Furthermore, preparing SLNs and NLCs can avoid using organic solvents and make it easy to scale up.

5.2.6. *LNCs*

LNCs are colloidal NPs with 20 to 200 nm particle sizes, composed of oil, water, PEG-derived amphiphilic surfactants, and lipid surfactants (Fig. 5F)[455]. LNCs can be prepared by the phase-inversion temperature method without organic solvents[456]. LNCs have a rigid surfactant layer on the surface, displaying a core-shell structure and having high physical stability[457]. LNCs have been used to improve oral bioavailability, enhance skin permeability, and cross the BBB[458-462]. Studies have shown that LNCs for nasal administration mainly enter the blood circulation through the nasal epithelium, and the olfactory pathway could be ignored[462].

The surface charge, particle size, and surface coating of LNCs affect PK. Solutol® HS-15 and Kolliphor® HS-15 are amphiphilic surfactants commonly in LNCs, both form short-chain coatings on the surface. However, DSPE-mPEG 2000 formed a long-chain coating, prolonging the circulating time *in vivo*[463]. PEGylated LNCs with different particle sizes had significantly different fates in rats after intravenous injection[464]. The elimination rate of LNCs with 50 nm particle size was higher than LNCs with 85 nm particle size. The renal excretion and instability in the bloodstream of small-sized LNCs may cause this. Pinton et al.[465] found that neutral and positively charged LNCs with 100 nm particle size were taken up through caveolae-mediated endocytosis. Neutral LNCs were directed toward bone marrow cells in the blood, and whiles positively charged ones were directed toward macrophages and tumor cells. PEGylated LNCs have passive targeting properties, and CPP or antibody-modified LNCs can actively deliver drugs. NFL-peptide can target glioma and neural stem cells in the subventricular zone[466]. Therefore, NFL-peptide-modified retinoic acid LNCs were used to treat demyelinating diseases[467].

5.3. *Inorganic carriers*

Inorganic carriers have intrinsic properties (electrical, magnetic, optical properties) and are widely used in bioimaging and drug delivery[468,469]. Common inorganic carriers include mesoporous materials, metal-based materials, and LDHs[470]. Drug loading, the ability to control drug release, and *in vivo* clearance are the main areas of concern for delivery carriers[471]. Mesoporous materials have adjustable specific surface area and pore volume, showing excellent drug loading. Drugs can sustain release and stimulate response release by adjusting the shape, pore size, and surface modification of inorganic carriers[471,472]. *In vivo*, clearance is related to safety and long-term toxicity and is the main challenge for inorganic carriers. The appearance of biodegradable inorganic carriers, such as silicon dioxide and iron oxide, holds promise for clinical translation[473]. Except for MSNs, other inorganic carriers are less commonly used for oral delivery. Similar to LNs, MSNs for oral administration also need to overcome biochemical, mucus, and epithelial barriers. The particle size, charge, and surface modification of MSNs could enhance mucus and intestinal epithelial permeability[474,475].

5.3.1. *MSNs*

After the first loading of IBU into MSNs, the research of MSNs in drug delivery and medical diagnosis has increased significantly[476,477]. Under physiological conditions, MSNs can be degraded into nontoxic silicic acid and polysilicic acid. Controlled degradation of MSNs *in vivo* can also be achieved by adjusting the size, shape, surface charge, and doping with metal ions or oxides[470,478]. In addition, MSNs have the advantages of high drug loading, simple preparation, controllable production, and good reproducibility[479].

Highly dispersed hydrophobic drugs in MSNs can inhibit drug crystallization and maintain drug amorphous[480]. Drugs in MSNs are released rapidly upon extensive contact with body fluids, increasing drug solubility and bioavailability. It is worth noting that appropriate pore volume, pore size and drug loading method can significantly improve drug dissolution[481]. Type et al.[482] loaded indomethacin and nimesulide into MSNs and carboxyl-modified MSNs (MSN−COOH), and the drugs were all present in the amorphous form. Due to the high wettability of MSN-COOH, the release medium was more accessible to the pores, which improved the dissolution rate *in vitro*. The bioavailability of indomethacin and nimesulide in MSN-COOH was 2 times and 3.6 times increased compared to the pure drug. The large pore volume and high drug loading of MSNs create favorable conditions for drug co-delivery. Tarannum et al.[483] coupled the cisplatin prodrugs to the MSN inner surface and the gemcitabine prodrugs to the MSN outer surface. The two drugs had differential release properties. Upon exposure to the tumor microenvironment, gemcitabine was released first and inhibited enzyme activity to prevent DNA repair, which increased the accumulation of cisplatin-DNA complexes and cytotoxicity. The tumor inhibition rate was 79%.

MSNs often suffer from premature drug leakage, and the application of gating materials is an effective solution (Fig. 6A). The gating materials are physically or chemically altered by various stimuli (pH, ROS, light, GSH, etc.)[484]. Zhang et al.[485] grafted fucoidan on the surface of MSNs through disulfide bonds. CUR was rapidly released under acidic or GSH conditions. Yang et al.[486] prepared adriamycin-loaded MSNs using gold nanoparticles (AuNPs) as gating materials for chemotherapeutic photodynamic synergistic therapy. AuNPs have strong photothermal conversion ability. Under near-infrared (NIR) light, the generated heat reduced the interaction between drugs and MSNs, prompting a step-like accelerated release. Unlike the above research, Yang et al.[487] introduced diselenide into the MSNs preparation process to construct self-destructive vehicles. The photosensitizers and adriamycin were loaded into MSNs. Under infrared light irradiation, ROS generated by photosensitizers

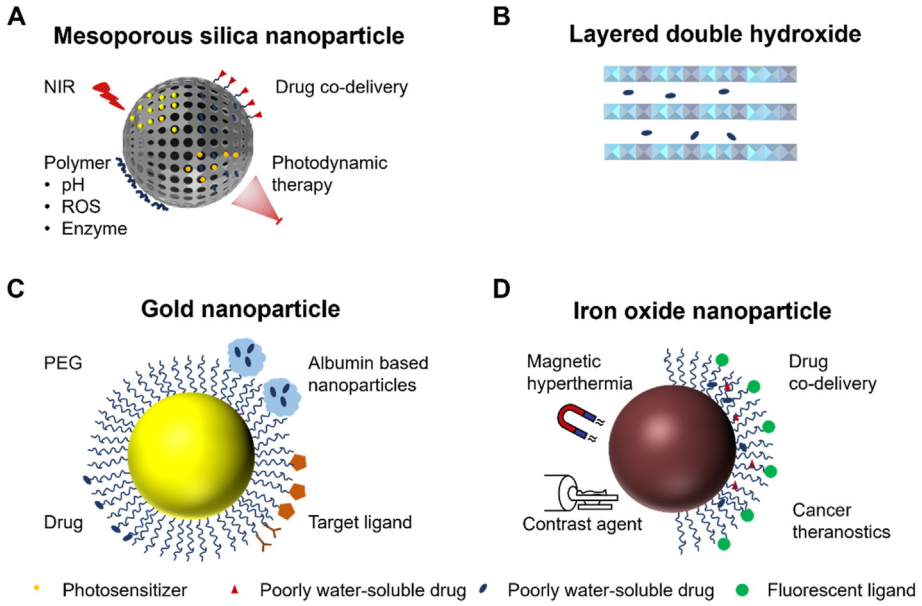

Figure 6 Inorganic carriers for solubilization. (A) Mesoporous silica nanoparticles. The mesoporous structure can encapsulate two drugs for co-delivery. Surface modification allows the stimulation response such as pH, ROS, enzyme and near-infrared light. (B) Layered double hydroxides as acid-responsive carriers. (C) Gold nanoparticles. Drugs, antibodies, and proteins are covalently attached to the nanoparticle surface. (D) Iron oxide nanoparticles. IONs are used as diagnostic agents in the clinic. Ferumoxytol® is the only approved therapeutic agent.

destroyed the diselenide, leading to MSNs' disintegration to release drugs.

MSNs for oral delivery cause intestinal microecology imbalance and intestinal inflammation[488,489]. One-year single-dose intravenous injection of MSNs did not cause liver inflammation and apparent chronic toxicity in mice[490]. The two different results may be caused by the different physicochemical properties of MSNs, dosage, administration frequency, and route of administration. Therefore, the safety, degradation and excretion processes of MSNs should be comprehensively explored to accelerate the clinical translation.

5.3.2. *MCNs*

MCNs have similar structures and properties to MSNs. MCNs have larger specific surface area and pore volume, improving the adsorption and drug loading. Spherically ordered MCNs showed a 3-fold increase in loading capacity compared to MSNs[491]. Gastrointestinal administration of MCNs has small intestinal uptake, rapid excretion, and low organ accumulation in mice, showing low toxicity and high biocompatibility[492,493].

MCNs could enhance the dissolution and bioavailability of PWSDs[494-496]. Lu et al.[496] modified chitosan and *N*-(2-hydroxypropyl) methacrylamide copolymer (pHPMA) on the surface of MCNs sequentially to deliver probucol (PB). PB was highly dispersed in MCNs in an amorphous form. The pHPMA polymer facilitated mucus permeation and could be degraded in time. The exposed chitosan mediated epithelial transport of MCNs. The oral bioavailability of PB was 2.76 times increased compared to the commercial formulation. The loading method of MCNs significantly affects drug release. Niu et al.[497] loaded fenofibrate into MCNs by incipient wetness impregnation, the solvent and melting methods. In melting methods, the drugs had a certain crystallinity and low dissolution rate due to the high viscosity of the molten drug. In incipient wetness impregnation, amorphous drugs were deposited at the entrance or surface of pores, showing a rapid release. In the solvent method, drugs distributed on the surface and in the mesopores, showing a rapid release followed by a sustained release.

5.3.3. *LDHs*

LDHs are layered materials consisting of hosts and guests (Fig. 6B). The positively charged host layer consists of divalent or trivalent metal ions and six octahedrally coordinated OH^-, balanced by the guest anions and water molecules between the layers[498]. Because of simple synthesis, high biocompatibility and broad source of raw materials, LDHs have been widely used in drug delivery, regenerative medicine and biological imaging[499,500]. Furthermore, a single layer or several layers of LDHs provide more binding sites, significantly improving drug loading[501,502]. The drug loading of LDHs with only 2−3 layers was 7.34 times higher than NPs[502].

LDHs have been used to improve the dissolution rate of PWSDs[503-507]. Berberine in LDHs showed significantly higher dissolution rates in water, PBS and 0.1 mol/L HCl ($P < 0.0001$) compared to the pure drug, requiring half the dose to achieve the same hypoglycemic effect[508]. There are two mechanisms of drug release from LDHs: ion exchange and corrosion[509]. Ion exchange refers to exchanging anions in the release medium with drug ions. Senapati et al.[510] controlled drug release by changing the charge density of interlayer anions. They used the ion exchange method to embed the raloxifene hydrochloride into LDHs with NO_3^-, CO_3^{2-}, and PO_4^{3-} as guest anions expressed as LN-R, LC-R, and LP-R, respectively. In LP-R, the disordered arrangement of drug molecules and the weak interaction caused rapid drug release. Due to the ordered arrangement of drug molecules and the strong interaction in LN-R and LC-R, drugs showed a biphasic rapid release followed by sustained release. In addition, the drug release rate in LDHs also depended on the buffers[511]. Corrosion refers to the gradual degradation of LDHs under acidic conditions. Therefore, LDHs have been studied as acid-responsive carriers.

MgAl-LDH could neutralize acid to promote ROS clearance of ceria oxide NPs, treating rheumatoid arthritis[512]. Peng et al.[501] loaded azithromycin and indocyanine green into monolayer LDHs. The cumulative release of azithromycin was less than 5%, 9.05% and 21.01% at pH 7.4, 6.5 and 5.0, respectively. The addition of NIR irradiation resulted in a pulsatile burst release.

5.3.4. *MNPs*

MNPs are nanoscale particles based on metallic elements, including gold, silver, iron oxide, and zinc oxide NPs[513]. AuNPs are the most commonly used pure MNPs. Due to the surface plasmon resonance effect, AuNPs have great potential for imaging and therapeutic applications[514,515]. AuNPs have various shapes, such as rods, spheres, nanocapsules, and nanoshells[516,517]. Gold nanorods with a specific aspect ratio can absorb NIR penetrating through the skin and are used in cancer imaging and photothermal therapy[518]. The internal space of gold nanocages and nanoshells is more suitable for encapsulating drugs[519,520]. AuNPs are mostly non-porous structures, and drugs are adsorbed or covalently attached to the surface (Fig. 6C)[521,522]. The surface of AuNPs can also be functionalized with polymers, antibodies, peptides, etc.[523]. PVP-coated AuNPs were coupled to CUR *via* amide bonds, and folic acid was then linked to CUR for active targeting[524]. PEG-coated AuNPs (PEG-AuNPs) can prolong circulation time and improve the stability. The terminal groups of PEG-AuNPs provide binding sites for the coupling drugs or targeting ligands[525]. Cisplatin was complexed to PEG-AuNPs with different types of terminal groups (carboxyl, methoxy, biotin). Based on the amide reaction between the terminal carboxyl group of PEG and the amine group of protein, PEG-AuNPs can co-couple targeted antibody and albumin-drug complexes[526]. Multiple AuNPs have turned to clinical trials[527]. CYT-6091, a recombinant human tumor necrosis factor-alpha directly coupled to PEG-AuNPs, demonstrated good safety, tolerability, and tumor-targeting properties in phase I clinical trials[528]. Wang et al.[529] loaded the PTX prodrug analog to CYT-6091 to form the novel nanomedicine CYT-21625 for targeted therapy in thyroid cancer.

Iron oxide nanoparticles (IONs) are the most commonly used metal oxide NPs. Due to inherent magnetism and biocompatibility, IONs are often used as contrast and thermotherapeutic agents for magnetic resonance imaging and magnetothermal therapy (Fig. 6D)[530,531]. Drugs can be directly coupled with IONs through covalent bonds or encapsulated in surface polymer coatings through weak electrostatic interaction[532,533]. IBU covalently bound to glycerol phosphate-functionalized IONs through amide bonds[534]. Yao et al.[535] encapsulated simvastatin in a zwitterionic polymer coating of ferroferric oxide NPs to treat triple-negative breast cancer. In addition, IONs can combine imaging and drug delivery to achieve diagnostic and treatment. Reichel et al.[536] coupled the hepthamethine cyanine to Ferumoxytol®, which was used for imaging and targeting gliomas. PTX and cisplatin were encapsulated in the polymer coating. After NIR irradiation, the fluorescence of the tumor lasted for 168 h, providing enough time for surgical resection. The targeted delivery of PTX and cisplatin significantly inhibited the growth of postoperative gliomas and improved the survival rate. IONs are mainly used as a diagnostic agent in the clinic. Ferumoxytol® is the only therapeutic agent approved for iron deficiency anemia[537]. IONs, as drug delivery carriers, have no products on the market, and related clinical trials have been terminated because of no significant curative effect[538].

6. Conclusions

We offer a comprehensive review of solubilization techniques, including the solubilization mechanism, limitations, and advantages (Table 9). With the application of combinatorial chemistry and high-throughput screening, the number of PWSDs has increased dramatically. Low solubility remains a significant challenge for drug development. Conventional solubilization techniques have limitations, such as adverse reactions caused by long-term use, requirements on drug structure, and difficulty in

Table 9 Solubilization techniques used to enhance the bioavailability of PWSDs.

Solubilization technique		Solubilization mechanism	Limitation	Advantage	Drug type
Crystallization strategy	Nanocrystals	Improving the dissolution rate	*In vivo* fate of nasal, pulmonary, ocular, and transdermal administration Controlling particle size and crystal morphology	High drug-loading Easy industrial production High safety Multiple absorption mechanisms	All PWSDs
	Cocrystals	Reducing lattice strength Improving the dissolution rate	Strict requirements for drug structure Time-consuming	Synergetic therapy Approved by 505 (b) (2) pathway	Drug molecules with hydrogen bond donors or acceptors
Ionic liquids		The interaction between drug molecules and ionic liquids	Mechanisms at the molecular level Long-term toxicity Lack of regulatory scenario	High adjustability Eliminate solid-state drug polymorphism Synergetic therapy Transdermal delivery	All PWSDs
Drug delivery systems	Polymer-based carriers	Encapsulation of PWSDs in carriers	Potential toxicity of carrier materials	Prolonging circulation time	All PWSDs
	Lipid-based carriers		Unclear PK and mechanism of nanocarriers	Stimulus-responsive release	Lipophilic drug
	Inorganic carriers		Difficulties in industrial production	Active targeted delivery Drug co-delivery Combination of diagnosis and therapy	All PWSDs

achieving precise drug delivery. With the development of novel DDSs, modifying poorly soluble drugs or packaging drugs in carriers are currently promising development directions.

Nanocrystals can deliver PWSDs *via* multiple routes. Compared with DDSs, the high drug loading of nanocrystals allows for increased drug content at the target site[539]. Compared with spherical NPs, rod-shaped nanocrystals are quickly deposited in pulmonary vessels, reducing phagocytosis and avoiding lysosomal destruction for intracellular delivery. Rod-shaped nanocrystals adsorb proteins or RNA through electrostatic action to obtain a co-delivery platform for synergistic treatment[540-542]. Therefore, the co-delivery platform has excellent potential for synergistic treatment of pulmonary diseases[543,544]. In addition, novel bioimaging techniques can elucidate nanocrystals' fate for nasal, pulmonary, ocular, and transdermal administration, further advancing nanosuspension development and launch[545].

ILs are simple to synthesize, with highly tunable physicochemical properties and biological activities. ILs represent a novel strategy to improve solubility, permeability, polymorphism and bioavailability. However, there are still barriers in the application. The biodegradability and toxicity need to be investigated systematically. Then, the mechanism of ILs at the molecular level should be further explored to design ILs that meet specific delivery needs. Finally, the FDA has not provided clear definitions and regulatory requirements for ILs and API-ILs, which may hinder product approval.

The surface functionalization and various materials endow DDSs with the ability to cross the BBB, targeted delivery, and stimulus-responsive release[546]. DDSs can co-deliver drugs or diagnostic agents, realizing disease diagnosis and synergistic treatment. Many articles and patents about nanocarriers exist, but only several related preparations have been approved[547]. Among the nanoparticle-based nanomedicines in clinical trials, the success rate of phase III clinical trials is only 14%[548]. The potential toxicity of carrier materials, unclear PK and mechanism of nanocarriers, and difficulties in industrial production limit the marketability of nanoformulations[549-551]. In addition, quality standards for nanoformulations should be clarified to ensure safety and efficacy[552].

It is expected that the most appropriate solubilization technique can be directly selected based on the drug's physicochemical properties and clinical needs. For BCS II drugs, dissolution is critical to the absorption. Therefore, micronization, crystallization strategy, and SDs can improve oral bioavailability by increasing dissolution rate. For BCS IV drugs, intestinal permeability should also be enhanced. Otherwise, supersaturated insoluble drugs always precipitate in the gastrointestinal tract, leading to poor drug absorption. The better option for improving the bioavailability of BCS IV drugs is to modify the chemical structure to form soluble prodrugs and salts. However, the methods are limited to BCS IV drugs that are ionizable or easily chemically modified. Nanocrystals are preferably absorbed in the intact state of the gastrointestinal tract[553]. Due to the adjustable physicochemical properties (particle size, charge, surface modification, and shape), nanocarriers can enhance oral absorption by opening tight junctions, penetrating mucus layers, enhancing epithelial permeability, or targeting lymphatic transport. Notably, drugs with high lipophilicity (log $P > 5$) and high long-chain triglyceride solubility (>50 mg/g) are more easily transported *via* lymphatic transport, which are more suitable for making SEDDSs. Prodrug nanocrystals injected intramuscularly show long-lasting release and are suitable for diseases that require long-term management. ILs enhance drug skin penetration and are indicated for treating psoriasis or skin infections. SLNs and NLCs cross the BBB, and their nasal delivery is used to treat brain diseases such as glioblastoma and Alzheimer's disease.

Machine learning can predict the characteristics of new prescriptions based on existing data. Therefore, integrating machine learning into drug formulation development helps reduce development time and costs. Recently, machine learning has been used to predict the effect of excipients on drug solubility, formulation stability, and drug release rates[554,555]. However, researchers still need to make significant efforts to obtain enough data for accurate predictions in the future. We believe that the clinical application of PWSDs will have excellent prospects.

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Author contributions

Bing Xie: Writing − review & editing, Writing − original draft. Yaping Liu: Writing − review & editing, Writing − original draft. Xiaotong Li: Writing − review & editing. Pei Yang: Writing − review & editing, Writing − original draft. Wei He: Writing − review & editing, Writing − original draft, Validation, Supervision, Funding acquisition, Formal analysis, Conceptualization.

Conflicts of interest

The authors have no conflicts of interest to declare.

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