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REVIEW

Advanced oral drug delivery systems: Current challenges and emerging technologies

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Abstract Oral dosage is the most commonly used and preferred method of drug administration due to its several advantages, including non-invasiveness, patient adherence, and ease of use. However, oral bioavailability can be influenced by several factors, such as drug solubility and mucosal permeability in the gastrointestinal tract, sometimes leading to poor and/or inconsistent absorption. In particular, low aqueous solubility presents a significant challenge in achieving adequate oral bioavailability and therapeutic effectiveness for many pharmaceutical compounds. Attempts to overcome these limitations have focused on deeper understanding of the physicochemical, biochemical, and biological barriers that limit overall drug bioavailability. To ensure better and stable pharmacokinetic behavior of orally administered drugs, various formulation strategies have been developed to enhance solubility, dissolution rate, membrane permeability, and overall oral bioavailability. This review article explores recent advancements in formulation techniques aimed at improving the biopharmaceutical properties of orally administered drugs. The challenges and development aspects of oral dosage forms are also addressed.

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1. Introduction

Oral drug administration is the most widely used route for drug delivery in both traditional and modern medicine due to its convenience, non-invasiveness, and high patient compliance[1,2]. The absorption of a drug can be classified into mainly two processes, dissolution and permeation. In the dissolution process, an oral formulation is disintegrated in the stomach, followed by its dispersion and dissolution in the gastrointestinal (GI) tract. Various physiological conditions in the GI tract, such as pH levels, gastric fluid volume, gastric emptying rate, intestinal transit time, and food intake, can theoretically influence drug dissolution[3]. These parameters could be intra- or inter-individually variable depending on many endogenous or exogenous factors[2]. The endogenous factors could be influenced by several physiological changes[4,5]. For example, aging changes several GI conditions to influence the dissolution and intestinal permeation of a drug, and some diseases could also alter the physiology in the GI tract endogenously. In addition to the impact of physiological changes on the absorption of drugs, a number of new drugs and drug candidates have been found to be hydrophobic compounds, mostly classified into biopharmaceutics classification system (BCS) class II drugs with low GI solubility and high permeability[6]. The dissolution behavior and oral absorption profile of these drugs tend to be affected by physiology in the GI tract, more than hydrophilic drugs. To ensure consistent oral absorption, solubilization technologies aimed at improving the dissolution behavior of hydrophobic drugs have been explored and continue to be investigated in both academic and industrial research.

Various pharmaceutical technologies have been developed to enhance the dissolution behavior of BCS class II (low solubility, high permeability) and class IV (low solubility, low permeability) drugs, aiming for more stable pharmacokinetic profiles and improved clinical outcomes[7]. These strategies include the use of micro- and nanoparticles, microenvironmental pH-modifiers, solid dispersion (SD), micelles, emulsions, and cyclodextrin complexation[7]. Particle size reduction is the simplest way to improve the dissolution rate of drugs, and especially nano-sized particles lead to accelerated dissolution of poorly soluble drugs[8]. Destruction of the crystalline lattice of a drug is needed for its dissolution, and the solubility of metastable forms or amorphous states of drugs could be higher than that of most thermodynamically stable states[9]. A promising strategy for achieving amorphization is amorphous solid dispersion (ASD) technology, where active pharmaceutical ingredients are dispersed in molecular and amorphous states within inert carriers[10]. Many marketed formulations have adopted this SD technology to enhance oral absorption of poorly soluble drugs, and SD of such drugs could improve their oral bioavailability in humans, compared with their crystalline forms[11].

These formulation technologies would not always be applicable to all BCS class II and IV drugs, as their effectiveness depends on the specific physicochemical properties of each drug. Leveraging accumulated knowledge and experience from previous biopharmaceutical investigations can facilitate the formulation design and development of oral dosage forms with consistent pharmacokinetic behavior. This article highlights various formulation strategies aimed at enhancing and stabilizing oral drug absorption and, thereby, better clinical outcomes. In this review, we discuss key factors influencing the pharmacokinetic behavior of drugs, explore various drug delivery strategies aimed at enhancing dissolution, and present examples of their practical applications.

2. Challenges in oral absorption of drugs

Despite their convenience and high patient compliance, oral dosage forms sometimes present significant challenges to achieving effective drug absorption. A range of physicochemical and biological barriers, including poor solubility, limited membrane permeability, change in physiological conditions, and food effects, can severely compromise the biopharmaceutical performance of many therapeutic agents. A comprehensive understanding of these obstacles, along with the development of effective strategies to overcome them, would be essential for better formulation design with consistent pharmacokinetic profiles.

2.1. Dissolution and precipitation

The dissolution rate is theoretically the rate-limiting step for oral absorption of poorly soluble drugs, particularly those classified as BCS class II, so that the slow dissolution of such drugs presents a significant challenge in pharmaceutical development. The dissolution process of drugs from solid forms has been extensively studied and explained in various research works[12-14]. The relationship between the drug dissolution rate (dC_b/dt) and saturation solubility of a drug substance is illustrated in Fig. 1A, and can be described using the Nernst−Noyes−Whitney equation[15]. The expression for the Nernst-Noyes-Whitney was calculated according to Eq. (1):

$$\frac{dC_b}{dt} = \frac{DS}{Vh}(C_s - C_b) \quad (1)$$

where t is the time, C_b is the drug concentration in bulk medium, S is the surface area of the dissolving solid, D is the diffusion coefficient, h is the thickness of the diffusion layer, V is the volume of the dissolution medium, and C_s is the saturation solubility of the drug at the solid interface. The Nernst−Noyes−Whitney equation was established according to the diffusion layer concept and Fick's second law[15]. For ionizable drugs, the relationship between the solubility of a drug and pH can be considered using the Henderson-Hasselbalch equations[16,17]. Expression for monoacidic drugs was calculated according to Eq. (2):

$$C_s = C_{s0}\,[1 + 10^{(\mathrm{Ph}-\mathrm{p}Ka)}] \quad (2)$$

and that for monobasic drugs according to Eq. (3):

$$C_s = C_{s0}\,[1 + 10^{(\mathrm{p}Ka-\mathrm{pH})}] \quad (3)$$

where C_s is the drug solubility at a specific pH and C_{s0} represents intrinsic solubility[18]. According to these equations, even a slight change in pH significantly affects the aqueous solubility of drugs. Specifically, for weakly basic drugs, solubility increases exponentially as pH decreases within the range between the drug's pK_a and the pH at which maximum solubility occurs in the pH-solubility profile.

With careful consideration of these concepts, several formulation approaches have been applied to poorly soluble drugs to improve dissolution and biopharmaceutical characteristics[7]. With the use of these formulation strategies, drugs in solution might be at a concentration above their saturation solubility, a state of supersaturation. Compared with the crystalline form, such a supersaturation state would be thermodynamically metastable, and the supersaturated drug often soon precipitates again due to the high

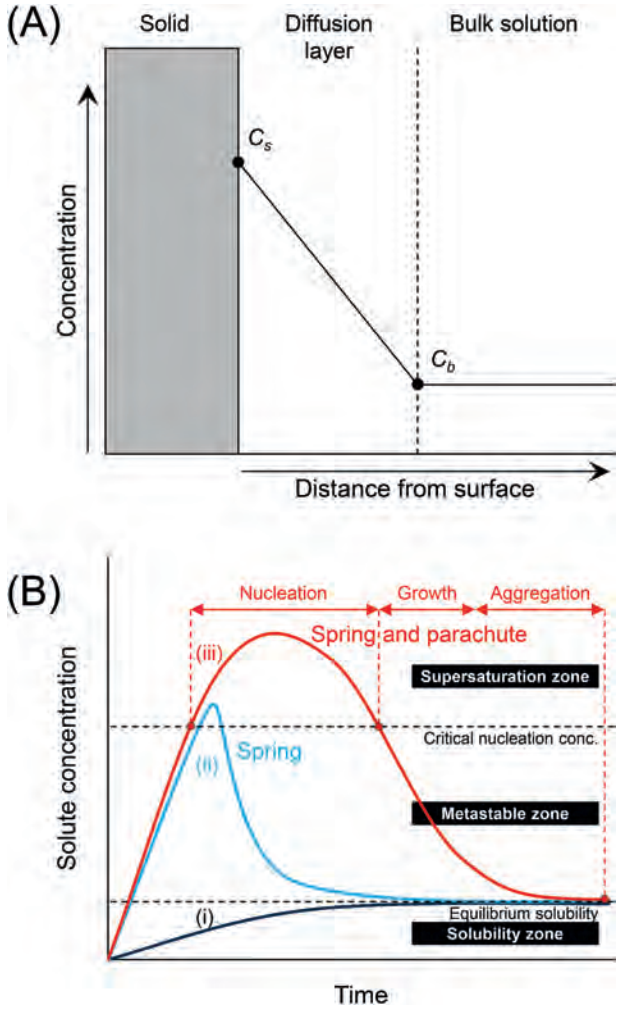

Figure 1 Dissolution and precipitation of poorly soluble drugs. (A) Diffusion layer model of drug dissolution from a solid. C_s, saturation solubility of the drug in the diffusion layer; and C_b, concentration of the drug in bulk medium. (B) Schematic diagram illustrating supersaturation and precipitation processes. (i) crystalline powder with poor solubility, (ii) short-lived metastable species with a spring effect, and (iii) highly soluble drug forms with spring and parachute effects.

energy of the system. The above concept describes the "spring" theory of the supersaturated state (Fig. 1B). Generation of the supersaturated state from various supersaturable formulations, including lipid-based formulations, amorphous forms, nanoparticles, and co-crystals, and crystalline salt forms, is referred to as "spring"[19]. Although supersaturation is the driving force of nucleation and crystal growth, the strategic use of precipitation inhibitors could promote a significant delay in the precipitation of drug molecules. This stabilization effect, mediated by a precipitation inhibitor, can be explained by the "parachute" theory, and the "parachute" effect in drug dissolution refers to the maintenance of a drug in a supersaturated state for an extended period, even after an initial rapid increase in concentration (the "spring" phase)[20,21]. As precipitation inhibitors, several polymers such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP) and Soluplus® have been employed since they form hydrogen bonds or steric barriers to hinder drug molecules from crystallization, and some surfactants are also available because of their high solubilizing potency and reduction of interfacial tension, resulting in prevention of drug precipitation. This formulation approach might last long enough to supersaturate a certain drug in the intestine, resulting in the increased and rapid absorption of drug molecules[10]. A clear understanding of "spring" and "parachute" theories would be required for the development of supersaturable formulations, and their combination may lead to improved bioavailability and clinical outcomes.

2.2. *Membrane permeability*

After oral administration, most drugs are primarily absorbed in the duodenum and jejunum, the upper parts of the GI tract. In contrast, the stomach has a lower drug-absorbing capacity due to its smaller surface area and thicker mucus layer. For a drug to be absorbed from the GI lumen, it must pass through multiple layers, including gastric juice, the pericellular matrix, and the mucus-rich layer, before reaching the epithelium, mucosa, and blood or lymph capillaries[22]. The intestinal mucosal barrier consists of microvilli on the luminal side, followed by a layer of epithelial cells anchored to the basement membrane at the lamina propria. Below the epithelial cells, the lamina propria contains nerves, as well as blood and lymph vessels. As shown in Fig. 2, drug molecules can cross these barriers *via* different pathways, including transcellular transport (through cell membranes), transcytosis, carrier-mediated uptake, or paracellular transport (between adjacent cells).

The transcellular route is recognized as the primary pathway for the absorption of small-molecule drugs. This process occurs through diffusion across the cell membrane, moving from an area of higher concentration (such as GI fluids) to an area of lower concentration (such as the bloodstream). While the diffusion rate is directly proportional to the concentration gradient, it is also influenced by several factors such as the drug's lipophilicity, molecular size, degree of ionization, and the surface area available for absorption. The cell membrane is lipidic, so that drug molecules with higher lipophilicity diffuse more rapidly. In addition to lipophilicity, drugs with a lower molecular weight tend to translocate across cellular membranes more rapidly than larger ones.

In paracellular transport, drug molecules are absorbed through both diffusion and convective volume flow *via* aqueous intercellular spaces[23]. However, absorption through this pathway is generally low, as the tight junctions between cells, with pore diameters of 4−8 Å, restrict the free passage of most drug molecules across the intestinal membrane. Tight junctions serve as the primary barrier to the permeation of ions and larger molecules, making paracellular transport a highly regulated process. Additionally, this pathway accounts for only 0.1%−0.01% of the total intestinal membrane surface area and becomes progressively less accessible from the jejunum to the colon, further limiting its role in drug absorption.

To enhance drug delivery across these biological barriers, significant efforts have focused on modifying the physicochemical properties of drugs and altering barrier characteristics. This has been achieved through chemical modifications of drug molecules and/or optimized formulation design.

2.3. *Physiological factors*

2.3.1. *pH of gastric fluid*

Physiological pH and the acid-base dissociation constant (pK_a) play a crucial role in determining the pharmacokinetics of orally administered drugs, particularly in relation to ionization and

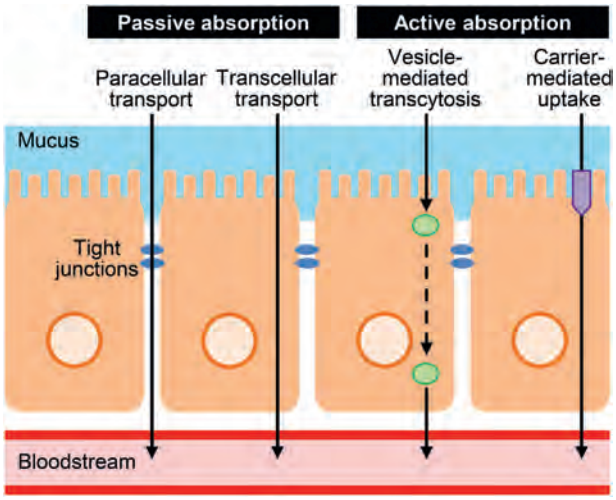

Figure 2 Schematic illustration of drug absorption and transport through the intestinal epithelium. After dispersion into the mucosal layer, drugs can be absorbed passively (*via* a paracellular or transcellular route) or actively (*via* vesicle-mediated transcytosis or carrier-mediated uptake).

protonation (Table 1 [2,7,24-43]). The pH of the gastrointestinal (GI) tract is especially significant for the dissolution of drugs with pH-dependent solubility. In healthy adults, the gastric fluid typically has a pH of approximately 1.0−3.0[24], and primarily regulated by gastric acid secretion. However, conditions such as aging and *Helicobacter pylori* infection can lead to hypochlorhydria, where gastric pH exceeds 5.0[25]. Additionally, the suppression of gastric acid secretion may occur following the use of medications for gastroesophageal reflux disease, such as proton pump inhibitors and H_2 blockers. An increase in gastric pH can reduce the oral bioavailability of weakly basic drugs, whereas consuming acidic beverages can significantly lower gastric pH, which in turn enhances the oral bioavailability of weakly basic drugs.

2.3.2. *Water volume in GI tract*

The disintegration of tablets, drug dispersion, and dissolution rate can be influenced by the water volume present in the gastrointestinal (GI) tract[33]. Consequently, the oral bioavailability of BCS class II and IV drugs may significantly decrease when water volume in the tract is low. In elderly individuals, GI secretions may decline, leading to a lower water volume in the tract compared to younger individuals[30]. However, the most significant factor affecting water volume in the GI tract is likely fluid intake. For example, after administering danazol with 800 mL of water instead of 200 mL, the area under the curve (AUC) increased by 155%[31]. Regarding drug absorption variability, the C_{max} of nifedipine demonstrated lower variability when the drug was taken with a larger volume of drinking water[32].

2.3.3. *Gastric emptying and intestinal transit time*

Gastric emptying time (GET) plays a crucial role in regulating the movement of drugs from the stomach to the small intestine, significantly impacting oral drug absorption (Table 1). A slower transition of a drug through the GI tract can prolong its contact with the absorption site, potentially enhancing its oral bioavailability. In contrast, rapid gastric emptying can reduce the oral bioavailability of poorly soluble drugs like gefitinib[37]. Similar to other physiological parameters, gastric motility can vary with aging[34]. Notably, patients with Parkinson's disease often experience delayed GET, which may lead to variability in the T_{max} of levodopa[26]. In addition, severe acute pain can suppress the vagus

Table 1 Physiological parameters affecting drug dissolution and absorption in gastrointestinal tract.

Physiological parameter	Endogenous factor	Exogenous factor	Key parameter influenced	Ref.
Gastric pH	Aging, hypochlorhydria, Crohn's disease	Food, drug (antacids, proton pump inhibitors, H_2 blockers), acidic beverage	Drug solubility, dissolution rate, stability of acid-labile drugs (erythromycin, penicillin), bioavailability, C_{max}	24−29
Water volume	Aging	Water volume, food	Drug solubility, dissolution rate, bioavailability (BCS class II/IV drugs)	2, 30−33
Gastric emptying time	Aging, Parkinson's disease, diabetes, suppression of vagus nerve (severe pain)	Food, drug (metoclopramide, propantheline)	Drug solubility, dissolution rate, stability of acid-labile drugs, bioavailability, T_{max}, onset and duration of action	26, 28, 29, 34−38
Small intestinal transit time	Diabetes, Crohn's disease, liver cirrhosis	Drug (propantheline)	Drug solubility, dissolution rate, bioavailability (BCS class III/IV drugs), C_{max}	27, 29, 36, 39, 40
Contents in gastrointestinal tract	Secretion of bile acid	Food	Drug solubility, dissolution rate, bioavailability, C_{max}, T_{max}, onset and duration of action	2, 7, 28, 29, 31, 38, 41−43

nerve, affecting GI secretion and motility, which may result in delayed and reduced oral drug absorption[35].

Small intestinal transit time (SITT) also influences the absorption of orally administered drugs. Previous studies have shown that metformin absorption varies with changes in SITT[36], with an increased AUC observed in patients taking propantheline to delay SITT compared to those not receiving the medication[40]. SITT may be accelerated in patients with liver cirrhosis[39], likely due to portal vein and intestinal wall blood stasis, as well as in patients with Crohn's disease who have undergone ileocecal resection[27]. In individuals with altered SITT, the absorption profile of drugs with low permeability or a limited absorption window in the GI tract may vary significantly.

2.3.4. Food intake

Food can influence the oral bioavailability of drugs through multiple mechanisms, including delayed gastric emptying, stimulation of bile flow, changes in GI pH, increased splanchnic blood flow, modifications in luminal drug metabolism, and physical or chemical interactions with dosage forms or drug substances (Table 1) [28,29,44-46]. These food-related effects on drug absorption can have clinically significant implications[31,41-43], potentially leading to variations in both drug efficacy and safety. Therefore, it is essential to evaluate the oral absorption profile of drugs under both fasting and fed conditions. Under fed conditions, gastric pH rises to approximately 3.0−5.0, which is higher than in the fasting state[47]. This increase in pH may lead to the precipitation of weakly basic drugs. Additionally, food intake can delay gastric emptying, with the extent of the effect often correlating with the meal's caloric content[38]. From a pharmacokinetic perspective, the impact of food is reflected in changes to both the rate and extent of drug absorption.

3. Use of the biopharmaceutical classification system for formulation design

Various physicochemical properties influence the biopharmaceutical characteristics of orally administered drugs, including structural complexity, molecular size and weight, lipophilicity, compound hydrogen bonding with solvents, intramolecular and intermolecular hydrogen bonding (crystal packing), crystallinity, polymorphic form, ionic charge status, pK_a, and salt form[48]. To enhance drug absorption and improve clinical efficacy, numerous formulation strategies have been extensively explored, taking these physicochemical properties into careful consideration[7]. Given the time constraints in pharmaceutical development, selecting an appropriate formulation strategy is essential for efficient progress. The Biopharmaceutics Classification System (BCS) has been recognized as a valuable tool for formulation decision-making, categorizing drug substances into four classes based on solubility and intestinal permeability[49]. These four categories are defined as follows: high solubility/high permeability (class I), low solubility/high permeability (class II), high solubility/low permeability (class III), and low solubility/low permeability (class IV). The viable formulation options based on BCS are summarized in Fig. 3. For BCS class I drugs, where oral absorption is not rate-limited, conventional tablet or capsule formulations are typically used to ensure rapid dissolution in the gastrointestinal (GI) tract. In contrast, BCS class II drugs face dissolution rate limitations, making dissolution enhancement a key strategy for improving biopharmaceutical properties. Various solubilization techniques, including crystal modification, particle size reduction, self-emulsification, pH modification, and amorphization, have been employed to address this challenge. For BCS class III drugs, where permeability in the GI tract is the rate-limiting factor, the use of permeation enhancers such as fatty acids, bile salts, surfactants, and polysaccharides may help improve bioavailability[50]. Meanwhile, BCS class IV drugs, which exhibit both low solubility and low permeability, pose the greatest formulation challenges. These drugs require advanced formulation strategies that consider both physicochemical and biopharmaceutical properties. Techniques similar to those used for BCS class II drugs have been applied to BCS class IV drugs, although absorption remains limited by poor membrane permeability[51]. Poorly soluble drugs such as paclitaxel, docetaxel, and indinavir are well-known substrates of P-glycoprotein (P-gp), an intestinal efflux transporter, and are categorized as the BCS class IV drugs. So far, various formulation strategies have been explored to effectively inhibit efflux of these BCS class IV drugs. These formulation strategies, either independently or in combination, include: (i) strategic use of another P-gp substrate or a specific inhibitor; and (ii) incorporation of a non-specific lipid and/or polymer excipient in the formulation to block P-gp activity. For instance, a microemulsion formulation of paclitaxel incorporating KR-3032, a P-gp inhibitor, demonstrated a marked improvement in oral bioavailability, rising from 4.6% to 41% compared to paclitaxel[52].

A comprehensive understanding of the physicochemical and biopharmaceutical characteristics of each BCS class, as well as the limitations of each formulation technique, can facilitate more effective formulation development, ultimately leading to improved clinical outcomes.

4. Advanced oral drug delivery systems

To overcome the inherent limitations of conventional oral formulations, a variety of advanced oral drug delivery systems have been developed by strategically addressing key physicochemical and biopharmaceutical barriers. Critical factors such as poor aqueous solubility, limited intestinal permeability, degradation in the GI tract, and extensive first-pass hepatic metabolism can significantly impair the oral absorption and bioavailability of many therapeutic agents. Therefore, innovative formulation strategies, such as pH-independent drug release systems, solid dispersions, polymeric nanoparticles, lipid-based carriers (*e.g.*, self-emulsifying drug delivery systems), and mucosal drug delivery platforms, have been engineered to improve drug solubility, permeability, stability, and other key biopharmaceutical profiles (Table 2 [7,8,19,53-83]). These advanced systems not only improve systemic drug exposure but also contribute to more consistent pharmacokinetic profiles and enhanced therapeutic outcomes.

4.1. Microenvironmental pH-modifier

Microenvironmental pH modulation is a commonly used strategy to enhance the solubility and dissolution rate of poorly soluble drugs with pH-dependent solubility[53]. A weak acid or base as a microenvironmental pH-modifier is commonly used to modify the microenvironmental pH inside matrices surrounding API particles/domains that favor drug dissolution, and electrostatic interaction and/or ion-pairing between drugs with counter-ions might result in long-term supersaturation (Fig. 4). In theory, the degree and duration of microenvironmental pH modulation are critical factors in enhancing the biopharmaceutical properties of drugs. Additionally, stabilizing the supersaturated state in bulk solution can be

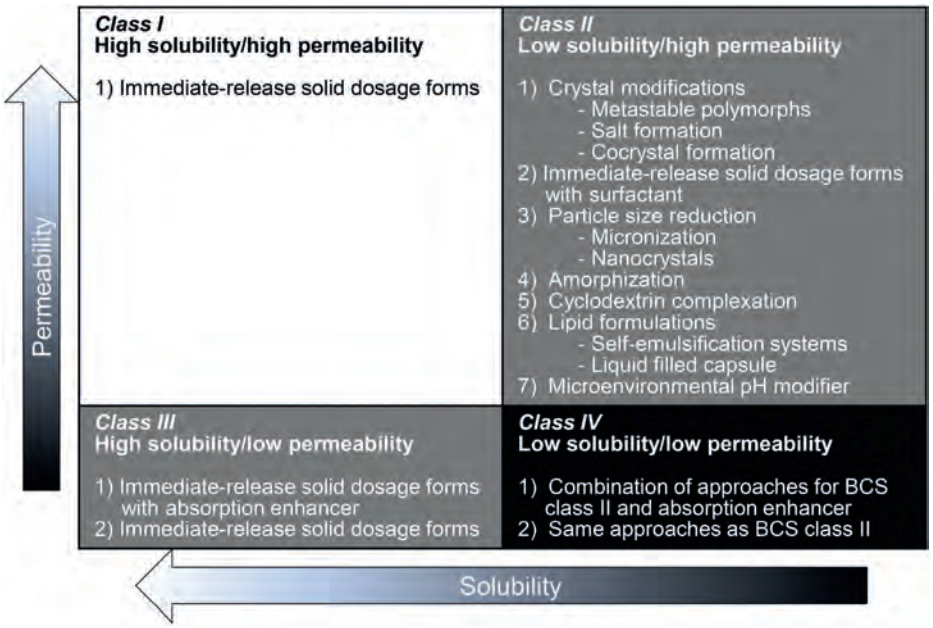

Figure 3 Biopharmaceutics classification system and viable formulation options based on it. Reprinted with permission from Ref. 7. Copyright © 2011, Elsevier.

a key strategy for improving drug exposure following oral administration through pH modification. This approach employs limited amount of a microenvironmental pH-modifier that does not alter the pH of the bulk dissolution media; however, it could enhance the *in vivo* dissolution and bioavailability of drug substances with pH-dependent solubility (Table 2)[54]. The microenvironment refers to a microscopic layer enveloping a solid particle, where the particle creates a saturated solution of adsorbed water. Careful consideration should be made before selecting and optimizing counter-ions in formulation designs with the microenvironmental pH-modification approach, since the microenvironmental pH can influence the physicochemical properties of solid dosage forms, including the hygroscopicity and chemical stability, as well as dissolution and supersaturation profiles[55]. Organic acids, such as citric, fumaric, succinic, and tartaric acids, are commonly employed as acidifiers for weakly basic drugs. In our earlier study, a granule formulation of dipyridamole, a weakly basic drug, was developed, in which fumaric acid was added as a microenvironmental pH-modifier[53]. In a rat model of hypochlorhydria, oral administration of dipyridamole resulted in limited and inconsistent systemic exposure. In contrast, a novel dipyridamole formulation with fumaric acid showed rapid and potent oral absorption even under hypochlorhydria, the pharmacokinetic behavior of which was found to be almost identical to that of dipyridamole in normal rats. Considering the enhanced systemic exposure observed shortly after oral administration in hypochlorhydric rats, the novel dipyridamole formulation utilizing the pH-modification strategy could potentially lead to improved clinical outcomes in patients with hypochlorhydria.

4.2. Solid dispersions

4.2.1. Amorphous solid dispersion

An amorphous solid dispersion (ASD) refers to the distribution of active pharmaceutical ingredients in molecular and amorphous states, encapsulated within inert carriers (Fig. 5A)[56]. The ASD approach can be used to modify the crystalline lattice of drugs to generate a higher energy state of the amorphous form, leading to higher saturated solubility and significant improvement of oral bioavailability (Table 2)[7,57]. The use of hydrophilic polymers as excipients for ASD can attenuate the nucleation of drug molecules, and they should be biologically inactive and less absorbed in the GI tract. Commonly used excipients are cellulose derivatives such as hydroxypropyl cellulose (HPC), HPMC, and hypromellose acetate succinate (HPMCAS), chitosan, poloxamers, PVP, polymethacrylates, polyvinylpyrrolidone-vinyl acetate copolymer (PVP/VA 64), and polyethylene glycol (PEG) derivatives[58]. There are various strategies for the preparation of ASD, including solvent-based methods (*e.g.*, freeze-drying, spray-drying, and supercritical fluid technology), melt-based methods (*e.g.*, hot-melt extrusion and KinetiSol® dispersing), wet granulation, and co-precipitation[59]. Numerous studies have shown that ASD technology can provide rapid dissolution and supersaturation of various poorly soluble drugs and chemicals, including itraconazole, nobiletin, and tacrolimus[60]. Also, the ASD formulation approach can provide more stable and improved pharmacokinetic behavior of orally taken drugs, including NSAIDs and carvedilol[60,61]. However, amorphous drugs are generally less chemically and physically stable than crystalline form. Over long-term storage, ASD formulations may undergo transformation from the amorphous to the crystalline state, which can reduce oral bioavailability. The use of suitable polymers can be effective for stabilization of ASD and potential prevention of crystallization; therefore, careful consideration should be made to select suitable polymers.

4.2.2. Self-micellizing solid dispersion

Thus, several polymers used for ASD have been found to be effective crystallization inhibitors, stabilizing supersaturated solutions; however, they sometimes showed slow but steady nucleation and crystal growth in some drug molecules[57], possibly leading to poor pharmacokinetic behavior and a shorter duration

Table 2 Advanced oral drug delivery systems.

Delivery system	Principle	Pros&Cons	Applications [brand names]	Ref.
Microenvironmental pH-modifier	Modulation of the microenvironmental pH inside matrices surrounding drug substances	[Pros] pH-independent drug release, supersaturated dissolution, stable pharmacokinetics, improved bioavailability [Cons] hygroscopicity, poor stability, drug-excipient incompatibility	Ciprofloxacin [Cipro® XR] Dipyridamole [Persantin® SR] Itraconazole [Sporanox®] Ritonavir [Norvir®]	53−55
Solid dispersions: Amorphous solid dispersion (ASD)	Dispersion of amorphous drugs in an inert polymer matrix for stabilization of amorphous drug	[Pros] enhanced dissolution rate, supersaturated dissolution, stabilization, improved bioavailability [Cons] poor storage stability (recrystallization, degradation), complex manufacturing, limited polymer compatibility	Etravirine [Intelence®] Ritonavir [Norvir®] Telaprevir [Incivek®] Venetoclax [Venclexta®]	7, 56−61
Solid dispersions: Self-micellizing solid dispersion (SMSD)	Dispersion of amorphous drugs in an amphiphilic polymer matrix for faster and prolonged solubilization	[Pros] In addition to pros of ASD, long-lasting supersaturated dissolution, prolonged systemic exposure [Cons] In addition to cons of ASD, complex formulation development, safety concerns on amphiphilic polymers	Celecoxib[a] Cyclosporine A[a] Indomethacin[a] Tranilast[a]	19, 57, 62−64
Nanocrystals	Increase of surface area and dissolution rate of drugs by reducing particle size to nanoscale	[Pros] enhanced dissolution rate, supersaturated dissolution, scalability, high stability, improved bioavailability [Cons] aggregation, crystal growth and/or polymorphism in long-term storage, safety concerns (nanotoxicity)	Aprepitant [Emend®] Fenofibrate [Tricor®] Megestrol acetate [Megace® ES] Sirolimus [Rapamune®]	7, 65−71
Emulsions: Self-emulsifying drug delivery systems (SEDDS)	Spontaneous formation of fine oil-in-water emulsions when exposed to gastrointestinal fluids	[Pros] enhanced solubility and dissolution rate, protection from enzymatic and/or acidic degradation, improved bioavailability, lymphatic transport [Cons] poor storage stability (phase separation, drug precipitation, degradation), formulation complexity, limited drug loading, high surfactant content	Cyclosporine A [Neoral®] Dutasteride [Avodart®] Saquinavir [Fortovase®] Tipranavir [Aptivus®]	7, 8, 72−75
Emulsions: Solid self-emulsifying drug delivery systems (S-SEDDS)	Solidified formulation of SEDDS, retaining biopharmaceutical advantages of liquid SEDDS	[Pros] In addition to pros of SEDDS, improved stability, improved manufacturability, better dose uniformity [Cons] In addition to cons of SEDDS, complex formulation development, potential loss of self-emulsification, excipient compatibility	Atorvastatin [Lipirex®] Azithromycin[a] Cyclosporine A [Gengraf®] Indomethacin[a]	76−78
Mucosal drug delivery systems: mucopenetrating nanoparticles	Reduction of interactions between nanoparticles and mucin molecules, enabling them to diffuse through the mucus layer	[Pros] enhanced mucus penetration, improved bioavailability, rapid onset of action [Cons] complex formulation development, manufacturing cost, potential mucosal irritation	Curcumin[a] Cyclosporine A[a] Insulin[a] Paclitaxel[a]	79−83
Mucosal drug delivery systems: mucoadhesive nanoparticles	Formation of specific interactions (hydrogen bonding, electrostatic interaction, chemical bonding, etc.) between nanoparticles and mucin molecules in the mucus layer	[Pros] localized drug release, prolonger retention at the mucosal site, improved bioavailability [Cons] Complex formulation development, manufacturing cost, limited penetration, potential mucosal irritation.	Cyclosporine A[a] Furosemide[a] Insulin[a] Verapamil[a]	79−82

[a]Under basic/preclinical investigation.

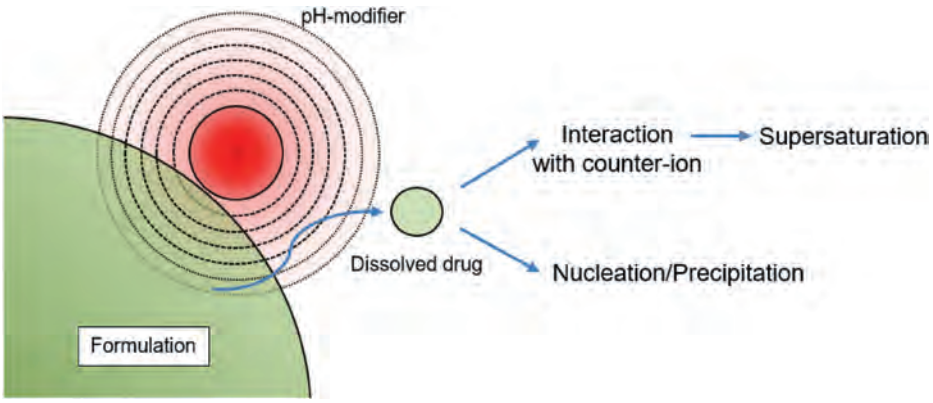

Figure 4 Concept of microenvironmental pH-modification approach for drugs with pH-dependent solubility. A small amount of counter-ions is employed for local pH adjustment in the immediate vicinity of drug particles, resulting in dissolution of poorly soluble drugs and prevention of precipitation.

of action. To address these limitations on ASD formulations, the concept of self-micellizing solid dispersion (SMSD) was established as a new solubilizing technology (Table 2)[62-64]. SMSD is an SD system that utilizes amphiphilic polymers, including poly(2-methacryloyloxyethyl phosphorylcholine-*co*-*n*-butyl methacrylate) [poly(MPC-*co*-BMA)] and Soluplus®. Unlike conventional SD systems, SMSD system offers enhanced and prolonged solubilization of poorly soluble drugs due to its self-micellization property. This occurs through hydrophobic interactions between the amphiphilic polymer and the lipophilic drug, leading to drug encapsulation (Fig. 5B). When the SMSD system was applied to tranilast[64] and cyclosporine A[63] with the use of poly(MPC-*co*-BMA), SMSD formulations demonstrated significantly improved dissolution behavior compared to their crystalline and amorphous counterparts. Then, the formation of micelle-like nanoparticles was observed in aqueous media, and NMR spectroscopy indicated molecular interactions between the drug and poly(MPC-*co*-BMA). Compared to crystalline or amorphous powders, SMSD formulations increased oral bioavailability by approximately 40−50-fold and significantly reduced inter-individual variability.

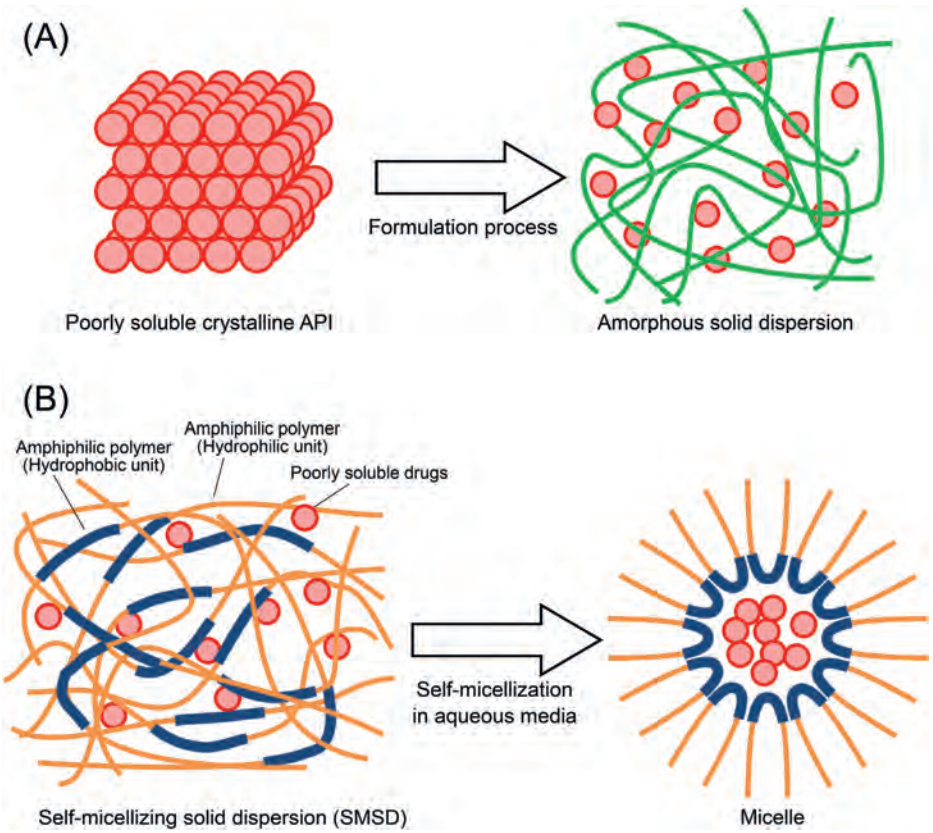

Figure 5 Schematic presentation of solid dispersion approaches for poorly soluble drugs. (A) Amorphous solid dispersion. (B) Self-micellizing solid dispersion.

Additionally, an SMSD formulation of celecoxib exhibited rapid micellization in aqueous media, forming nanoparticles with a mean diameter of 153 nm and demonstrating rapid dissolution even under acidic conditions[62]. In a rat model with impaired gastric motility induced by propantheline, orally administered crystalline celecoxib showed a prolonged mean absorption time (MAT) and a significant reduction in AUC_{0-4}, reaching only 12% of the value observed in normal rats. However, the SMSD formulation of celecoxib mitigated both the delay and reduction in oral absorption under these conditions. These findings suggest that the SMSD approach employing amphiphilic polymers may serve as an effective dosage strategy for poorly soluble drugs, offering improved and stable oral absorption.

4.3. Drug nanocrystals

The particle size reduction approach is widely utilized to enhance drug dissolution rates, as smaller drug particles result in a larger surface area, thereby accelerating dissolution (Table 2)[7]. According to the Prandtl boundary layer equation, reducing the diffusion layer thickness, particularly by decreasing particle size to less than 5 μm, can significantly enhance dissolution rates[8]. Marked attention has been focused on nanodrug approaches, particularly drug nanocrystal technology, in the pharmaceutical field. With this strategy, nanosuspensions of drugs can be produced by nanofabrication processes, such as the so-called 'bottom-up' (controlled precipitation, inclusion complexation, coacervation, electrospraying, and supercritical fluid technique) and 'top-down' (wet-milling with beads, ultrasonication, and high-pressure homogenization) approaches[65-67]. While the bottom-up method forms nanoparticles from molecular or atomic units, the top-down technique reduces larger crystalline drug particles into nanosized particles. In both approaches, hydrophilic polymers and/or surfactants are commonly used to enhance colloidal stability.

The top-down method offers advantages such as consistency in particle size, shape, and geometry, along with a monodisperse particle population, high yield, and excellent encapsulation efficiency[68]. This approach converts large crystalline drug particles into nanosized particles through mechanical forces, allowing for industrial-scale production with high reproducibility. However, the top-down approach also has several drawbacks, including high equipment costs, requirement of an intensive amount of energy, uncontrolled particle growth, and the risk of product contamination. In a previous investigation, a conventional wet-milling system as a top-down method was applied to coenzyme Q_{10} (CoQ_{10}) to obtain a nanosuspension; however, due to the heat generated during the nano-pulverization process, partial melting of the particles led to large aggregate formation[70]. Generation of high energy and friction heat in the nano-pulverization process might be part of reasons for amorphization and aggregation of CoQ_{10} because of its low melting point (ca. 48 °C). To mitigate this issue, a cold wet-milling system with temperature control was developed, successfully producing a CoQ_{10} nanosuspension with a mean particle diameter of approximately 129 nm. In comparison with crystalline CoQ_{10}, marked improvements in aqueous dissolution and oral absorption were noted for the nanosuspension of CoQ_{10} prepared with the cold wet-milling system. Herein, the cold wet-milling system would be a promising top-down technology to improve the efficacy of poorly soluble drugs with a low melting point[69,70].

The bottom-up method for nanoparticle preparation offers several advantages, particularly for pharmaceutical and biomedical applications[66]. As well as precise control over particle size, shape, and composition, the bottom-up method typically involves milder processing conditions, making it suitable for heat-sensitive drugs, and often results in higher purity and crystallinity. Additionally, bottom-up techniques can enhance the solubility and bioavailability of poorly water-soluble drugs and offer flexibility for surface functionalization, making them ideal for targeted and controlled drug delivery systems. As one bottom-up approach, flash nano precipitation (FNP) has been widely explored for nanoparticle preparation using a wide variety of drug molecules[71]. FNP employs a rapid mixing process based on kinetically controlled nanoprecipitation, allowing precise control over nanoparticle size and surface properties through the formulation of unique compositions with stabilizers[84]. This method involves two key kinetic processes: micromixing and stabilizer adsorption. Micromixing in confined jet mixers facilitates antisolvent mixing, generating supersaturation levels as high as 10,000 within 1.5 ms, leading to extremely high nucleation rates and the rapid formation of nanoparticles at high solution concentrations[85]. The rapid and diffusion-limited aggregation is then controlled by stabilizer adsorption, ensuring precise size regulation. There are two main types of confined impinging jet mixers used in FNP: two-jet mixers and multi-inlet vortex mixers (MIVM), which provide more precise control over inlet stream concentrations[86]. The FNP approach with use of MIVM has been applied to produce nanoparticles from various poorly soluble drugs and nutraceuticals, including cyclosporine A[71], astaxanthin[87], fuzapladib[88], ibuprofen[89], and curcumin[90].

Numerous studies have demonstrated that nanotechnology-based formulations significantly improved the biopharmaceutical properties of pharmaceuticals and nutraceuticals[8]. In theory, upon oral administration, these nanocrystals would undergo a series of complex *in vivo* processes that ultimately determine their therapeutic outcomes[91]. These include dispersion in gastrointestinal fluids, interaction with mucus and intestinal membranes, dissolution into molecular form, and absorption into systemic circulation. The *in vivo* fate of drug nanocrystals can be influenced by various factors such as particle size, surface properties, stabilizers, and gastrointestinal physiology. In the nano-sized formulation approach, C_{max} and bioavailability have been shown to increase by several folds compared to conventional formulations with micrometer-sized particles.

4.4. Emulsions

Emulsions have been extensively studied to enhance the biopharmaceutical properties and/or therapeutic index of drugs[8]. In recent years, self-emulsifying drug delivery systems (SEDDS) have emerged as a promising strategy to improve the oral bioavailability of poorly soluble drugs, particularly highly lipophilic drugs[7]. Self-emulsifying formulations are isotropic mixtures of oil, surfactant, co-solvent, and a solubilized drug, and the SEDDS approach would require effective dissolution and chemical stability of the drug in the oil phase. These formulations rapidly form oil-in-water (O/W) fine emulsions upon dispersion in GI fluid, making them a valuable solution for the poor oral absorption of lipophilic drugs (Table 2), especially those classified as BCS class II and IV[7].

SEDDS can be classified into (i) self-microemulsification drug delivery systems (SMEDDS) and (ii) self-nanoemulsification drug

delivery systems (SNEDDS) based on the size of their oil droplets[7]. SMEDDS produce microemulsions with droplet sizes ranging from 100 to 250 nm, while SNEDDS generate nanoemulsions with droplet sizes below 100 nm. The rapid emulsification of these formulations in the GI tract contributes to improved oral absorption and more consistent plasma concentration profiles[7]. It has been well-established that the droplet size of an emulsion can influence the biopharmaceutical properties of orally taken drugs. For example, there are two SEDDS formulations of cyclosporine A on the market: (i) Sandimmune®, a coarse SMEDDS formulation, and (ii) Neoral®, a fine SNEDDS formulation. The aqueous solubility of Sandimmune® is not high enough, and this SMEDDS formulation requires the presence of bile and pancreatic enzymes for its absorption[72]. Also, marked intra- and inter-individual variability was noted regarding its pharmacokinetic profiles, and oral absorption was affected by the concomitant intake of food. In contrast, Neoral® forms nanoemulsions in GI fluids, enabling more rapid and consistent absorption. Clinical studies in adults demonstrated that Neoral® could increase systemic exposure and achieve higher peak concentrations compared with similar doses of Sandimmune®.

The enhanced oral absorption of drugs delivered *via* SEDDS occurs through multiple complementary mechanisms[73,74]. Firstly, the increase in surface area and solubilization can improve dissolution kinetics, allowing for a higher concentration gradient across the intestinal epithelium, a key determinant for membrane permeability. Secondly, the presence of lipids facilitates the stimulation of bile secretion and the formation of mixed micelles, which can assist in the solubilization and transport of lipophilic drugs across the unstirred water layer of the intestine. Thirdly, certain components of SEDDS, such as long-chain triglycerides, might promote lymphatic transport by facilitating chylomicron formation in enterocytes, enabling the drug to bypass hepatic first-pass metabolism and directly enter systemic circulation[75]. Moreover, surfactants and co-solvents within SEDDS can alter membrane fluidity, and open tight junctions, further enhancing intestinal permeability and drug uptake. Some SEDDS formulations might also reduce enzymatic degradation in the GI tract, increasing drug stability during transit. Herein, these mechanisms can contribute to the improved oral absorption of lipophilic and poorly soluble drugs upon SEDDS a highly effective and versatile platform in oral drug delivery.

Despite their biopharmaceutical advantages, SEDDS formulations still face several challenges, including physical and chemical instability, potential leakage during storage, and restricted use in solid-dosage forms. These factors can impact patient adherence and large-scale production feasibility. To overcome these limitations, solidification of SEDDS has gained marked attention, and several approaches have been established for the preparation of solid SEDDS (S-SEDDS)[77,78]. S-SEDDS can primarily be developed through several methods such as solid carrier adsorption, melt extrusion, spray-drying, dry emulsion, and solid dispersion. These formulations can then be conveniently transformed into pellets, tablets, and capsules[76]. The S-SEDDS approach combines the advantages of SEDDS in liquid form and solid dosage form with greater stability, portability, ease of manufacturing, dosage form variety, and patient compliance (Table 2). Additionally, these formulations offer improved drug-loading capacity, controlled-release characteristics, and are well-suited to contemporary manufacturing methods, presenting a strong alternative to traditional liquid SEDDS.

4.5. Mucosal drug delivery systems

In the GI tract, the mucosal layer functions as a lubricating barrier, and mucus is present either as a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. This mucus is primarily composed of water (approximately 95%), while the remaining portion consists of glycoproteins, soluble proteins, enzymes, lipids, and immune factors[79]. Serving as the first line of defense, the mucus layer protects against microorganisms, digestive enzymes and acids, digested food particles, and food-related toxins. However, this protective function also acts as a "barrier" that restricts the diffusion of orally administered drugs toward the epithelium, making drug delivery challenging. In this context, overcoming this barrier has become a critical aspect of achieving effective oral drug absorption. For more effective and sufficient oral absorption of drugs, avoiding protective mechanisms and/or even turning barrier mechanisms has been a key consideration. As one of the viable formulation approaches, the mucosal drug delivery system (mDDS) has drawn significant attention, since it could offer strategic control of diffusive properties of drug molecules within the mucus layer (Table 2)[81,82]. Three types of mDDS offer new possibilities for more efficient mucosal drug delivery: (i) mucopenetrating delivery systems, (ii) mucoadhesive delivery systems, and (iii) mucoadhesive-to-mucopenetrating delivery systems[79,80]. The mDDS approach with mucoadhesive and mucopenetrating potentials can be developed by changing the interactions between the mucin layer and surface of nanoparticles. Mucoadhesive-to-mucopenetrating delivery systems can be simply defined as the integration of mucoadhesive delivery systems and mucus-penetrating delivery systems into one entity.

Mucopenetrating nanoparticles are designed to effectively spread across the mucosal layer and penetrate deeper mucus regions, eventually reaching the underlying epithelium (Fig. 6A)[79,83]. This property can be achieved using PEG coatings, which reduce interactions between the drug and mucus, thereby enhancing translocation across the mucus layer. Additionally, a zwitterionic micelle platform can mimic viral surface properties, facilitating efficient mucus penetration and transporter-mediated epithelial absorption without the need to open tight junctions. Another interesting approach involves conjugating nanoparticles with mucolytic or mucus-clearing agents to disrupt the mucus layer, allowing for easier access to the epithelial membrane. Moreover, self-propelled micro-/nano-motors have attracted interest due to their ability to move autonomously[92]. In drug delivery applications, they have demonstrated significantly improved tissue penetration and high drug-loading capacity, resulting in superior therapeutic outcomes compared to passive-targeted nanoparticles.

In contrast to mucopenetrating nanoparticles, upon suitable surface modification and/or particle design, mDDS with mucoadhesive properties are designed to show prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcomes. Possible mechanisms for mucoadhesion are complicated, and involve various types of adhesion, such as physical entanglement, electrostatic interactions, dehydration, covalent bonding between thiol groups in mucin, and weaker forces like hydrogen bonding and van der Waals forces (Fig. 6B)[79]. Mucoadhesion occurs in two stages: contact and consolidation. Initially, nanoparticles must be in close contact with the mucus layer surface, and then the adhered particles may easily be removed by GI motions and physiological turnover of the mucus layer if the attractive forces between

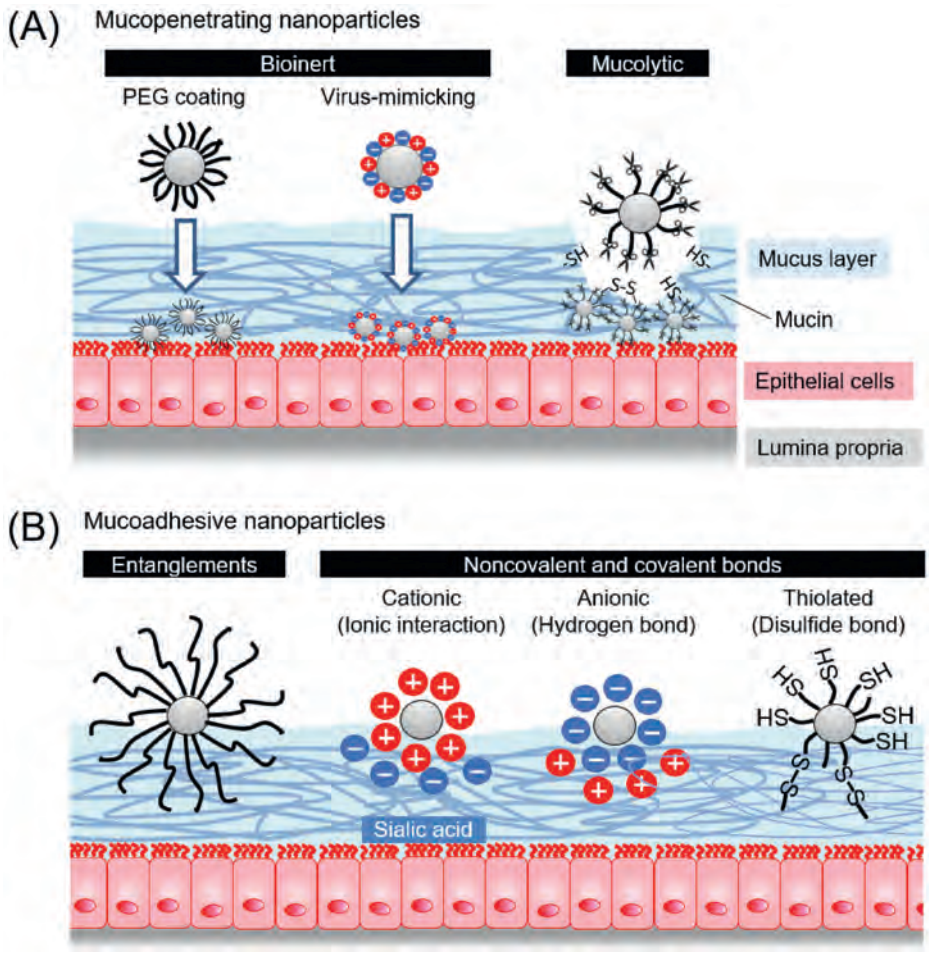

Figure 6 Schematic illustrations of mucosal drug delivery systems. (A) Mucopenetrating nanoparticles with high spreading ability over the mucosa. (B) Mucoadhesive nanoparticles with prolonged retention in the mucosal layer.

nanoparticles and the mucus layer are weaker than repulsive forces. There is still a need for consolidation to achieve long-lasting adherence of nanoparticles to the mucus layer. This process can strengthen mucoadhesive joints through mechanical and/or chemical interactions, possibly leading to resistance to mechanisms clearing nanoparticles from the mucus layer.

Herein, mDDS with mucoadhesive properties can extend the absorption process, possibly resulting in long-lasting systemic exposure to orally taken drugs, and mDDS with mucopenetrating properties can achieve faster and higher rates of absorption. In a previous investigation, two mDDS formulations of cyclosporine A with different surface charges were prepared, and they exhibited mucopenetrating and mucoadhesive properties[81]. Based on outcomes of a fluorescent imaging study, orally taken mucopenetrating nanoparticles were observed to reach the vicinity of the GI epithelium, while mucoadhesive nanoparticles were localized on the luminal side of the GI mucus layer. Also, after oral administration in rats, mucopenetrating nanoparticles exhibited markedly enhanced oral bioavailability and the shortest T_{max}. In contrast, mucoadhesive nanoparticles showed delayed T_{max}, suggesting longer retention in the GI tract. These observations were in agreement with the concept and theory of the mDDS strategy. A better understanding of the mechanisms of diffusion and/or adhesion in the mucus layer would enable formulators in both academia and industries to identify, select, and develop materials for the design of mDDS formulations with potent biopharmaceutical properties.

5. Perspectives and concluding remarks

Despite the rapid advancement of new modalities such as biologics, gene therapies, and cell-based treatments, small-molecule drugs still remain essential in modern medicine. Compared with new modalities, the advantages of small molecules, including oral bioavailability, cost-effectiveness, and well-established manufacturing processes, ensure their continued relevance. However, as reviewed in this article, various challenges such as solubility, stability, and efficient delivery persist; therefore, improved technologies still need to overcome the potential issues of current strategies. In this context, an advanced DDS approach may play a crucial role in enhancing the efficacy and safety of small molecules by improving their absorption, stabilization, and controlled-release profiles. As the pharmaceutical landscape evolves, the integration of DDS technologies will be vital to maximize the potential of both traditional and emerging therapeutic approaches. Also, for the suitable selection and integration of DDS technologies, the use of artificial intelligence (AI) might be transforming pharmaceutical research and development. Formulation design with the strategic use of AI would enhance drug targeting and

efficacy, reduce side effects, and personalize treatments, hopefully providing faster development cycles. Through consideration of multiple factors, including drug properties, carrier materials, targeting mechanisms, and patient-specific parameters, AI might be revolutionizing formulation design by enhancing precision and efficiency, and reducing cost and development time. Despite its potential, AI-driven formulation development still faces significant challenges in data reliability, AI model performance, patient variability, and regulatory hurdles. Addressing these issues would require improved AI transparency, better regulatory frameworks, and robust validation studies to ensure safe and effective implementation.

A number of efforts have been made to develop new functional polymers used for advanced DDS formulation. While these functional polymers offer various advantages such as improved membrane permeability, controlled release, improved drug stability, and targeted delivery, they have not yet been approved for clinical use, posing a significant challenge in the development of novel clinical formulations. In most cases, regulatory approval requires extensive evaluation of their biocompatibility, biodegradability, and long-term safety. The lack of established clinical data for many polymers limits their immediate application in human medicine. To facilitate the clinical adoption of polymer-based DDS approaches, further intense research, rigorous safety assessments, and clear regulatory guidelines will be essential.

Although nanotechnologies have been shown to be much more efficient in both diagnosis and therapy, potential druggability still needs to be carefully evaluated before clinical application. Particularly, the toxicity of nanoparticles, so-called nanotoxicity, has gained renewed interest. Due to their unique physicochemical and biopharmaceutical properties, nanosystems can interact with biological systems in complicated ways, potentially leading to toxic symptoms or long-term toxic events. Upon chronic administration, comprehensive safety evaluation, including pharmacokinetics, biocompatibility, and potential immunogenicity assessments, would be essential to mitigate risks and ensure patient safety. As research and development in nanomedicine continue to advance, rigorous regulatory frameworks and standardized evaluation methods will also be crucial to facilitate the safe and effective use of nanoparticle-based therapies. Also, the development of nanomedicine requires a multidisciplinary approach, combining drug chemistry, material science, pharmacokinetics, and patient-centric design. Therefore, collaborations between formulators and physiologists are likely to remain fundamental to product development, with the aim of creating innovative oral dosage forms that ensure stable efficacy and a high standard of safety.

In conclusion, the absorption of orally taken drugs can be complex and influenced by various factors; however, advanced oral DDS approaches hold marked promise in improving the efficacy, convenience, and patient compliance of therapeutics. Further advancements in formulation technologies, such as microenvironmental pH-modifiers, nanoparticle carriers, controlled-release mechanisms, and mDDS approaches, are expected to overcome various challenges related to drug solubility, membrane permeability, and bioavailability. The development of innovative oral DDS may enable more precise and sustained drug delivery, reducing the dosing frequency and minimizing side effects. As research continues, the integration of cutting-edge technologies will further overcome several limitations and potential problems of oral dosage forms, making treatments more efficient and accessible for patients with a wide range of diseases.

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Author contribution

Satomi Onoue, Hideyuki Sato, and Kohei Yamada designed the research. Satomi Onoue wrote the original draft. Satomi Onoue, Hideyuki Sato, and Kohei Yamada revised the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

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