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Review Article

Formulation Technique To Improve Solubility Of Poorly Soluble Drug Substance And Thereby Improving The Bioavailability

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ABSTRACT

Oral route of administration is most prominent route of administration considering the patient acceptance, convenience, cost-effectiveness, and easy to manufacturing. However, solubility is rate limiting step for bioavailability of many drugs having poor aqueous solubility belonging to BCS class II and IV drug, inadequate dissolution, low intestinal permeability, extensive first-pass metabolism, and efflux mediated by membrane transporters. These challenges are particularly for drug belonging Biopharmaceutics Classification System (BCS) Class II and Class IV, where as lower solubility and/or lower permeability result in variable gastrointestinal absorption and thereby lower therapeutic outcomes. Considering these, improving solubility of poorly soluble drug substance and hence to improve oral bioavailability has major focus in pharmaceutical formulation development. This review article provides a summary of parameters or factor affecting the solubility and hence oral bioavailability, including the physico-chemical properties of drug substance, physiological characteristics of the gastrointestinal tract with respect to absorption, formulation variables, and patient-related factors. The article discussed formulation approaches to improve the solubility of poorly solubility of drug substance; including particle size reduction, salt formation, crystal engineering (i.e., polymorphism), Solid dispersions, Inclusion complexation (i.e., cyclodextrin complexation), co-solvency by using the co-solvent, hydrotropy, Solubilizer i.e., surfactant -based systems, lipid-based drug delivery systems, nanocrystals, polymeric and lipid nanoparticles, permeation enhancers, modulation of in-vivo protein which affecting the bioavailability (i.e., P-glycoprotein) and in-vivo enzyme (i.e., cytochrome P450 enzymes), mucoadhesive and gastroretentive drug delivery systems, and prodrug design. The underlying mechanisms responsible for bioavailability enhancement, along with their advantages, limitations, and representative pharmaceutical applications, are comprehensively summarized. Recent advances in material science, nanotechnology, and drug delivery system with respect to pharmaceutical product development for improving the solubility of drug substance and

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thereby improving the in-vivo performance i.e., Bioavailability. The integration of rational formulation design with an improved understanding of drug–excipient interactions and gastrointestinal physiology is expected to the get right approach for the development of more efficient oral dosage forms. Overall, this review highlights current progress, emerging technologies, and future perspectives in oral bioavailability enhancement, providing a valuable resource for formulation scientists, pharmaceutical researchers, and drug development professionals involved in the development of novel drug delivery system oral solid dosage form which help to society for better improvement of the health by preparing the medicine having good bioavailability.

INTRODUCTION

Oral drug delivery is most prominent route of drug administration because of its easy to administered, patient acceptability, convenience, and cost-effective. In addition, oral solid dosage forms having a more advantages with respect to manufacturing process, formulation flexibility, and improved patient acceptance compared with parenteral dosage forms.

Although oral drug delivery offers several advantages, but the formulation development of oral drug delivery system having major challenges considering the solubility and thereby bioavailability challenges to get desired therapeutic effective concentration (1–3).

Oral bioavailability, defined as the rate and extent of unchanged drug reaches the systemic circulation after oral administration to provide therapeutic efficacy and which is determined by rate (i.e., C_{max}) and extent of absorption (i.e., AUC) as well as t_{max} whereas maximum therapeutic concentration achieved. Due to poor bioavailability result in lower drug exposure in-vivo and thereby increasing dosing frequency to get clinical effect which causes inconsistent clinical outcomes (2–4).

Recently the most of the drug substances having poor solubility is major challenges and 40 to 70% of NCE (New chemical entity) and 90% if compound in the drug discovery pipeline having poor aqueous solubility and hence, dissolution is rate limiting for the absorption followed by bioavailability. (5–7).

Based on solubility and permeability; drug substance is classified as BCS class II and IV as per Biopharmaceutical classification system (BCS). BCS II drug having low solubility and high permeability and BCS class IV drug having low solubility and low permeability. Particularly for BCS II drug Poor aqueous solubility limits dissolution, while the lower intestinal permeability of BCS Class IV drugs further restricts absorption, resulting in reduced oral bioavailability. In addition, polymorphism of drug substance, p-gp substrate mediated efflux, presystemic metabolism, food effects and inherent variability of drug substance belonging to BCS class II and IV category further complicate the oral drug delivery system. (1,4,6,8).

To address these challenges, numerous formulation and drug substance design technique have been developed to improve the solubility, dissolution, permeability, and thereby improving systemic exposure of low aqueous solubility of drug substances. Conventional techniques like to reduce particle size, salt formation, polymorphism, and polymer matrix of solid dispersion, inclusion complexation by preparing physical complex with cyclodextrin, lipid-based formulation by preparing emulsion, self-emulsifying drug delivery system, nanocrystals, polymeric and lipid nanoparticles, permeation enhancers, transporter modulation, gastroretentive formulations, and prodrug design. These technologies aim to overcome one or more barriers limiting oral drug absorption while maintaining drug stability, manufacturability, and therapeutic performance (3,5,7–10).

Recent advances in pharmaceutical materials, nanotechnology, computational formulation design, and mechanistic understanding of gastrointestinal physiology have further expanded the opportunities for enhancing oral bioavailability. Rather than relying on a single formulation strategy, modern product development increasingly integrates multiple complementary approaches to address the complex interplay between drug physicochemical properties and biological barriers. Such integrated strategies have enabled the successful commercialization of several formulations that significantly improve the clinical performance of low aqueous solubility of drug substance (5,9,10).

The review provides an overview of the fundamental principles governing oral bioavailability and critically discusses the major physicochemical, physiological, formulation-related, and patient-specific factors influencing oral drug absorption. Furthermore, recent development in formulation approaches to improve bioavailability of low aqueous solubility of drug substance are summarized along with mechanisms of action, advantages, limitations, representative pharmaceutical applications, and future prospects. The review aims to provide formulation scientists and pharmaceutical researchers with an up-to-date understanding of current strategies with the rationale for development of oral drug delivery systems to improve therapeutic performance.

Factor affecting Bioavailability:

Oral bioavailability is a multifactorial phenomenon that depends on the coordinated interaction between the drug substance, physiological conditions of gastrointestinal tract, formulation attributes, and patient-specific variables. Following oral administration, a drug solubilized in gastrointestinal fluid, remain sufficiently stable within the gastrointestinal environment, permeate the intestinal epithelium, avoid extensive presystemic metabolism and transporter-mediated efflux, and subsequently reach the systemic circulation at therapeutically relevant concentrations. The efficiency of each of these sequential processes directly influences systemic drug exposure and ultimately determines the dosage form performance with respect to clinical outcome.

Improving the therapeutic performance of orally administered drugs requires a detailed understanding of the factors influencing drug absorption and disposition, particularly for drug substance having poor aqueous solubility and variable gastrointestinal absorption. The principal factors influencing oral bioavailability are categorized into physicochemical, physiological, formulation-related, and patient-related factors, as described below(1–3,11–15).

Characteristics of Drug Substance (i.e., Physical and chemical properties)

Physical and chemical properties of drug substance play a significant role in oral absorption. Parameters like solubility, rate of dissolution with respect to time, particle size and surface area, polymorphic form, salts form, ionization constant (pKa), lipophilicity (log P) characteristics significantly influence the solubilization of drug substance in gastrointestinal tract and permeate biological membranes. Variations in these properties may alter dissolution kinetics, intestinal permeability, chemical stability, and ultimately systemic drug exposure. Consequently, various techniques are employed to overcome the challenges associated with BCS Class II and Class IV drug substance, particularly those related to poor solubility and limited absorption. (1,2,11,12).

Physiological Factors

The gastrointestinal environment affect the absorption of orally administered drugs. Physiological parameters including pH of gastric fluid and intestinal fluid, gastric emptying rate, Gastro-intestinal transit time, gastrointestinal fluid composition, bile salt secretion, food intake, intestinal permeability, P-glycoprotein (P-gp) mediated efflux transport, and enzyme mediated metabolism affect the *in-vivo* drug solubilization and thereby dissolution, membrane transport, and presystemic metabolism. Interindividual variability in these physiological parameters often contributes to differences in oral drug exposure and therapeutic response among patients (2,3,13,14).

Formulation Factors

The composition and manufacturing process of an oral dosage form affect the dissolution and thereby affecting *in-vivo* absorption. The selection of excipients, dosage form design, manufacturing process techniques for solubility enhancement techniques can modify the dissolution behaviour and gastrointestinal performance of low aqueous soluble drug substance. Now a days novel formulation development approaches with respect to manufacturing process i.e., spray drying and hot melt extrusion to prepare amorphous solid dispersions which improve the solubility of low aqueous soluble drug substance, cyclodextrin inclusion complexes, lipid-based formulation like preparation of self-emulsifying drug delivery system, nanocrystals, nanosuspensions, surfactant-assisted formulations, and particle engineering technologies, have demonstrated to enhance the solubility of poorly soluble intact drug substance and followed by dissolution rate, maintaining supersaturation at *in-vivo*, and hence, improve *in-vivo* absorption and ultimately improve the bioavailability of low aqueous soluble drug substances (3,11–15).

Patient-Related Factors

Patient-specific characteristics also contribute to variability in oral bioavailability. Factors such as age, disease state, gastrointestinal disorders, hepatic and renal function, concomitant medications, genetic polymorphisms affecting drug-metabolizing enzymes and transport proteins, dietary habits, and medication adherence may alter drug absorption and systemic exposure. These variables should be considered during dosage form development and clinical evaluation to ensure consistent therapeutic outcomes across diverse patient populations (2,3,14,15).

Considering the all challenges for lower bioavailability in oral solid dosage form, following techniques are used for improving bioavailability by increasing the solubility of low aqueous soluble drug substance.

Techniques for improving solubility and thereby bioavailability

The improving aqueous solubility is most effective technique for increasing absorption of many low aqueous soluble drug substances, it alone may not ensure optimal systemic exposure. Oral bioavailability is governed by multiple interconnected processes, including drug dissolution, intestinal permeability, presystemic metabolism, transporter-mediated efflux, gastrointestinal residence time, and lymphatic uptake. Consequently, formulation strategies designed solely to enhance solubility may be insufficient for compounds whose absorption is additionally limited by low permeability or pre-systemic metabolism. Therefore, appropriate bioavailability enhancement technique used by understanding of the physical and chemical characteristics of the drug substance and biological barriers encountered following oral administration (1–3,13).

Over the past several decades, a wide range of formulation development and molecular approaches have been developed to overcome the limitations of the solubility and permeability subsequently improve the bioavailability for improving drug delivery system for oral route. Conventional techniques include reduce the particle size and increase the surface area, salt formation of free base drug, modification of pH, co-solvency, hydrotropy, surfactant-mediated solubilization, cyclodextrin complexation, and crystal engineering. More recently, advanced formulation technologies such as amorphous solid dispersions, lipid-based formulation by preparing self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), nanocrystals, nanosuspensions, polymeric nanoparticles, mesoporous carriers, micellar systems, phospholipid complexes techniques have demonstrated for improving the solubility and thereby oral bioavailability. These technologies improve drug absorption through one or more mechanisms, including enhancement of apparent solubility, acceleration of dissolution, maintenance of supersaturation, promotion of intestinal permeation, inhibition of efflux transporters, protection from chemical or enzymatic degradation, and stimulation of intestinal lymphatic transport (2,16–19).

The choice of a suitable bioavailability enhancement strategy depends on several factors, including the Biopharmaceutics Classification System (BCS) classification, molecular properties, dose, stability, therapeutic requirements, manufacturing feasibility, and regulatory considerations. Consequently, no single formulation approach is universally applicable, and an appropriate technique should be selected based on the specific absorption limitations of the drug candidate. The following sections critically review the principles, mechanisms of action, advantages, limitations, and recent advances associated with the major techniques employed to improve oral bioavailability.

Reduction of particle size and increase surface area (By Micronization & Nanonization):

Reduction in particle size and increase the surface area is conventional techniques of formulation strategies for increasing the solubility of low aqueous soluble drug substance and thereby increasing oral bioavailability. Being BCS II drug substance; solubility is rate limiting for *in-vivo* absorption and it can be overcome by reducing the particle size & increase the surface area which improve the solubility and ultimately improve the rate and extent of absorption *in-vivo* (3,20,21).

Particle size reduction done by using the milling techniques in which particle size reduction upto micron and nano range by using different mill like air jet mill, ball milling. Spray drying process also used for reducing the particle size by optimizing the process parameters like atomization pressure, feed pump etc.(2,3,21).

Nanonization is an advanced particle engineering approach in which drug particles are reduced to the nanometre range (100 to 1000 nm). Owing to their extremely small size, nanocrystals exhibit a markedly increased surface area and higher saturation solubility, resulting in faster dissolution and improved oral bioavailability. Furthermore, nanocrystals may enhance adhesion to the gastrointestinal mucosa and increase the driving force for drug diffusion across the intestinal membrane, thereby promoting drug absorption. Nanonization has emerged an effective for several poorly soluble drug substance to improve dissolution and oral bioavailability e.g., fenofibrate, sirolimus, and aprepitant, demonstrating significant improvements in systemic drug exposure (21–23).

Although particle size reduction is a relatively simple and scalable strategy, its applicability is influenced by drug-specific factors and process-related considerations. Consequently, careful optimization of particle size distribution, stability, and formulation composition is essential to achieve consistent improvements in oral bioavailability (3,22).

Table 1 - Following examples of drug substance improve the solubility by size reduction technique;

Drug	BCS Class	Technique	Outcome	Reference
Fenofibrate	II	Nanocrystals	Improved dissolution rate and oral bioavailability compared with conventional formulation	Merisko-Liversidge and Liversidge, 2011 (21)
Sirolimus	II	Nanocrystal technology (Rapamune®)	Enhanced the bioavailability with reduce the absorption variability	Merisko-Liversidge and Liversidge, 2011 (21)
Aprepitant	II	Nanocrystals (Emend®)	Significantly increased dissolution and oral bioavailability compared with micronized drug	Junghanns and Müller, 2008 (23)
Danazol	II	Nanosuspension	Increased dissolution rate and improved oral absorption in vivo	Keck and Müller, 2006 (22)
Itraconazole	II	Nanocrystals	Enhanced dissolution and systemic exposure compared with coarse particles	Junghanns and Müller, 2008 (23)
Naproxen	II	Micronization	Faster dissolution and improved absorption due to increased surface area	Aulton and Taylor, 2022 (3)
Griseofulvin	II	Micronization	Improved dissolution and increased oral bioavailability; marketed as ultramicrosize formulation	Shargel and Yu, 2022 (2)
Nifedipine	II	Nanocrystals	Increased dissolution rate and enhanced oral absorption	Keck and Müller, 2006 (22)

Salt formation:

Salt formation technique is appropriate approach for increasing the solubility and thereby increasing bioavailability of ionizable drug molecules for oral route. This strategy involves converting an acidic or basic drug into a pharmaceutically acceptable salt by reacting it with a suitable counterion. The resulting salt form often exhibits enhanced aqueous solubility, faster dissolution, improved wettability, and better chemical stability compared with the parent drug, thereby facilitating increased

drug absorption following oral administration (3,24,25).

The success of salt formation depends primarily on the ionization characteristics of drug substance and its ionization constant i.e., pKa and appropriate counterion. Basic drugs are commonly converted into hydrochloride, sulfate, mesylate, or maleate salts, whereas acidic drugs are frequently formulated as sodium, potassium, calcium, or meglumine salts. Salt formation improving the solubility of poorly soluble free base drug which maintain the supersaturation in-vivo as well as increase the driving force for drug diffusion across the intestinal membrane and resulting in enhanced oral bioavailability (25,26).

Several marketed pharmaceutical products have successfully utilized salt formation to improve clinical performance. Examples include diclofenac sodium, naproxen sodium, amlodipine besylate, metoprolol succinate, and imatinib mesylate, all of which demonstrate improved dissolution characteristics and more consistent oral absorption than their corresponding free-base or free-acid forms (2,3,26).

Salt formation can improve drug solubility; however, its applicability is limited to ionizable compounds and may not sufficiently enhance the oral performance of highly insoluble drugs. Furthermore, salt form having some concern regarding hygroscopicity, polymorphic conversion, disproportionation, and stability during storage should be carefully considered during salt selection and formulation development. Therefore, systematic screening of suitable salt forms is an essential step in pharmaceutical development to identify candidates with optimal physicochemical and biopharmaceutical properties (2,24,25).

Crystal engineering (polymorphism and co-crystals)

Crystal engineering has emerged technique to increase solubility and thereby increasing bioavailability of low aqueous soluble drug substances. This approach involves modifying the crystal structure of drug substance without altering the chemical identity of drug substance, thereby enabling optimization of properties such as solubility, rate of dissolution and solid-state properties. Polymorphism and co-crystal formation are promising crystal engineering strategies for enhancing drug properties without affecting the pharmacological activity of the parent molecule (3,27,28).

Polymorphism means drug substance having more than one crystalline form that differ in molecular packing and crystal lattice arrangement. Although polymorphs possess the same chemical composition, they may exhibit significant differences in melting point, hygroscopicity, mechanical properties, dissolution behaviour, and thermodynamic stability. Metastable polymorphs generally display higher apparent solubility and faster dissolution than the corresponding stable forms, potentially leading to improved oral bioavailability. However, maintaining the stability of these solid forms during processing and storage remains a significant challenge in pharmaceutical development (3,29).

Pharmaceutical co-crystals are multicomponent crystalline systems formed by an API and suitable co-formers through non-covalent interactions, mainly hydrogen bonding. Unlike salt formation, the generation of drug–coformer crystalline systems do not require the drug molecule to be ionizable, thereby expanding its applicability to a wider range of compounds. By modifying the crystal lattice, co-crystals can improve aqueous solubility, dissolution rate, physical stability, and

manufacturability while preserving the chemical structure and pharmacological activity of the drug. Consequently, co-crystal technology has become an attractive alternative for improving the oral bioavailability of low aqueous soluble drug substance (28,30,31).

Crystal engineering technique relies on appropriate selection of the crystal form or co-former, together with the drug substance characteristic properties i.e., solubility, stability and polymorphism behaviour. Therefore, polymorphism screening and co-crystal design have become integral components of modern pharmaceutical development for optimizing the biopharmaceutical performance of oral drug products (3,30).

Table 2- Following examples of drug substance improve the solubility by crystal engineering technique

Drug	Crystal engineering approach	Outcome	Reference
Carbamazepine	Co-crystal with nicotinamide	Improved dissolution rate and enhanced oral absorption	(30,31)
Itraconazole	Metastable polymorph	Increased dissolution compared with the stable crystalline form	(3,29)
Indomethacin	Amorphous/metastable polymorph	Enhanced apparent solubility and dissolution	(3,28)
Caffeine	Co-crystal with oxalic acid	Improved physicochemical properties and dissolution	(30)
Theophylline	Co-crystal with suitable co-formers	Enhanced dissolution and solid-state performance	(30,31)

Amorphization and Polymeric matrix i.e., Solid dispersion

Amorphization is appropriate formulation technique for improving the solubility of poorly soluble drug substance and thereby improving oral bioavailability. Amorphization and solid dispersion technique in which crystalline drug substance converted into a high-energy amorphous state. Amorphous systems lack long-range molecular order, resulting in higher Gibbs free energy and increased molecular mobility. Consequently, amorphous drugs generally exhibit higher solubility & dissolution, and the ability to generate supersaturated solutions, thereby increasing the concentration gradient for intestinal absorption and enhancing oral bioavailability (10,32,33).

Although the amorphous form offers superior dissolution characteristics, its thermodynamic instability often leads to recrystallization during storage or after administration, which may reduce its biopharmaceutical performance. To overcome this limitation, amorphous solid dispersions (ASDs) have been developed by dispersing of drug within a polymeric carrier. Povidone, Co-povidone, Hypromellose phthalate, HPMC-AS etc. polymers are commonly used for dispersing agent in solid dispersion which prevent the recrystallization, maintain supersaturation, and improve physical stability of drug substance in drug product (3,10,33,34).

Amorphous solid dispersions can be prepared using various process techniques i.e., Spray drying process, Hot melt extrusion and freeze drying etc. Now a days in industry; Hot-melt extrusion and

spray drying techniques are used considering the scalability & reproducibility. Low soluble drug substance as like Itraconazole, posaconazole, vemurafenib, ivacaftor, olaparib and enzalutamide have been successfully formulated as amorphous solid dispersions by using the spray drying and HME process resulting in significant improvements in dissolution behaviour and systemic drug exposure (3,10,34,35).

Despite their advantages, the successful development of ASDs requires suitable polymers, solvent for spray drying process as well as process temperature considering the HME process to get amorphous solid dispersion which crystallinity absent which improve the solubility and thereby bioavailability. Therefore, understanding drug-polymer interactions and supersaturation maintenance is essential for designing robust amorphous formulations with improved oral bioavailability by using spray drying, HME process (33–35).

Table 3- Following examples of drug substance improve the solubility by solid dispersion technique

Drug	Polymeric carrier	Crystal engineering approach	Outcome	Reference
Itraconazole	HPMC	Spray drying	Increased dissolution and oral bioavailability	(33,34)
Posaconazole	HPMCAS	Hot-melt extrusion	Improved dissolution and enhanced systemic exposure	(3,10)
Vemurafenib	Polymer-based ASD	Spray drying	Increased oral bioavailability compared with crystalline drug	(10,35)
Ivacaftor	HPMCAS	Amorphous solid dispersion	Enhanced dissolution and oral absorption	(34,35)
Ritonavir	PVP-VA	Amorphous solid dispersion	Improved solubility and bioavailability	(10,33)

Cyclodextrin complexation

Cyclodextrin complexation is used for enhancing the aqueous solubility and oral bioavailability of poorly water-soluble drugs. Cyclodextrins (CDs) are cyclic oligosaccharides composed of α-(1→4)-linked glucopyranose units having hydrophilic outer surface and hydrophobic central cavity. Cyclodextrin make a non-covalent interaction with hydrophobic drug and thereby improving the solubility and subsequently dissolution of drug product and *in-vivo* absorption (7,36,37).

Complex formation occurs through the partial or complete accommodation of the hydrophobic moiety of a drug molecule within the cyclodextrin cavity, where stabilization is primarily mediated by hydrophobic interactions, van der Waals forces, and hydrogen bonding

The dynamic and reversible host–guest interaction maintains an increased concentration of dissolved drug in the gastrointestinal environment. Furthermore, the inclusion complex can provide protection against chemical degradation, decrease gastrointestinal mucosal irritation, and enhance the physicochemical stability of the final dosage form (3,36,37).

α-Cyclodextrin, β-cyclodextrin, and γ-cyclodextrin are naturally occurring cyclodextrins most commonly used for drug complexation. β-Cyclodextrin is used for pharmaceutical application as complexation preparation with drug substance considering the cavity size of its. However, its high level affects the kidney and nephrotoxicity occurred. Hence, to overcome the toxicity concern associated with naturally occurred β-cyclodextrin; modified β-cyclodextrin derivatives developed i.e., hydroxypropyl-β-cyclodextrin (HP-β-CD), sulfobutyl ether-β-cyclodextrin (SBE-β-CD), and methylated β-cyclodextrins. Modified cyclodextrin has higher aqueous solubility and complexation efficiency as compared to the naturally occurred beta cyclodextrin which make more effective for increasing the solubility and thereby *in-vivo* absorption and bioavailability of low aqueous water-soluble drugs. (3,19,38).

Although cyclodextrin complexation offers several advantages, its effectiveness depends on ratio of drug substance to the cyclodextrin as well as cavity size, stability of complex. Therefore, appropriate selection of the cyclodextrin derivative and optimization of formulation variables are essential for achieving consistent improvements in drug dissolution and oral absorption (36,38).

Table 4- Following examples of drug substance improve the solubility by complexation technique

Drug	Cyclodextrin derivative	Outcome	Reference
Itraconazole	HP-β-CD	Increased dissolution and oral absorption	(19,37)
Piroxicam	β-Cyclodextrin	Enhanced dissolution rate and faster absorption	(36,38)
Carbamazepine	HP-β-CD	Increased dissolution and oral absorption	(37,38)
Curcumin	HP-β-CD	Improved solubility, stability, and systemic exposure	(3,36)
Nimodipine	β-Cyclodextrin	Enhanced dissolution and bioavailability	(19,38)

Co-solvent and hydrotropy

Solubility enhancement of low aqueous soluble drug substance by Co-solvency and hydrotropy techniques are simple and cost effective in pharma industry. Owing to their ease of implementation and compatibility with conventional pharmaceutical manufacturing processes, these approaches are used in pharmaceutical industry for oral, parenteral & topical dosage form (3,39,40).

Co-solvency techniques involve use of solvent for improving the solubility of low aqueous solubility of drug substance. Solvents like ethanol, propylene glycol, polyethylene glycol (PEG 400), glycerol, and dimethyl sulfoxide (DMSO) used for this technique to improve the solubility and thereby bioavailability. Concentration of solvent level in drug product should be optimized to maintain the supersaturation and prevent the recrystallization which affect the absorption and hence affect the therapeutic outcome (2,39,40).

Hydrotropy is another solubilization technique in which high concentrations of hydrotropic agents increase the solubility of poorly aqueous soluble compounds through weak molecular interactions i.e., π–π interactions, self-association and hydrogen bonding. Unlike surfactants, hydrotropic agents generally do not form micelles. It is simple and cost-effective technique to improve solubility instead of using any solvent. Example of hydrotropy agent i.e., nicotinamide, sodium

benzoate, sodium salicylate, sodium citrate, sodium acetate, and urea. (2,40,41).

Although both technique effectively improve solubility of poorly aqueous soluble drug substance, their practical application depends on the physical and chemical parameters of drug substance, drug excipient physical and chemical compatibility followed by stability of the drug product. Consequently, these techniques are often used alone or in combination with other formulation strategies to achieve improved oral bioavailability and product performance (3,39,41).

Table 5- Following examples of drug substance improve the solubility by co-solvency and hydrotropy for bioavailability enhancement

Drug	Technique	Solubilizing agent	Outcome	Reference
Diazepam	Co-solvency	Ethanol, Propylene glycol	Improved aqueous solubility and formulation performance	(2,39)
Phenytoin	Co-solvency	PEG 400, Propylene glycol	Enhanced dissolution and drug solubilization	(39)
Curcumin	Hydrotropy	Nicotinamide	Increased aqueous solubility and dissolution	(40,41)
Ibuprofen	Hydrotropy	Sodium benzoate	Improved apparent solubility and dissolution rate	(40)
Aceclofenac	Hydrotropy	Sodium citrate	Enhanced solubility and formulation development	(41)

Nanocrystals and nanosuspensions

Nanocrystals and nanosuspensions is novel and effective formulation technique for improving the oral bioavailability of poorly aqueous soluble drug substance. Nanocrystals are the drug substance particle prepared in range of 100 to 100 nm and further nanocrystals are stabilized by polymer and surfactant to prevent agglomeration. Nanosuspension can be prepared by using these crystals only and its dispersed in aqueous medium to get nano suspension. (21,22,47).

Nanocrystals as well as nano suspension in which nano sized drug substance particles having larger surface area for improving the dissolution rate followed by improving oral bioavailability. Furthermore, the small particle size provide driving force for drug diffusion across the intestinal membrane, thereby promoting drug absorption (22,23,47).

Despite their significant advantages, nanocrystals and nanosuspensions require careful optimization of stabilizer selection, particle size distribution, and storage conditions to prevent aggregation and crystal growth. Nevertheless, their high drug-loading capacity, broad applicability to poorly soluble compounds, and compatibility with conventional solid dosage forms have established support their use in improving the oral bioavailability of poorly water-soluble drugs. (2,3,22).

Table 6- Following examples of nanocrystals and nanosuspensions for bioavailability enhancement

Drug	Technology	Outcome	Reference
Sirolimus	Nanocrystals (Rapamune®)	Improved dissolution and oral bioavailability	(3,47)

Aprepitant	Nanocrystals (Emend®)	Enhanced dissolution and increased systemic exposure	(2,47)
Fenofibrate	Nanocrystals (Triglide®)	Improved oral absorption and reduced variability	(3,22)
Danazol	Nanosuspension	Increased dissolution rate and oral bioavailability	(2,23)
Itraconazole	Nanosuspension	Enhanced dissolution and improved oral absorption	(22,23)

Polymeric nanoparticles and lipid nanoparticles

These technique is novel technique to prepare nano sized drug substance particle by using polymer as well as lipidic excipient which improve the bioavailability by increasing surface area, improve drug dissolution, protect the drug from chemical or enzymatic degradation, and facilitate interaction with the intestinal epithelium Depending on the carrier material, nanoparticles are broadly classified into polymeric nanoparticles and lipid nanoparticles, both of which have demonstrated significant potential for enhancing oral drug absorption (48–50).

Polymeric nanoparticles are prepared using biodegradable and biocompatible polymers like polycaprolactone (PCL), poly (lactic-co-glycolic acid) (PLGA), chitosan, alginate, and Eudragit®. Drug substance is encapsulated within the polymer matrix (nanospheres) or enclosed within a polymer shell surrounding a drug-containing core (nanocapsules). These systems improve bioavailability by increasing drug stability, enabling controlled drug release, enhancing mucosal adhesion, and facilitating drug transport across the intestinal epithelium. In addition, certain polymers, such as chitosan, transiently loosen tight junctions, thereby promoting paracellular drug absorption (3,49–51).

Lipid nanoparticles are prepared by using lipidic excipient i.e., phospholipids and stabilized by lipidic solubilizer. These carrier system help to drug in disperse phase which improve the dissolution as well as permeation as it is lipidic in nature. Being a lipidic based formulation; absorption may be mediated through lymphatic route which prevent the presystemic metabolism and thereby improving the oral bioavailability. (3,50,52).

Despite their promising advantages, nanoparticle-based formulations needs to be optimized with respect to particle size, morphology, drug loading & entrapment efficiency, physical stability, and manufacturing scalability. Advances in nanoparticle engineering and surface functionalization continue to expand their applications in oral drug delivery, offering new opportunities for enhancing the therapeutic performance of challenging drug candidates (49,51,52).

Table 7- Following example of polymeric and lipid nanoparticles for bioavailability enhancement

Drug	Nanocarrier	Outcome	Reference
Curcumin	PLGA nanoparticles	Improved solubility, stability, and oral bioavailability	(49,51)

Drug	Nanocarrier	Outcome	Reference
Paclitaxel	Chitosan nanoparticles	Enhanced intestinal absorption and systemic exposure	(3,50)
Insulin	Chitosan nanoparticles	Improved oral absorption through mucoadhesion and enhanced permeability	(3,51)
Quercetin	Solid lipid nanoparticles (SLNs)	Increased dissolution and oral bioavailability	(3,52)
Fenofibrate	Nanostructured lipid carriers (NLCs)	Improved solubility and enhanced oral absorption	(50,52)

Permeation enhancers

Permeation enhancers are pharmaceutical excipients are used to increase permeability of drug substance across the gastrointestinal epithelium for improving the drug absorption. These excipients and these techniques are used for BCS class IV drug substance having rate limiting step is permeability for the absorption (3,53,54).

Permeation enhancers improve drug absorption by modulating tight junctions, membrane properties, mucus barriers, and enzymatic activity. An ideal enhancer should increase permeability temporarily without damaging intestinal barrier function.(3,54,55).

Permeation enhancers, including sodium caprate and chitosan, improve intestinal drug absorption by temporarily increasing epithelial permeability (2,54–56).

Permeation enhancers require optimization to improve absorption while ensuring safety and maintaining intestinal integrity. (2,3,56).

Table 8- Following examples of permeation enhancers for oral bioavailability improvement

Drug	Permeation enhancer	Mechanism	Outcome	Reference
Semaglutide	Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate	Enhances transcellular absorption and protects against gastric degradation	Improved oral bioavailability; marketed oral formulation (Rybelsus®)	(2,54)
Insulin	Sodium caprate	Reversible opening of tight junctions	Increased intestinal absorption in experimental studies	(3,56)
Heparin	Chitosan	Enhanced paracellular transport	Improved oral absorption	(55,56)

Calcitonin	Bile salts	Increased membrane permeability	Enhanced gastrointestinal absorption	(3,55)
Mannitol (model compound)	Sodium caprate	Increased paracellular permeability	Improved intestinal transport	(56)

P-glycoprotein and CYP450 modulation

P-gp and CYP450 enzymes are key barriers affecting oral drug bioavailability. P-gp limits absorption through intestinal efflux, whereas CYP3A4 and related enzymes reduce systemic availability through presystemic metabolism, collectively lowering the absorption of many orally administered drug (2,3,57).

Modifying these biological barriers can help improve oral drug absorption. Some excipients, like vitamin E TPGS, polysorbate 80, Cremophor® EL, and Pluronic® polymers, can reduce P-gp activity and increase drug absorption. Certain compounds can also inhibit CYP450 enzymes and increase drug levels in the body. However, these effects must be carefully controlled to avoid drug interactions and side effects (3,58,59).

Several clinically important drugs, including cyclosporine, tacrolimus, paclitaxel, digoxin, and certain anticancer agents are P-gp substrates and CYP3A4. Consequently, formulation approaches that simultaneously improve drug solubility while reducing efflux transport and presystemic metabolism have demonstrated considerable potential for enhancing oral bioavailability. Modern drug delivery systems, particularly lipid-based formulations and nanocarrier platforms, frequently exploit these mechanisms to maximize intestinal drug absorption and improve therapeutic performance (2,16,59).

Although modulation of P-gp and CYP450 offers significant opportunities for improving oral bioavailability, the safety and regulatory implications of transporter and enzyme inhibition must be carefully evaluated during formulation development. Therefore, this strategy is generally employed in combination with other formulation techniques including solid dispersions, lipid-based systems and nanoparticulate formulations, to achieve consistent bioavailability enhancement while minimizing the potential for clinically significant drug interactions (3,5).

Table 9 - Following examples of P-glycoprotein and CYP450 modulation for bioavailability enhancement.

Drug	Modulator/ Formulation	Target	Outcome	Reference
Cyclosporine	Cremophor® EL	P-gp inhibition	Enhanced intestinal absorption and oral bioavailability	(3,5)
Paclitaxel	Vitamin E TPGS	P-gp inhibition	Increased intestinal uptake and systemic exposure	(58,59)
Digoxin	Tween® 80	P-gp modulation	Improved intestinal absorption in experimental studies	(2,5)

Drug	Modulator/ Formulation	Target	Outcome	Reference
Tacrolimus	Lipid-based formulation	Reduced P-gp-mediated efflux	Improved oral bioavailability	(3,59)
Ritonavir	CYP3A4 inhibition	Reduced first-pass metabolism	Increased systemic exposure of co-administered drugs	(2,57)

Mucoadhesive and Gastroretentive Drug Delivery Systems

Mucoadhesive and gastroretentive drug delivery systems (GRDDS) have been developed to enhance oral bioavailability by prolonging the residence time of dosage forms within the gastrointestinal tract. These systems are particularly beneficial for drugs that exhibit a narrow absorption window in the upper intestine, are preferentially absorbed in the stomach or proximal small intestine, or possess pH-dependent solubility. By extending gastrointestinal retention, these approaches provide a longer period for drug dissolution and absorption, thereby improving systemic drug exposure and reducing variability in therapeutic response (3,60,61)

Mucoadhesive drug delivery systems employ polymers capable of adhering to the mucus layer covering the gastrointestinal epithelium. Polymers such as chitosan, carbopol, sodium alginate, hydroxypropyl methylcellulose (HPMC), and polycarbophil establish intermolecular interactions with mucin, enabling prolonged contact between the formulation and the absorptive surface. This intimate contact can enhance local drug concentration, increase the duration available for absorption, and, in some cases, improve intestinal permeability through transient modulation of epithelial tight junctions (3,60,62)

Gastroretentive drug delivery systems are designed to remain in the stomach for an extended period using mechanisms such as floating, swelling, expandable, high-density, or bioadhesive technologies. Prolonged gastric residence can improve the dissolution of drugs that are more soluble in acidic conditions and increase the absorption of compounds with a limited intestinal absorption window. Floating drug delivery systems are among the most extensively investigated GRDDS because they remain buoyant on gastric contents while gradually releasing the drug over an extended period (3,62,63)

Several marketed and investigational formulations have demonstrated the clinical utility of gastroretentive systems. Examples include Madopar® HBS (levodopa/benserazide), Glumetza® (metformin hydrochloride), and Proquin® XR (ciprofloxacin), which utilize prolonged gastric residence to improve drug release characteristics and therapeutic performance. Despite these advantages, the effectiveness of mucoadhesive and gastroretentive systems may be influenced by physiological factors such as gastric emptying, food intake, gastrointestinal motility, and mucus turnover. Therefore, formulation design should consider both drug properties and patient-related variables to achieve consistent bioavailability enhancement (62–64)

Table 10- Following examples of mucoadhesive and gastroretentive systems for bioavailability enhancement

Drug	Delivery system	Bioavailability enhancement mechanism	Outcome	Reference
Metformin HCl	Floating gastroretentive tablet (Glumetza®)	Prolonged gastric residence and controlled drug release	Improved absorption and sustained plasma concentration	(60,61)
Levodopa/ Benserazide	Hydrodynamically balanced system (Madopar® HBS)	Extended gastric retention	Improved therapeutic response and reduced plasma fluctuations	(64)
Ciprofloxacin	Floating extended-release tablet (Proquin® XR)	Increased gastric residence time	Improved drug release and patient compliance	(3,60)
Insulin	Chitosan-based mucoadhesive nanoparticles	Mucoadhesion and enhanced epithelial contact	Improved oral absorption in experimental studies	(62)
Amoxicillin	Floating gastroretentive formulation	Prolonged gastric retention for local action against *Helicobacter pylori*	Enhanced gastric residence and therapeutic efficacy	(3,63)

Prodrug and Molecular Modification Approaches

Prodrug and molecular modification strategies represent molecular-level approaches for enhancing drug absorption and overcoming solubility and permeability related limitations, chemical instability, or extensive first-pass metabolism.

Unlike conventional formulation techniques, these approaches involve the intentional modification of the chemical structure of the drug substance to optimize its biopharmaceutical properties while ensuring that the pharmacologically active drug is regenerated after absorption through enzymatic or chemical conversion (65–67).

A prodrug is a chemically modified derivative of an drug substance that exhibits reduced or no pharmacological activity until it is converted into the active form through metabolic processes in the body. Structural modification of the parent drug substance can be used to improve aqueous solubility, enhance lipophilicity, increase membrane permeability, minimize presystemic metabolism, or promote transport through intestinal carriers. Common prodrug design strategies include esterification, amidation, and amino acid conjugation, which are selected based on the functional groups and chemical properties of the parent compound. Numerous orally administered drugs, including enalapril, valacyclovir, oseltamivir, and cefuroxime axetil, have successfully utilized the prodrug concept to achieve improved oral absorption and therapeutic efficacy (3,66,67).

Molecular modification encompasses broader structural optimization strategies that improve the physicochemical and pharmacokinetic characteristics of drug candidates without necessarily following the classical prodrug approach. These modifications may involve changes in functional groups, optimization of lipophilicity (log P/log D), reduction of molecular flexibility, or adjustment of ionization properties (pKa) to enhance passive diffusion, metabolic stability, and oral absorption. Such modifications

are commonly applied during lead optimization in drug discovery to achieve a favorable balance between solubility, permeability, potency, and safety (2,3,66).

Although prodrug and molecular modification approaches can substantially improve oral bioavailability, they require extensive evaluation of metabolic activation, pharmacokinetics, safety, and regulatory considerations. Therefore, these strategies are generally employed when formulation-based approaches alone are insufficient to overcome the intrinsic biopharmaceutical limitations of the parent drug molecule (2,67,68).

Table 11- Following examples of prodrugs for oral bioavailability enhancement

Parent drug	Prodrug	Bioavailability enhancement mechanism	Outcome	Reference
Acyclovir	Valacyclovir	Carrier-mediated intestinal transport via PEPT1	Approximately 3–5-fold higher oral bioavailability than acyclovir	(67,68)
Enalaprilat	Enalapril	Increased lipophilicity and intestinal absorption	Improved oral bioavailability	(3,66)
Oseltamivir carboxylate	Oseltamivir	Enhanced oral absorption and subsequent enzymatic activation	High oral bioavailability	(3,67)
Ampicillin	Bacampicillin	Increased lipophilicity and membrane permeability	Improved oral absorption	(2,68)
Cefuroxime	Cefuroxime axetil	Improved membrane permeability through esterification	Enhanced oral bioavailability	(2,66)

CONCLUSION

Oral drug administration remains the most preferred route of administration due to patient convenience, enhanced patient adherence, economic advantages as well as low cost manufacturing as compared to other dosage form. Nevertheless, the oral bioavailability of numerous drug candidates is often compromised by factors such as poor aqueous solubility, limited dissolution rate, insufficient intestinal permeability, extensive presystemic metabolism, and active drug efflux mechanisms. These limitations are associated with BCS Class II and Class IV drugs, which represent a considerable fraction of newly developed pharmaceutical compounds. Therefore, enhancing the solubility and permeability of poorly aqueous soluble drug

for improving the oral bioavailability is main objective for pharmaceutical development (1–3,5).

In recent years, considerable progress has been achieved in the development of formulation and molecular approaches to overcome these challenges associated with the solubility and permeability related challenges which is rate limiting for drug absorption. Conventional techniques like milling for particle size reduction, salt formation, crystal modification, and amorphization including amorphous solid dispersions, cyclodextrin inclusion complexes, lipid-based formulation, nano formulation like nano crystals, nanoparticles, permeation enhancers, transporter modulation strategies, gastroretentive systems, and prodrug design. These approaches enhance oral drug absorption through various mechanisms, including improving drug solubility and dissolution, maintaining supersaturation, increasing intestinal permeability, protecting drugs from degradation, reducing presystemic metabolism, and prolonging residence time within the gastrointestinal tract (2,5,9,10).

The selection of a suitable bioavailability enhancement strategy depends on various factors, including the drug substance physical and chemical parameters, biopharmaceutical characteristics with respect to solubility and permeability, therapeutic requirements, formulation feasibility, stability, scalability, and regulatory considerations. In many cases, combining complementary formulation approaches provides greater improvements in oral absorption than reliance on a single technology, highlighting the importance of rational formulation design during pharmaceutical development (3,9,19).

Recent advances in pharmaceutical materials, nanotechnology, computational modeling, and mechanistic understanding of gastrointestinal physiology are transforming the development design for oral route. These innovations enable to develop more efficient, patient-centric formulations capable of delivering poorly soluble drug molecules with improved therapeutic performance. Future research is expected to focus on multifunctional drug delivery platforms, predictive in vitro–in vivo correlation models, artificial intelligence-assisted formulation development, and personalized medicine approaches to further optimize oral drug absorption (10,55,59,69).

Overall, continued integration of pharmaceutical sciences, material engineering, drug product development and delivery system play a significant role in overcoming the limitations of solubility and permeability related to the drug substance which affect the bioavailability. A comprehensive understanding related factors governing drug absorption, together with the rational application of advanced formulation strategies, will facilitate the effective development which is commercially feasible and cost effective for solid oral dosage form for upcoming new chemical entity.

REFERENCES

1. Amidon GL, Lennernäs H, Shah VP, Crison JR. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. Pharm Res. 1995 Mar;12(3):413–20. doi:10.1023/A:1016212804288
2. Ducharme MP SL eds. Shargel and Yu's Applied Biopharmaceutics and Pharmacokinetics. 8th edition. 2022. 55–57 p.

3. Aulton ME, & TKMG. Aulton's pharmaceutics: The design and manufacture of medicines. 6th ed. Elsevier; 2022.
4. Wagner JG. Wagner, J. G. (1975). Fundamentals of clinical pharmacokinetics. Drug Intelligence Publications. 1975.
5. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, et al. Strategies to Address Low Drug Solubility in Discovery and Development. Pharmacol Rev. 2013 Jan;65(1):315–499. doi:10.1124/pr.112.005660
6. Lipinski CA. Lead- and drug-like compounds: the rule-of-five revolution. Drug Discov Today Technol. 2004 Dec;1(4):337–41. doi:10.1016/j.ddtec.2004.11.007
7. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. Journal of Pharmacy and Pharmacology. 2010 Nov 1;62(11):1607–21. doi:10.1111/j.2042-7158.2010.01030.x
8. Benet LZ. The Role of BCS (Biopharmaceutics Classification System) and BDDCS (Biopharmaceutics Drug Disposition Classification System) in Drug Development. J Pharm Sci. 2013 Jan;102(1):34–42. doi:10.1002/jps.23359
9. Porter CJH, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov. 2007 Mar;6(3):231–48. doi:10.1038/nrd2197
10. Baghel S, Cathcart H, O'Reilly NJ. Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs. J Pharm Sci. 2016 Sep;105(9):2527–44. doi:10.1016/j.xphs.2015.10.008
11. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. 7th edi. wolters Kluwer; 2017.
12. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000 Jul;44(1):235–49. doi:10.1016/S1056-8719(00)00107-6
13. Dressman JB, Reppas C. In vitro–in vivo correlations for lipophilic, poorly water-soluble drugs. European Journal of Pharmaceutical Sciences. 2000 Oct;11:S73–80. doi:10.1016/S0928-0987(00)00181-0
14. Stegemann S, Leveiller F, Franchi D, de Jong H, Lindén H. When poor solubility becomes an issue: From early stage to proof of concept. European Journal of Pharmaceutical Sciences. 2007 Aug;31(5):249–61. doi:10.1016/j.ejps.2007.05.110
15. Khonsary SA. Goodman and Gilman's The Pharmacological Basis of Therapeutics. Surg Neurol Int. 2023 Mar 17;14:91. doi:10.25259/SNI_184_2023
16. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, et al. Strategies to Address Low Drug Solubility in Discovery and Development. Pharmacol Rev. 2013 Jan;65(1):315–499. doi:10.1124/pr.112.005660
17. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B. 2015 Sep;5(5):442–53. doi:10.1016/j.apsb.2015.07.003
18. Schenck L, Boyce C, Frank D, Koranne S, Ferguson HM, Strotman N. Hierarchical Particle Approach for Co-Precipitated Amorphous Solid Dispersions for Use in Preclinical In Vivo Studies. Pharmaceutics. 2021 Jul 7;13(7):1034. doi:10.3390/pharmaceutics13071034

19. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. Journal of Pharmacy and Pharmacology. 2010 Nov 1;62(11):1607–21. doi:10.1111/j.2042-7158.2010.01030.x
20. Dissolution. In: Essentials of Pharmaceutical Preformulation. Wiley; 2012. p. 86–97. doi:10.1002/9781118423226.ch5
21. Merisko-Liversidge E, Liversidge GG. Nanosizing for oral and parenteral drug delivery: A perspective on formulating poorly-water soluble compounds using wet media milling technology. Adv Drug Deliv Rev. 2011 May;63(6):427–40. doi:10.1016/j.addr.2010.12.007
22. KECK C, MULLER R. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. European Journal of Pharmaceutics and Biopharmaceutics. 2006 Jan;62(1):3–16. doi:10.1016/j.ejpb.2005.05.009
23. Müller R, Junghanns. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine. 2008 Oct;295. doi:10.2147/IJN.S595
24. Berge SM, Bighley LD, Monkhouse DC. Pharmaceutical Salts. J Pharm Sci. 1977 Jan;66(1):1–19. doi:10.1002/jps.2600660104
25. Guillory JK. Handbook of Pharmaceutical Salts: Properties, Selection, and Use Edited by P. Heinrich Stahl and Camile G. Wermuth. VHCA, Verlag Helvetica Chimica Acta, Zürich, Switzerland, and Wiley-VCH, Weinheim, Germany. 2002. vix + 374 pp. 17.5 × 24.5 cm. ISBN 3-906390-26-8. $130.00. J Med Chem. 2003 Mar 1;46(7):1277–1277. doi:10.1021/jm030019n
26. Serajuddin ATM. Salt formation to improve drug solubility. Adv Drug Deliv Rev. 2007 Jul;59(7):603–16. doi:10.1016/j.addr.2007.05.010
27. S. Byrn RP and JS. Solid State Chemistry of Drugs 2nd Edition. 1999.
28. Brittain HG, editor. Polymorphism in Pharmaceutical Solids. CRC Press; 2018. doi:10.3109/9781420073225
29. Hilfiker R, editor. Polymorphism. Wiley; 2006. doi:10.1002/3527607889
30. Schultheiss N, Newman A. Pharmaceutical Cocrystals and Their Physicochemical Properties. Cryst Growth Des. 2009 Jun 3;9(6):2950–67. doi:10.1021/cg900129f
31. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: An overview. Int J Pharm. 2011 Oct;419(1–2):1–11. doi:10.1016/j.ijpharm.2011.07.037
32. Hancock BC, Zografi G. Characteristics and Significance of the Amorphous State in Pharmaceutical Systems. J Pharm Sci. 1997 Jan;86(1):1–12. doi:10.1021/js9601896
33. Van den Mooter G. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discov Today Technol. 2012 Jun;9(2):e79–85. doi:10.1016/j.ddtec.2011.10.002
34. Pantazos I, Poimenidou M, Kouskouridas D, Tzaferas E, Karava V, Cholevas C, et al. Influence of Drug Properties, Formulation Composition, and Processing Parameters on the Stability and Dissolution Performance of Amorphous Solid Dispersions-Based Tablets. Polymers (Basel). 2025 Sep 14;17(18):2484. doi:10.3390/polym17182484
35. Newman A, Knipp G, Zografi G. Assessing the performance of amorphous solid dispersions. J Pharm Sci. 2012 Apr;101(4):1355–77. doi:10.1002/jps.23031
36. Del Valle EMM. Cyclodextrins and their uses: a review. Process Biochemistry. 2004 May;39(9):1033–46. doi:10.1016/S0032-9592(03)00258-9

37. LOFTSSON T, DUCHENE D. Cyclodextrins and their pharmaceutical applications. Int J Pharm. 2007 Feb 1;329(1–2):1–11. doi:10.1016/j.ijpharm.2006.10.044
38. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev. 2007 Jul;59(7):645–66. doi:10.1016/j.addr.2007.05.012
39. Yalkowsky SH. Solubilization by Cosolvents. In: Techniques of Solubilization of Drugs. Marcel Dekker; 1981.
40. Maheshwari R, Jagwani Y. Mixed hydrotropy: Novel science of solubility enhancement. Indian J Pharm Sci. 2011;73(2):179. doi:10.4103/0250-474X.91585
41. Rasool AA, Hussain AA, Dittert LW. Solubility Enhancement of Some Water-Insoluble Drugs in the Presence of Nicotinamide and Related Compounds. J Pharm Sci. 1991 Apr;80(4):387–93. doi:10.1002/jps.2600800422
42. Florence AT AD. Physicochemical Principles of Pharmacy. 6th ed. Pharmaceutical Press; 2016.
43. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev. 2000 Dec;45(1):89–121. doi:10.1016/S0169-409X(00)00103-4
44. Torchilin VP. Structure and design of polymeric surfactant-based drug delivery systems. Journal of Controlled Release. 2001 Jun;73(2–3):137–72. doi:10.1016/S0168-3659(01)00299-1
45. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. European Journal of Pharmaceutical Sciences. 2000 Oct;11:S93–8. doi:10.1016/S0928-0987(00)00167-6
46. Date AA, Desai N, Dixit R, Nagarsenker M. Self-Nanoemulsifying Drug Delivery Systems: Formulation Insights, Applications and Advances. Nanomedicine. 2010 Dec 14;5(10):1595–616. doi:10.2217/nnm.10.126
47. Müller RH, Keck CM. Twenty years of drug nanocrystals: Where are we, and where do we go? European Journal of Pharmaceutics and Biopharmaceutics. 2012 Jan;80(1):1–3. doi:10.1016/j.ejpb.2011.09.012
48. Couvreur P, Vauthier C. Nanotechnology: Intelligent Design to Treat Complex Disease. Pharm Res. 2006 Jul 21;23(7):1417–50. doi:10.1007/s11095-006-0284-8
49. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. Colloids Surf B Biointerfaces. 2010 Jan;75(1):1–18. doi:10.1016/j.colsurfb.2009.09.001
50. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 2002 Nov;54:S131–55. doi:10.1016/S0169-409X(02)00118-7
51. des Rieux A, Fievez V, Garinot M, Schneider YJ, Préat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. Journal of Controlled Release. 2006 Nov;116(1):1–27. doi:10.1016/j.jconrel.2006.08.013
52. Mehnert W. Solid lipid nanoparticles Production, characterization and applications. Adv Drug Deliv Rev. 2001 Apr 25;47(2–3):165–96. doi:10.1016/S0169-409X(01)00105-3
53. Maher S, Leonard TW, Jacobsen J, Brayden DJ. Safety and efficacy of sodium caprate in promoting oral drug absorption: from in vitro to the clinic. Adv Drug Deliv Rev. 2009 Dec;61(15):1427–49. doi:10.1016/j.addr.2009.09.006
54. Buckley ST, Bækdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Rønne J, et al. Transcellular stomach absorption of a

derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018 Nov 14;10(467). doi:10.1126/scitranslmed.aar7047
55. Brayden DJ, Hill TA, Fairlie DP, Maher S, Mrsny RJ. Systemic delivery of peptides by the oral route: Formulation and medicinal chemistry approaches. Adv Drug Deliv Rev. 2020;157:2–36. doi:10.1016/j.addr.2020.05.007
56. SALAMATMILLER N, CHITTCHANG M, JOHNSTON T. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev. 2005 Nov 3;57(11):1666–91. doi:10.1016/j.addr.2005.07.003
57. Lin JH, Yamazaki M. Role of P-Glycoprotein in Pharmacokinetics. Clin Pharmacokinet. 2003;42(1):59–98. doi:10.2165/00003088-200342010-00003
58. Varma M. P-glycoprotein inhibitors and their screening: a perspective from bioavailability enhancement. Pharmacol Res. 2003 Oct;48(4):347–59. doi:10.1016/S1043-6618(03)00158-0
59. Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KLR, Chu X, et al. Membrane transporters in drug development. Nat Rev Drug Discov. 2010 Mar;9(3):215–36. doi:10.1038/nrd3028
60. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opin Drug Deliv. 2006 Mar 28;3(2):217–33. doi:10.1517/17425247.3.2.217
61. Patil H, Tiwari R V., Repka MA. Recent advancements in mucoadhesive floating drug delivery systems: A mini-review. J Drug Deliv Sci Technol. 2016 Feb;31:65–71. doi:10.1016/j.jddst.2015.12.002
62. Roy S, Pal K, Anis A, Pramanik K, Prabhakar B. Polymers in Mucoadhesive Drug-Delivery Systems: A Brief Note. Des Monomers Polym. 2009 Jan 2;12(6):483–95. doi:10.1163/138577209X12478283327236
63. SMART J. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev. 2005 Nov 3;57(11):1556–68. doi:10.1016/j.addr.2005.07.001
64. Erni W, Held K. The Hydrodynamically Balanced System: A Novel Principle of Controlled Drug Release. Eur Neurol. 2008 Feb 5;21–7. doi:10.1159/000116171
65. Stella VJ. Prodrugs: Some Thoughts and Current Issues. J Pharm Sci. 2010 Dec;99(12):4755–65. doi:10.1002/jps.22205
66. Rautio J, Kumpulainen H, Heimbach T, Oliyai R, Oh D, Järvinen T, et al. Prodrugs: design and clinical applications. Nat Rev Drug Discov. 2008 Mar;7(3):255–70. doi:10.1038/nrd2468
67. Huttunen KM, Raunio H, Rautio J. Prodrugs—from Serendipity to Rational Design. Pharmacol Rev. 2011 Sep;63(3):750–71. doi:10.1124/pr.110.003459
68. Testa B. Prodrugs: bridging pharmacodynamic/pharmacokinetic gaps. Curr Opin Chem Biol. 2009 Jun;13(3):338–44. doi:10.1016/j.cbpa.2009.04.620
69. Pang KS, Maeng HJ, Fan J. Interplay of Transporters and Enzymes in Drug and Metabolite Processing. Mol Pharm. 2009 Dec 7;6(6):1734–55. doi:10.1021/mp900258z.

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