International Journal of Pharmaceutics 420 (2011) 1–10

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Mini review

Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications

Yohei Kawabata[a,b], Koichi Wada[b], Manabu Nakatani[b], Shizuo Yamada[a], Satomi Onoue[a,*]

[a] Department of Pharmacokinetics and Pharmacodynamics and Global Center of Excellence (COE) Program, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan
[b] Department of Chemistry, Manufacturing and Control, Kobe Pharma Research Institute, Nippon Boehringer Ingelheim Co., Ltd., 6-7-5, Minatojima-minamimachi, Chuo-ku, Kobe, Hyogo, 650-0047, Japan

ARTICLE INFO

Article history:
Received 13 June 2011
Received in revised form 26 July 2011
Accepted 16 August 2011
Available online 30 August 2011

Keywords:
Bioavailability
Biopharmaceutics classification system
Formulation development
Nanoparticle
Poorly water-soluble drugs
Solid dispersion

ABSTRACT

The poor oral bioavailability arising from poor aqueous solubility should make drug research and development more difficult. Various approaches have been developed with a focus on enhancement of the solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs. To complete development works within a limited amount of time, the establishment of a suitable formulation strategy should be a key consideration for the pharmaceutical development of poorly water-soluble drugs. In this article, viable formulation options are reviewed on the basis of the biopharmaceutics classification system of drug substances. The article describes the basic approaches for poorly water-soluble drugs, such as crystal modification, micronization, amorphization, self-emulsification, cyclodextrin complexation, and pH modification. Literature-based examples of the formulation options for poorly water-soluble compounds and their practical application to marketed products are also provided. Classification of drug candidates based on their biopharmaceutical properties can provide an indication of the difficulty of drug development works. A better understanding of the physicochemical and biopharmaceutical properties of drug substances and the limitations of each delivery option should lead to efficient formulation development for poorly water-soluble drugs.

1. Introduction

Combinatorial chemistry and high-throughput screening used in drug discovery have resulted in an increase of poorly water-soluble drug candidates (Lipinski, 2000; Lipinski et al., 2001). In drug discovery, the number of drug candidates defined as having low solubility has increased, and ca. 70% of new drug candidates have shown poor aqueous solubility in recent years (Ku and Dulin, 2010). Currently, approximately 40% of the marketed immediate-release (IR) oral drugs are categorized as practically insoluble (<100 μg/mL) (Takagi et al., 2006).

There are many problems arising from the poor solubility of drug candidates in drug research and development. The aqueous solubility of a drug is a critical determinant of its dissolution rate. The limited dissolution rate arising from low solubility frequently results in the low bioavailability of orally administered drugs, and compounds with aqueous solubility lower than 100 μg/mL generally present dissolution-limited absorption (Horter and Dressman, 2001). In such cases, dose escalation would be required until the blood drug concentration reaches the therapeutic drug concentration range. This dose escalation sometimes causes topical toxicity in the gastrointestinal tract upon oral administration, and such toxicity could lead to a reduction in patient compliance. In drug product development, the formulation design of a drug product with high drug load is generally difficult. Increasing drug load might result in poor powder properties, such as poor powder flowability and sticking tendency during granulation and tableting. In addition, the manufacturing cost would increase since a large amount of active pharmaceutical ingredient (API) might be consumed to develop and manufacture the drug product. The poor solubility of new drug candidates might also affect *in vitro* assay performance in drug discovery stage. In drug discovery, a number of *in vitro* cell culture assays are conducted to evaluate several biological properties of drug candidates, such as efficacy, membrane permeation properties, and genotoxicity. The solubility limitation or precipitation of a drug in the test medium may yield invalid information on the

Abbreviations: API, active pharmaceutical ingredient; ASD, amorphous solid dispersion; AUC, area under the curve; BA, bioavailability; BCS, biopharmaceutics classification system; CSD, crystalline solid dispersion; EMEA, European Medicines Agency; FDA, U.S. Food and Drug Administration; IR, immediate-release; JP, the Japanese Pharmacopoeia; SEDDS, self-emulsifying drug delivery systems; SMEDDS, self-microemulsifying drug delivery systems; SNEDDS, self-nanoemulsifying drug delivery systems; WHO, World Health Organization.

* Corresponding author. Tel.: +81 54 264 5633; fax: +81 54 264 5635.
E-mail address: onoue@u-shizuoka-ken.ac.jp (S. Onoue).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.08.032

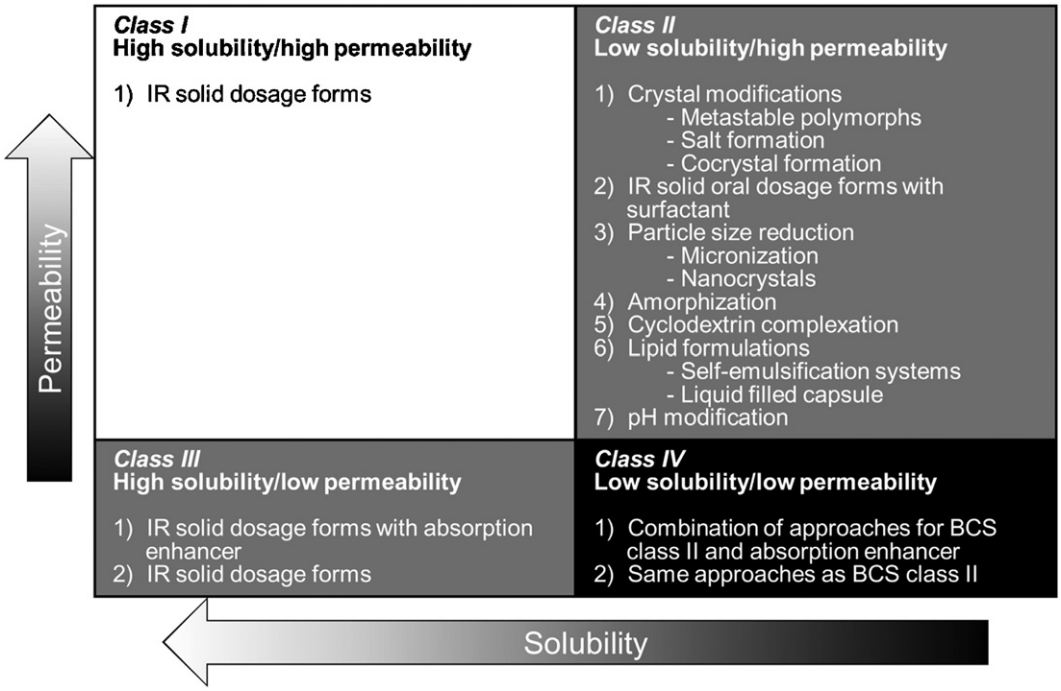

Fig. 1. Biopharmaceutics classification system (BCS) and viable formulation options based on the BCS.

drug properties *in vitro*. In preclinical development, the solubility limitation could also impair data quality on *in vivo* toxicity assessments since toxicological studies usually require higher exposure than that in pharmacological or pharmacokinetic studies to assure its safety. In clinical use, the poor bioavailability of a drug substance might result in limited therapeutic potential, thereby leading to insufficient clinical outcomes.

Various approaches to overcome the poor aqueous solubility of drug candidates have been investigated in drug research and development. Changing the chemical structure in the lead optimization phase is considered to be an option to increase the solubility of drug candidates. Prodrug approaches might also enhance the aqueous solubility of drug candidates by introducing a polar functional group into the structure of a molecule (Stella and Nti-Addae, 2007). In addition to these attempts, a number of approaches have been investigated to increase the dissolution of poorly water-soluble drugs. In the present article, we review viable formulation options based on the biopharmaceutical properties of drug substances. Basic approaches for poorly water-soluble drugs are also reviewed with an emphasis on enhancing solubility, dissolution rate, and oral bioavailability. Literature-based examples of the formulation options for poorly water-soluble compounds and their practical application to marketed products are also provided.

2. Formulation strategies based on biopharmaceutics classification system

2.1. Biopharmaceutics classification system

A better understanding of the physicochemical and biopharmaceutical properties of drugs would be of great help for developing pharmaceutical products. Biopharmaceutics classification system (BCS) is a useful tool for decision-making in formulation development from a biopharmaceutical point of view (Amidon et al., 1995). The BCS categorizes drug substances into one of four categories based on their solubility and intestinal permeability, and 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) (Fig. 1). A drug substance is considered "highly permeable" when the extent of absorption in humans is determined to be 90% or more of an administered dose (FDA, 2000). At an early stage in development, *in vitro* permeability assays using Caco-2 or MDCK cells or artificial membranes are frequently utilized for prediction of drug substance permeability from the gut lumen into the bloodstream (Artursson et al., 2001; Sugano et al., 2003; Volpe, 2008). A drug substance is considered "highly soluble" when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1–7.5 at 37 °C (FDA, 2000). The highest estimated human dose could be alternatively used to classify the solubility property of drugs in early drug development.

Regulatory agencies have utilized the BCS to allow the use of *in vitro* dissolution data for establishing the *in vivo* bioequivalence of drug products. The U.S. Food and Drug Administration (FDA), World Health Organization (WHO), and European Medicines Agency (EMEA) allowed a BCS-based biowaiver for drug products containing BCS class I drugs when the drug products exhibit rapid dissolution (FDA, 2000; EMEA, 2010; WHO, 2006). WHO has extended the BCS-based biowaiver for some BCS class II drugs with weak acidic properties. Moreover, WHO and EMEA have extended the BCS-based biowaiver for drug products within BCS class III.

Recently, the concept of the BCS has been used not only for the biowaiver but also for formulation design from early to clinical stages (Cook et al., 2008; Ku, 2008). Classification of drug candidates based on the BCS can provide an indication of the difficulty of the development works. For BCS class I or III drugs, formulations are designed with a simple strategy. However, for BCS class II or IV drugs, deliberate formulation designs based on both the physicochemical and biopharmaceutical properties of the drugs are required to obtain sufficient and reproducible bioavailability after oral administration. The viable formulation options based on the BCS are summarized in Fig. 1.

2.1.1. Formulations for BCS class I drugs

BCS class I drugs are defined as being highly soluble and highly permeable. For instance, metoprolol, propranolol, and theophylline

are categorized into this class (Wu and Benet, 2005). For BCS class I drugs, there would be no rate-limiting step for oral absorption. IR solid oral dosage forms, for example, conventional tablet or capsule formulations, are commonly designed to ensure rapid dissolution in the gastrointestinal tract.

2.1.2. Formulations for BCS class II drugs

The molecular characteristics of BCS class II drugs are identified as low solubility and high permeability. For instance, cyclosporine, griseofulvin, and itraconazole are categorized into this class (Wu and Benet, 2005). Generally, the bioavailability of a BCS class II drug is rate-limited by its dissolution, so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability (Lobenberg and Amidon, 2000). Therefore, an enhancement of the dissolution rate of the drug is thought to be a key factor for improving the bioavailability of BCS class II drugs. Several physicochemical factors control the dissolution rate of the drugs. According to the modification of the Noyes-Whitney equation, the factors affecting the drug dissolution rate are defined as the effective surface area, the diffusion coefficient, the diffusion layer thickness, the saturation solubility, the amount of dissolved drug, and the volume of dissolution media (Horter and Dressman, 2001). Increases in the saturation solubility and the effective surface area have a positive impact on the dissolution rate of the drugs, and these factors could be increased by efforts of preformulation study and formulation design. Crystal modification (Blagden et al., 2007), particle size reduction (Xia et al., 2010), self-emulsification (He et al., 2010a), pH modification (Tran et al., 2010), and amorphization (Kaushal et al., 2004) are considered to be effective for improving the dissolution behavior of BCS class II drugs.

2.1.3. Formulations for BCS class III drugs

Drugs with high solubility and low permeability are classified as BCS class III. For instance, atenolol, cimetidine, and metformin are categorized into this class (Wu and Benet, 2005). The bioavailability of BCS class III drugs is rate-limited by the membrane permeability in the gastrointestinal tract. In theory, there are three transepithelial pathways for the drugs from the intestinal lumen to the bloodstream: transcellular carrier-mediated active or facilitated transport, transcellular passive transport, and paracellular transport (Fasano, 1998). A majority of orally administered drugs are absorbed via transcellular passive transport. In this case, the intrinsic lipophilicity of the drug is a determinant of the drug transport across the enterocytes, and drug with relatively high lipophilicity would have high membrane permeability. The intrinsic lipophilicity of a drug is determined by its chemical structure; therefore, it is necessary to return to the lead optimization phase to increase the permeability via the transcellular route.

Hydrophilic drugs generally penetrate the intestinal membrane via the paracellular route. Permeation enhancers, such as fatty acid, bile salts, surfactants, and polysaccharides, play a role in enhancing the permeability of drugs via the paracellular pathway; however, some of them are known to have membrane damaging effects (Fasano, 1998; Thanou et al., 2001). Since far less is known about the efficacious and safe dosage options for BCS class III drugs, IR solid dosage forms should be practically designed for clinical use, although the absorption could be limited by membrane permeation.

2.1.4. Formulations for BCS class IV drugs

BCS class IV drugs exhibit challenging molecular properties such as low solubility and low permeability. Since both solubility and permeability are rate-limiting steps for absorption, it would be considered that physiological factors, for example, gastric emptying time and gastrointestinal transit time, highly influence the absorption of BCS class IV drugs. Therefore, the drugs categorized in BCS class IV could exhibit large inter- and intra-subject variability in terms of absorption (Horter and Dressman, 2001). This variability in absorption could result in the challenging drug development of BCS class IV drugs as well as their formulation design. There are viable formulation options focusing on improvement of the dissolution behavior that are commonly applied to BCS class II drugs. However, the approaches for enhancing their permeability are still at an early investigational stage, and their safety is not well established. In this context, formulation approaches similar to those for BCS class II drugs could be practically applied to BCS class IV drugs, even though the absorption could be limited by the poor permeability after dissolving in the gastrointestinal tract.

3. Delivery options for poorly water-soluble drugs

3.1. Crystal modifications

3.1.1. Metastable polymorphs

Polymorphism in crystalline solids is defined as materials with the same chemical composition, but different lattice structures and/or different molecular conformations (Rodriguez-Spong et al., 2004). The vast majority of drugs can crystallize into several polymorphs. Each polymorph has a different energy, showing different physicochemical properties, such as melting point, density, solubility, and stability. Generally, the solubility of metastable polymorphs is kinetically higher than that of a thermodynamically more stable polymorph (Blagden et al., 2007). The differences of the solubility among polymorphs have been reported to be typically less than 2.0-fold (Pudipeddi and Serajuddin, 2005). Although the utilization of metastable polymorphs is one of the effective approaches to enhance the dissolution rate of a drug, the metastable forms eventually transform to the thermodynamically stable form. It is necessary to monitor the polymorphic transformation during both manufacturing and storage of dosage forms to ensure reproducible bioavailability after oral administration (Zhang et al., 2004).

3.1.2. Salt formation

In the pharmaceutical industry, salt formation approach is commonly used for an ionizable drug to increase solubility and dissolution rate. Salts are formed via proton transfer from an acid to a base. A stable ionic bond can be formed when the difference of pK_a between an acid and a base (ΔpK_a) is greater than 3 (Childs et al., 2007). The counter ion containing salt changes the pH at the dissolving surface of a salt particle in the diffusion layer, resulting in a higher dissolution rate of the salts compared with that of the corresponding free forms (Serajuddin, 2007). According to the Henderson-Hasselbalch equations, the change of pH highly influences the aqueous solubility of an ionizable drug (Avdeef, 2007). In theory, the solubility of a weak basic drug increases exponentially with decreasing pH at the pH range between its pK_a and pH_{max} (pH of maximum solubility in the pH-solubility profile). The increased saturation solubility on the dissolving surface contributes to the higher dissolution rate by salt formation. Celecoxib, a poorly water-soluble weak acidic drug, showed an enhanced dissolution rate and oral bioavailability with a combination of Na salt formation and the use of a precipitation inhibitor compared with the corresponding free acid form (Guzman et al., 2007).

The solubility and dissolution rate of salt are influenced by the counter ion containing the salt. The solubility of haloperidol mesylate was significantly higher than that of its hydrochloride salt at a lower pH range (Li et al., 2005). The aqueous solubility of a moderately soluble hydrochloride salt for a basic drug is sometimes reduced in solution containing chloride ion, such as gastric fluids (common-ion effects). An appropriate salt form should be developed from the viewpoints of both physicochemical and

biopharmaceutical properties, especially for poorly water-soluble drugs.

3.1.3. Cocrystal formation

In recent years, much attention has been drawn to cocrystal for improving the dissolution rate of poorly water-soluble drugs. Cocrystal is broadly defined as crystalline materials comprised of at least two different components (Schultheiss and Newman, 2009). Pharmaceutical cocrystal is typically composed of an API and a non-toxic guest molecule (cocrystal former) in a stoichiometric ratio. Unlike salt formation, proton transfer between the API and cocrystal former does not take place in cocrystal formation. In many cases, the API and cocrystal former require hydrogen bonding to form a stable cocrystal. Generally, ΔpK_a is one of the reliable indicators for distinguishing between salts and cocrystals, and the molecular complexes can be defined as a cocrystal when the ΔpK_a is less than 0 (Childs et al., 2007). When the ΔpK_a is between 0 and 3, they can be salts or cocrystals or can contain sheared protons or mixed ionization states that cannot be assigned to either category. There have been several studies demonstrating the enhanced dissolution rate and oral bioavailability by cocrystal formation (Jung et al., 2010; McNamara et al., 2006). AMG-517 (Amgen) is a potent and selective VR1 antagonist (Bak et al., 2008). AMG-517 is a free base, but insoluble at physiological pH because there is no pK_a value in the physiological range. The cocrystal of AMG 517 and sorbic acid showed a higher dissolution rate in fasted state simulated intestinal fluid, and 9.4-fold enhancement in AUC_{0-inf} was observed compared with that of its free base form after oral administration to dog (500 mg/kg). In addition to other crystal engineering approaches, such as metastable polymorphs and salt formation, cocrystal approach could be an alternative option for improving the dissolution rate of poorly water-soluble drugs, especially for the drug candidates that are not ionized at physiological pH.

3.2. Particle size reduction

3.2.1. Micronization

Particle size reduction approach is widely used to increase dissolution rate as well as salt formation. The dissolution rate of a drug proportionally increases with increasing surface area of drug particles (Horter and Dressman, 2001). According to the Prandtl boundary layer equation, the decrease of diffusion layer thickness by reducing particle size, particularly down to <5 μm, would result in accelerated dissolution (Mosharraf and Nyström, 1995). Thus, the increased surface area and the decreased diffusion layer thickness would lead to an enhanced dissolution rate of the drug. Micronization approach successfully enhanced the bioavailability of poorly water-soluble drugs such as griseofulvin, digoxin, and felodipine (Atkinson et al., 1962; Jounela et al., 1975; Scholz et al., 2002).

The common method to obtain micronized drug particles is mechanical pulverization of larger drug particles. Jet milling, ball milling, and pin milling are commonly used for dry milling. For solid powders, the lowest particle size that can be achieved by conventional milling is about 2–3 μm. The milling does not always result in significantly enhancing the dissolution rate of the drug. Micronization sometimes increases agglomeration of the drug particles, which may decrease the surface area available for the dissolution. In such case, wetting agents, such as a surfactant, would play a major role in increasing the effective surface area.

3.2.2. Nanocrystals

Particle size reduction to nano-meter range (<1 μm) is an attractive approach for poorly water-soluble drugs. As described in Section 3.2.1, particle size reduction could lead to an increase of the surface area and a decrease of the diffusion layer thickness, which could provide an enhanced dissolution rate for drugs. In addition to these factors, an increase in the saturation solubility is also expected by reducing the particle size to less than 1 μm, as described by Ostwald–Freundlich's equation (Müller and Peters, 1998). The nanocrystal formulations are commonly produced by wet-milling with beads, high-pressure homogenization, or controlled precipitation (Shegokar and Muller, 2010). Hydrophilic polymer and/or surfactant are typically used to stabilize nanocrystal suspension. The nanocrystalline drug particles are dispersed into inert carriers after a drying process, such as spray drying or lyophilization. Herein, the solidified nanocrystal formulations can be defined as crystalline solid dispersion (CSD). There have been numerous studies demonstrating the enhanced oral bioavailability of pharmaceuticals and neutraceuticals by nanocrystal technologies (Table 1) (Fakes et al., 2009; Hanafy et al., 2007; Hecq et al., 2006; Jia et al., 2002, 2003; Jinno et al., 2006, 2008; Kawabata et al., 2010; Kondo et al., 1993; Liversidge and Cundy, 1995; Onoue et al., 2010b; Sylvestre et al., 2011; Wu et al., 2004; Xia et al., 2010). Nanocrystal formulations have been found to show 1.7–60-fold and 2–30-fold enhancement in C_{max} and AUC compared with crystalline formulations with micrometer particle size. Among all the nanocrystal formulations listed in Table 1, neutral or acidic compounds such as danazol (Liversidge and Cundy, 1995), cilostazol (Jinno et al., 2006, 2008), tranilast (Kawabata et al., 2010), and curcumin (Onoue et al., 2010b) showed better improvements in the pharmacokinetic parameters than basic compounds by using nanocrystal technologies. Currently, five nanocrystal oral formulations using NanoCrystal® (Elan Drug Technologies) and IDD-P® (SkyePharma) technologies are available on the market (Table 2).

3.3. Amorphization

Amorphous solids have higher energy than crystalline solids. Typically, the solubility of an amorphous drug is higher than that of the corresponding crystalline drug. The differences of the solubility between amorphous form and crystalline form have been reported to be between 1.1- and 1000-fold (Hancock and Parks, 2000; Huang and Tong, 2004). The marked enhancement in the saturated solubility of amorphous drug may lead to a significant improvement of oral bioavailability. Stable amorphous formulations can be obtained by solid dispersion techniques. Amorphous solid dispersion (ASD) is defined as a distribution of active ingredients in molecular and amorphous forms surrounded by inert carriers (Chiou and Riegelman, 1971). The ASD formulations can be prepared by spray drying, melt extrusion, lyophilization, and use of supercritical fluids with polymeric carriers and/or surfactant (Vasconcelos et al., 2007). Numerous studies have demonstrated the marked enhancement of oral absorption by ASD approaches (Chen et al., 2004; Chiba et al., 1991; Dannenfelser et al., 2004; Fakes et al., 2009; Fukushima et al., 2007; He et al., 2010b; Joshi et al., 2004; Kai et al., 1996; Kennedy et al., 2008; Kohri et al., 1999; Kondo et al., 1994; Kubo et al., 2009; Kushida et al., 2002; Lakshman et al., 2008; Law et al., 2004; Liu et al., 2006; Newa et al., 2008; Onoue et al., 2010a, 2011; Sinha et al., 2010; Van Eerdenbrugh et al., 2009; Vaughn et al., 2006; Yamashita et al., 2003; Zerrouk et al., 2001; Zheng et al., 2007). Of all the ASD formulations listed in Table 1, the ASD approaches were found to show 1.5–82-fold and 1.6–113.5-fold enhancements in C_{max} and AUC compared with crystalline formulation containing bulk API or a physical mixture of API and carriers. The AUC enhancement ratio of the majority of the listed drugs was found to be less than 20-fold. However, a more than 20-fold improvement in the pharmacokinetic parameters was observed in a few cases. ER-34122 (Eisai) is a 5-lipoxygenase/cyclooxygenase inhibitor with low aqueous solubility (<10 ng/mL) (Kushida et al., 2002). Surprisingly, the amorphous formulation of ER-34122 showed ca. 200-fold

Table 1
Literature-based nanocrystal and amorphous solid dispersion formulations for poorly water-soluble pharmaceuticals and neutraceuticals.

	Solubility in water	pK_a (acid/base)	BCS class	PK parameters after oral administration	References
Nanocrystal formulations					
BMS-488043 (Bristol-Myers Squibb)	40 μg/mL (pH 4–8)	2.6 (base), 9.3 (acid)	II	C_{max}: 4.7-fold↑; AUC_{0-24h}: 4.6-fold↑ (vs. crystalline API, D_{95} < 23 μm) in dogs	Fakes et al. (2009)
Carbendazim	8 μg/mL (pH 7) 29 μg/mL (pH 4) 25 mg/mL (pH 1)	4.48 (base), 10.80 (acid)	N/A	Relative BA: 1.7-fold↑(vs. crystalline API, 7 μm) in rats	Jia et al. (2003), Ni et al. (2002)
Cilostazol	3 μg/mL	–	II	C_{max}: 9.2-fold↑; AUC: 6.7-fold↑(vs. crystalline API, 13 μm) in dogs C_{max}: 8.3-fold↑; AUC: 11.6-fold↑(vs. commercial tablet) in dogs	Jinno et al. (2006) Jinno et al. (2008)
Curcumin	0.011 μg/mL	7.8 (acid), 8.5 (acid), 9.0 (acid)	IV	BA: 16-fold↑(vs. crystalline API, 20 μm) in rats	Onoue et al. (2010b), Tonnesen et al. (2002), Wahlang et al. (2011)
Danazol	10 μg/mL	–	II	C_{max}: 15.1-fold↑; AUC: 16.5-fold↑(vs. crystalline API, 10 μm) in dogs	Liversidge and Cundy (1995), Wu and Benet (2005)
Fenofibrate	0.8 μg/mL	–	II	C_{max}: 2.3-fold↑; AUC_{0-inf}: 1.9-fold↑(vs. crystalline API, 5 μm) in rats	Hanafy et al. (2007), Jamzad and Fassihi (2006), Kesisoglou et al. (2007)
HO-221 (Green cross/Mitsubishi Tanabe)	0.055 μg/mL	N/A	N/A	C_{max}: 1.7-fold↑; AUC_{0-48h}: 1.8-fold↑(vs. crystalline API, 17.2 μm) in rats C_{max}: 1.7-fold↑; AUC_{0-48h}: 2.1-fold↑(vs. crystalline API, 4.2 μm) in dogs	Kondo et al. (1993)
Megestrol acetate	2 μg/mL	–	II	C_{max}: 2.3-fold↑; AUC_{0-24h}: 2.7-fold↑(vs. crystalline API, 3.1 μm) in rats	Kesisoglou et al. (2007), Sylvestre et al. (2011)
MK-0869 (Aprepitant, Merck)	3–7 μg/mL (pH 2–10) 130 μg/mL (pH 1)	9.7 (base)	IV	C_{max}: 3.7-fold↑; AUC_{0-72h}: 4.3-fold↑(vs. crystalline API, 5.5 μm) in dogs	Wu et al. (2004)
Nitrendipine	ca. 2.0 μg/mL at 37 °C	–	II	C_{max}: 8.7-fold↑; $AUC_{0-\infty}$: 5.5-fold↑(vs. crystalline API, 36.6 μm) in rats	Xia et al. (2010)
PG301029 (Procter & Gamble)	~50 μg/mL	N/A	N/A	C_{max}: 2.8-fold↑; AUC_{0-8h}: 4.2-fold↑(vs. crystalline API, 7 μm) in rats	Jia et al. (2002)
Tranilast	14.5 μg/mL 0.7 μg/mL (pH 1.2)	3.25 (acid)	N/A	C_{max}: 60-fold↑; AUC_{0-inf}: 31-fold↑(vs. crystalline API, 61.4 μm) in rats	Kawabata et al. (2010)
ucb-35440–3 fumarate (UCB S.A.)	~650 μg/mL (pH 3) ~200 μg/mL (pH 5) <30 μg/mL (pH 6.5)	5.7 (base), 9.6 (base)	N/A	C_{max}: 3.1-fold↑; AUC: 4.2-fold↑(vs. crystalline API, 140 μm) in rats	Hecq et al. (2006)
Amorphous formulations					
ABT-963 (Abbott)	16 μg/mL	N/A	N/A	C_{max}: 1.9-fold↑; AUC: 1.9-fold↑(vs. crystalline API) in dogs	Chen et al. (2004)
Albendazole	1 μg/mL (pH 6.0)	2.68 (base), 11.83 (base)	II/IV	C_{max}: 2.8-fold↑; AUC_{0-24h}: 3.9-fold↑(vs. physical mixture) in rabbits	Galia et al. (1999), Kohri et al. (1999)
AMG 517 (Amgen)	≤7 μg/mL (pH 2–7) ≤0.3 μg/mL (pH 7.1)	Low (base)	N/A	C_{max}: 1.5-fold↑; AUC_{0-inf}: 1.6-fold↑(vs. micronized API suspension) in monkeys	Kennedy et al. (2008)
Baicalein	≤130 μg/mL	5.3 (acid)	II	C_{max}: 3.6-fold↑; AUC_{0-12h}: 2.3-fold↑(vs. crystalline API) in rats	He et al. (2010b), Yoshizuka et al. (1996)

Table 1 (*Continued*)

	Solubility in water	pK_a (acid/base)	BCS class	PK parameters after oral administration	References
Benzimidazole derivative (Bristol-Myers Squibb)	<1 μg/mL (pH 3.5–5.5) ~100 μg/mL (pH 1.3–1.6)	~5.5 (base)	N/A	BA: 21.0-fold (vs. crystalline API, 7–10 μm) in dogs	Joshi et al. (2004)
Benzopyrimidine derivative (Novartis)	30 μg/mL (pH 1) ≤3 μg/mL (pH 3–9)	2.9 (base), 10.0 (base)	N/A	BA: 7.0-fold↑(vs. crystalline API with poloxamer 188) in dogs	Lakshman et al. (2008)
BMS-232632 (Bristol-Myers Squibb)	N/A	4.7 (base)	II	C_{max}: 7.8-fold↑; $AUC_{0-\infty}$: 3.4-fold↑(vs. crystalline API) in rats	Fukushima et al. (2007)
BMS-488043 (Bristol-Myers Squibb)	40 μg/mL (pH 4–8)	2.6 (base), 9.3 (acid)	II	C_{max}: 15.0–18.0-fold↑; $AUC_{0-24\,h}$: 7.0–9.0-fold↑(vs. wet-milled crystalline API) in dogs	Fakes et al. (2009)
Carbamazepine	170 μg/μL	–	II	C_{max}: 3.5-fold↑; $AUC_{0-\infty}$: 2.0-fold↑(vs. pure drug) in rabbits	Wu and Benet (2005), Zerrouk et al. (2001)
Cyclosporin A	7.3 μg/mL	–	II	C_{max}: 5.1-fold↑; AUC_{0-inf}: 5.2-fold↑(vs. amorphous API) in rats Relative C_{max}: 91.8%; relative $AUC_{0-60\,h}$: 98.2% (vs. Neoral®) in rats	Onoue et al. (2010a) Liu et al. (2006)
Danazol	10 μg/mL	–	II	C_{max}: 2.1-fold↑; $AUC_{0-24\,h}$: 2.3-fold↑(vs. physical mixture) in mice C_{max}: 1.9-fold↑; $AUC_{0-24\,h}$: 3.8-fold↑(vs. physical mixture) in mice	Vaughn et al. (2006)
ER-34122 (Eisai)	≤0.01 μg/mL (pH 2–8)	N/A	N/A	C_{max}: 82.0-fold↑; $AUC_{0-24\,h}$: 113.5-fold↑(vs. crystalline API) in dogs	Kushida et al. (2002)
HO-221 (Green cross/Mitsubishi Tanabe)	0.055 μg/mL	N/A	N/A	C_{max}: 7.4-fold↑; $AUC_{0-48\,h}$: 6.6-fold↑(vs. micronized API, 0.32 μm) in dogs	Kondo et al. (1994)
Ibuprofen	53 μg/mL (pH 1.2) 433 μg/mL (pH 5.5) 2010 μg/mL (pH 6.8)	4.5 (acid)	II	C_{max}: 10.0-fold↑; AUC: 10.2-fold↑(vs. crystalline API) in rats	Newa et al. (2008), Wu and Benet (2005)
Itraconazole	~0.001 μg/mL (neutral pH) ~4 μg/mL (pH 1)	1.5–2 (base, estimated), 4 (base)	II	C_{max}: 11.7-fold↑; $AUC_{0-\infty}$: 9.8-fold↑(vs. crystalline API) in rats	Van Eerdenbrugh et al. (2009)
LAB687 (Novartis)	0.17 μg/mL	–	II	C_{max}: 6.3-fold↑; $AUC_{0-48\,h}$: 10.1-fold↑(vs. micronized API) in dogs	Dannenfelser et al. (2004)
Mebendazole	0.95 μg/mL	N/A	II	C_{max}: 3.0-fold↑; $AUC_{0-8\,h}$: 5.9-fold↑(vs. physical mixture) in rabbits	Chiba et al. (1991), Wu and Benet (2005)
MFB-1041 (Roussel Morishita/Ajinomoto)	1.2 μg/mL	N/A	N/A	AUC: 6.0–16.9-fold↑(vs. crystalline API) in dogs	Kai et al. (1996)
Nimodipine	3.86 μg/mL 8.4 μg/mL (0.1 M HCl)		II	C_{max}: 2.7-fold↑; AUC: 2.9-fold↑(vs. crystalline API) in dogs	Sun et al. (2008), Zheng et al. (2007)
Nobiletin	16.2 μg/mL	–	N/A	C_{max}: 7.0-fold↑; AUC_{0-inf}: 9.2-fold↑(vs. crystalline API) in rat	Onoue et al. (2011)
Probucol	5 ng/mL	13.5 (acid)	N/A	BA: 5.7–38.2-fold↑(vs. crystalline API) in rabbits	Kubo et al. (2009)
Ritonavir	400 μg/mL (0.1 N HCl) 1 μg/mL (pH 6.8)	1.76 (base), 2.56 (base)	II	C_{max}: 14.9-fold↑; $AUC_{0-\infty}$: 6.1-fold↑(vs. crystalline API) in rats C_{max}: 13.7-fold↑; $AUC_{0-\infty}$: 22-fold↑(vs. crystalline API) in dogs	Sinha et al. (2010), Wu and Benet (2005) Gimenez et al. (2004), Law et al. (2004)
Tacrolimus	1–2 μg/mL	–	II	C_{max}: 10.0-fold↑; $AUC_{0-8\,h}$: 9.9-fold↑(vs. crystalline API) in dogs	Wu and Benet (2005), Yamashita et al. (2003)

API, active pharmaceutical ingredient; AUC, area under the curve of plasma or serum concentration vs. time; BA, bioavailability; C_{max}, maximum concentration; IR, immediate-release; N/A, not available; PK, pharmacokinetic

Table 2
Examples of clinically used delivery options for oral administration.

Active ingredients	Delivery options	Trade name	Developer	Approved date (FDA)
Griseofulvin	Solid dispersion	Gris-PEG®	PEDINOL	1975
Isotretinoin	SEDDS	Accutane®[a]	ROCHE	1982
Nabilone	Solid dispersion	Cesamet®	MEDA PHARMS	1985
Nimodipine	Solid dispersion	Nimotop®[a]	BAYER	1988
Nilvadipine	Solid dispersion	Nivadil®	ASTELLAS	1989[b]
Cyclosporin A	SEDDS	Sandimmune®	NOVARTIS	1990
Itraconazole	Solid dispersion	Sporanox®	JANSSEN	1992
Tacrolimus	Solid dispersion	Prograf®	ASTELLAS	1994
Cyclosporin A	SEDDS	Neoral®	NOVARTIS	1995
Ritonavir	SEDDS	Norvir®	ABBOTT	1996
Saquinavir	SEDDS	Fortovase®[a]	ROCHE	1997
Troglitazone	Solid dispersion	Rezulin®[a]	PFIZER	1997
Amprenavir	SEDDS	Agenerase®[a]	GLAXOSMITHKLINE	1999
Cyclosporin A	SEDDS	Gengraf®	ABBOTT	2000
Sirolimus	Nanoparticle (NanoCrystal®)	Rapamune®	WYETH	2000
Aprepitant	Nanoparticle (NanoCrystal®)	Emend®	MERCK	2003
Fenofibrate	Nanoparticle (NanoCrystal®)	TriCor®	ABBOTT	2003
Rosuvastatin calcium	Solid dispersion	Crestor®	ASTRAZENECA	2003
Tretinoin	SEDDS	Vesanoid®[a]	ROCHE	2004
Fenofibrate	Nanoparticle (IDD-P®)	Triglide®	SHIONOGI	2005
Liponavir/Ritonavir	Solid dispersion	Kaletra®	ABBOTT	2005
Megestrol acetate	Nanoparticle (NanoCrystal®)	Megace® ES	PAR PHARM	2005
Tipranavir	SEDDS	Aptivus®	BOEHRINGER INGELHEIM	2005
Etravirine	Solid dispersion	Intelence®	TIBOTEC	2008
Ritonavir	Solid dispersion	Norvir®	ABBOTT	2010
Everolimus	Solid dispersion	Certican®/Zortress®	NOVARTIS	2010

FDA, U.S. Food and Drug Administration; SEDDS, self-emulsifying drug delivery systems.
[a] Discontinued product in USA.
[b] Approved date in Japan.

enhancement in the solubility in JP 2 medium compared with ER-34122 alone, and both C_{max} and AUC after oral administration of the amorphous formulation were ca. 100 times higher than those of pure drug in dog.

Generally, ASD formulations tend to be chemically and physically less stable than the corresponding crystalline solid. The transformation from amorphous form to crystalline form in ASD formulation would lead to a reduction of oral bioavailability of the incorporated drugs. In contrast to the CSD formulations, the ASD approaches might be unsuitable for amorphous drugs with low stability.

3.4. Cyclodextrin complexation

Cyclodextrins are oligosaccharides containing a relatively hydrophobic central cavity and hydrophilic outer surface (Loftsson and Brewster, 1996). Cyclodextrins have been widely used in pharmaceutical product development, and there are currently more than 10 marketed cyclodextrin-containing solid dosage forms. Cyclodextrins and their derivatives increase the apparent solubility of poorly water-soluble drugs by forming inclusion complexes. Numerous studies have demonstrated the enhancement of the oral bioavailability of poorly water-soluble drugs by the cyclodextrin inclusion complex (Rajewski and Stella, 1996). The physical mixture of drug and cyclodextrins has been reported to show no or limited bioavailability enhancement after oral administration. However, enhanced bioavailability was observed by forming complex of drug and cyclodextrins, and the AUC enhancement ratio by complexation has been reported to be 1.1–46-fold compared with that of control formulations such as crystalline drugs and lyophilized drugs (Brewster and Loftsson, 2007).

3.5. Self-emulsification

In recent years, self-emulsification drug delivery systems (SEDDS) have been utilized to enhance the oral bioavailability of poorly water-soluble drugs, especially for highly lipophilic drugs. Self-emulsification formulations are isotropic mixtures of oil, surfactant, cosolvent, and solubilized drug (Gursoy and Benita, 2004). These formulations can rapidly form oil in water (w/o) fine emulsions when dispersed in aqueous phase under mild agitation. SEDDS are additionally classified into self-microemulsification drug delivery systems (SMEDDS) and self-nanoemulsification drug delivery systems (SNEDDS) according to the size range of their oil droplets (Kohli et al., 2010). SMEDDS form microemulsions ranging in droplet size from 100 to 250 nm. Finer microemulsions of less than 100 nm can be obtained using SNEDDS. The rapid emulsification of these formulations in the gastrointestinal tract can provide both improved oral bioavailability and a reproducible plasma concentration profile. The droplet size of the emulsion would influence the extent of absorption of the orally administered drugs. Neoral®, a cyclosporin SNEDDS formulation, is a good example of the effectiveness of the utilization of droplets of a smaller size. Neoral® showed increased C_{max} and AUC compared with Sandimmune®, a coarse SMEDDS formulation, in human (Mueller et al., 1994). SEDDS would require a relatively high intrinsic lipophilicity of the drug substance since the active ingredient should be dissolved in a limited amount of oil. High chemical stability of the dissolved drug in oil phase would also be required for the lipid formulations.

3.6. pH modification

pH modification in solid dosage forms is considered to be an alternative option for an ionizable drug to improve the solubility and dissolution rate. The pH change significantly influences the saturation solubility of an ionizable drug by dissociation, as described in Section 3.2.1. The incorporation of pH modifiers in the dosage form can alter the microenvironmental pH. Microenvironment is a term used to represent a microscopic layer surrounding a solid particle in which the solid forms a saturated solution of adsorbed water (Stephenson et al., 2011). The microenvironmental pH would affect the performance of the solid dosage form, such as the chemical stability of the drug substance and the dissolution profile (Badawy and Hussain, 2007). There have been several studies

demonstrating the pH-independent release of basic drugs form controlled release dosage forms by using pH modification technologies (Kranz et al., 2005; Streubel et al., 2000; Tatavarti and Hoag, 2006). However, the examples of application of pH modification system to IR formulation are limited (Badawy et al., 2006). BMS-561389 (razaxaban, Bristol-Myers Squibb) is a weak basic drug with poor intrinsic solubility (~0.2 μg/mL). BMS-561389 showed an enhanced dissolution rate from IR tablet by incorporating tartaric acid in the tablet compared with that of the tablet without tartaric acid under non-sink condition (pH 5.5). Furthermore, the tartaric acid-containing tablets showed significant improvements in AUC and C_{max} compared with the control tablets in famotidine-pretreated dogs. These results suggested that pH modification in dosage form could reduce the variability in the absorption of administered drugs.

The solubility, dissolution rate, and pK_a of pH modifier would influence the dissolution rate of the drug. To obtain the complete dissolution of the drug from dosage form, the pH modifier may need to coexist with the drug particles in tablet or granule until the containing drug is completely dissolved. Accordingly, the excipients and manufacturing methods would affect the dissolution performance of the drug from the pH-modified solid dosage forms. The estimation of the microenvironmental pH in the dosage form is thought to be helpful in designing pH-modified dosage forms.

4. Conclusions and future outlook

Several types of approaches have been proposed to improve the aqueous solubility of poorly water-soluble drugs. In particular, for BSC class II drugs, increasing their solubility and/or dissolution rate would be a promising approach to enhance the oral bioavailability. In the preformulation research phase, approaches for improving dissolution behavior of drug candidates would include salt formation, cocrystal formation, and utilization of metastable crystalline forms. In the pharmaceutical industry, it is generally preferable to select the most thermodynamically stable crystalline form to avoid the polymorphic transformation from metastable form to more stable forms during manufacturing and storage. The selection of the metastable form would be challenging for further drug product development because of its thermodynamic instability. Since the most thermodynamically stable crystalline forms could be obtained from salt and cocrystal, these approaches would be preferable from an industrial perspective. Conventional salt screening is performed by slow cooling, solvent evaporation and slurry methods in multiwell plate. Whereas, the most promising methods to reveal cocrystal formation were reported as slurry and co-grinding methods (Zhang et al., 2007). However, these screening methods generally require a relatively large amount of bulk and take a long time compared with conventional salt screening methods. Cocrystal formation would provide an alternative solution for improving the physicochemical properties of poorly water-soluble drugs; therefore, the establishment of more efficient screening methods is expected in the near future.

In the phase of formulation design, particle size reduction, amorphization, emulsification, cyclodextrin complexation, and pH modification would be viable formulation options to improve the dissolution behavior of poorly water-soluble drugs. Micronization of drug particles is commonly used to enhance the dissolution rate of a drug. If the pulverization of the drug particle to micron size does not provide sufficient absorption, nanocrystal technology could be an alternative option to obtain higher absorption of drugs. Formulation technologies based on solid dispersion and SEDDS have been applied to commercial products since the 1970s–1980s. Over the past decade, the breakthrough in nanocrystal technology has provided nanocrystal formulations on the market, such as Rapamune®, Emend®, TriCor®, Triglide®, and Megace® ES. In addition to solid dispersions, SEDDS formulations, and cyclodextrin-containing formulations, nanocrystal formulations have been considered as one of the viable options for the final market image formulation. In spite of various attractive formulation strategies, use of each delivery option might be limited by various factors. The nanocrystal approach employing wet-milling techniques might be unsuitable for drug substances with low melting points since the generation of friction heat would result in partial amorphization during the wet-milling process. Liquid formulation, for example, SEDDS, might be unsuitable for drugs with low solubility in lipid excipients and with low stability in the liquid state. The amorphous approach might be unsuitable for drug substances with low chemical and physical stability since amorphous solids are typically unstable compared with crystalline solids. Thus, each molecular/physicochemical property of the drug substance, as well as the nominated clinical dose, could affect the strategic selection of delivery options.

In general, salt formation, micronization, and pH modification in dosage forms are categorized into conventional technologies, and other technologies, such as nanocrystal formation, amorphization, and SEDDS, can be identified as non-conventional technologies. These non-conventional formulations can be prepared in laboratory-scale experiments; however, scale-up manufacturing might be problematic. In addition, in order to supply a large amount of pharmaceutical products to the market, these non-conventional technologies require extensive investment in the manufacturing process, including spray dryer, hot melt extruder, bead milling equipment, and high-pressure homogenizer. There is also a very limited scalable process available for manufacturing some non-conventional formulations. In contrast, several scalable manufacturing processes have been developed to produce ASD formulations, which include the melting method, the solvent-evaporation method, and the solvent-wetting method. Considering the current situation of the technologies available for poorly water-soluble drugs, the ASD approach might be promising from the viewpoint of scalability, as well as a marked improvement in dissolution behavior and oral bioavailability.

In conclusion, a number of delivery options have been developed for improving the physicochemical and pharmacokinetic behaviors of poorly water-soluble drugs in academic and industrial research. A better understanding of the physicochemical properties of drug substances and the limitations of each delivery option would lead to efficient formulation development for poorly water-soluble drugs.

References

Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical Research 12, 413–420.

Artursson, P., Palm, K., Luthman, K., 2001. Caco-2 monolayers in experimental and theoretical predictions of drug transport. Advanced Drug Delivery Reviews 46, 27–43.

Atkinson, R.M., Bedford, C., Child, K.J., Tomich, E.G., 1962. Effect of particle size on blood griseofulvin-levels in man. Nature 193, 588–589.

Avdeef, A., 2007. Solubility of sparingly-soluble ionizable drugs. Advanced Drug Delivery Reviews 59, 568–590.

Badawy, S.I., Gray, D.B., Zhao, F., Sun, D., Schuster, A.E., Hussain, M.A., 2006. Formulation of solid dosage forms to overcome gastric pH interaction of the factor Xa inhibitor, BMS-561389. Pharmaceutical Research 23, 989–996.

Badawy, S.I., Hussain, M.A., 2007. Microenvironmental pH modulation in solid dosage forms. Journal of Pharmaceutical Sciences 96, 948–959.

Bak, A., Gore, A., Yanez, E., Stanton, M., Tufekcic, S., Syed, R., Akrami, A., Rose, M., Surapaneni, S., Bostick, T., King, A., Neervannan, S., Ostovic, D., Koparkar, A., 2008. The co-crystal approach to improve the exposure of a water-insoluble compound: AMG 517 sorbic acid co-crystal characterization and pharmacokinetics. Journal of Pharmaceutical Sciences 97, 3942–3956.

Blagden, N., de Matas, M., Gavan, P.T., York, P., 2007. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advanced Drug Delivery Reviews 59, 617–630.

Brewster, M.E., Loftsson, T., 2007. Cyclodextrins as pharmaceutical solubilizers. Advanced Drug Delivery Reviews 59, 645–666.

Chen, Y., Zhang, G.G., Neilly, J., Marsh, K., Mawhinney, D., Sanzgiri, Y.D., 2004. Enhancing the bioavailability of ABT-963 using solid dispersion containing Pluronic F-68. International Journal of Pharmaceutics 286, 69–80.
Chiba, Y., Kohri, N., Iseki, K., Miyazaki, K., 1991. Improvement of dissolution and bioavailability for mebendazole, an agent for human echinococcosis, by preparing solid dispersion with polyethylene glycol. Chemical & Pharmaceutical Bulletin 39, 2158–2160.
Childs, S.L., Stahly, G.P., Park, A., 2007. The salt-cocrystal continuum: the influence of crystal structure on ionization state. Molecular Pharmaceutics 4, 323–338.
Chiou, W.L., Riegelman, S., 1971. Pharmaceutical applications of solid dispersion systems. Journal of Pharmaceutical Sciences 60, 1281–1302.
Cook, J., Addicks, W., Wu, Y.H., 2008. Application of the biopharmaceutical classification system in clinical drug development—an industrial view. The AAPS Journal 10, 306–310.
Dannenfelser, R.M., He, H., Joshi, Y., Bateman, S., Serajuddin, A.T., 2004. Development of clinical dosage forms for a poorly water soluble drug I: Application of polyethylene glycol-polysorbate 80 solid dispersion carrier system. Journal of Pharmaceutical Sciences 93, 1165–1175.
EMEA, 2010. Guideline on the investigation of bioequivalence. Avaiable at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf (Last accessed 13 April 2011).
Fakes, M.G., Vakkalagadda, B.J., Qian, F., Desikan, S., Gandhi, R.B., Lai, C., Hsieh, A., Franchini, M.K., Toale, H., Brown, J., 2009. Enhancement of oral bioavailability of an HIV-attachment inhibitor by nanosizing and amorphous formulation approaches. International Journal of Pharmaceutics 370, 167–174.
Fasano, A., 1998. Innovative strategies for the oral delivery of drugs and peptides. Trends in Biotechnology 16, 152–157.
FDA, 2000. Guidance for Industry, Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf (Last accessed 13 April 2011).
Fukushima, K., Terasaka, S., Haraya, K., Kodera, S., Seki, Y., Wada, A., Ito, Y., Shibata, N., Sugioka, N., Takada, K., 2007. Pharmaceutical approach to HIV protease inhibitor atazanavir for bioavailability enhancement based on solid dispersion system. Biological & Pharmaceutical Bulletin 30, 733–738.
Galia, E., Horton, J., Dressman, J.B., 1999. Albendazole generics—a comparative in vitro study. Pharmaceutical Research 16, 1871–1875.
Gimenez, F., Fernandez, C., Mabondzo, A., 2004. Transport of HIV protease inhibitors through the blood-brain barrier and interactions with the efflux proteins, P-glycoprotein and multidrug resistance proteins. Journal of Acquired Immune Deficiency Syndrome 36, 649–658.
Gursoy, R.N., Benita, S., 2004. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedicine & Pharmacotherapy 58, 173–182.
Guzman, H.R., Tawa, M., Zhang, Z., Ratanabanangkoon, P., Shaw, P., Gardner, C.R., Chen, H., Moreau, J.P., Almarsson, O., Remenar, J.F., 2007. Combined use of crystalline salt forms and precipitation inhibitors to improve oral absorption of celecoxib from solid oral formulations. Journal of Pharmaceutical Sciences 96, 2686–2702.
Hanafy, A., Spahn-Langguth, H., Vergnault, G., Grenier, P., Tubic Grozdanis, M., Lenhardt, T., Langguth, P., 2007. Pharmacokinetic evaluation of oral fenofibrate nanosuspensions and SLN in comparison to conventional suspensions of micronized drug. Advanced Drug Delivery Reviews 59, 419–426.
Hancock, B.C., Parks, M., 2000. What is the true solubility advantage for amorphous pharmaceuticals? Pharmaceutical Research 17, 397–404.
He, C.X., He, Z.G., Gao, J.Q., 2010a. Microemulsions as drug delivery systems to improve the solubility and the bioavailability of poorly water-soluble drugs. Expert Opinion on Drug Delivery 7, 445–460.
He, X., Pei, L., Tong, H.H., Zheng, Y., 2010b. Comparison of spray freeze drying and the solvent evaporation method for preparing solid dispersions of baicalein with pluronic F68 to improve dissolution and oral bioavailability. AAPS PharmSciTech.
Hecq, J., Deleers, M., Fanara, D., Vranckx, H., Boulanger, P., Le Lamer, S., Amighi, K., 2006. Preparation and in vitro/in vivo evaluation of nano-sized crystals for dissolution rate enhancement of ucb-35440-3, a highly dosed poorly water-soluble weak base. European Journal of Pharmaceutics and Biopharmaceutics 64, 360–368.
Horter, D., Dressman, J.B., 2001. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Advanced Drug Delivery Reviews 46, 75–87.
Huang, L.F., Tong, W.Q., 2004. Impact of solid state properties on developability assessment of drug candidates. Advanced Drug Delivery Reviews 56, 321–334.
Jamzad, S., Fassihi, R., 2006. Role of surfactant and pH on dissolution properties of fenofibrate and glipizide—a technical note. AAPS PharmSciTech 7, E33.
Jia, L., Wong, H., Cerna, C., Weitman, S.D., 2002. Effect of nanonization on absorption of 301029: ex vivo and in vivo pharmacokinetic correlations determined by liquid chromatography/mass spectrometry. Pharmaceutical Research 19, 1091–1096.
Jia, L., Wong, H., Wang, Y., Garza, M., Weitman, S.D., 2003. Carbendazim: disposition, cellular permeability, metabolite identification, and pharmacokinetic comparison with its nanoparticle. Journal of Pharmaceutical Sciences 92, 161–172.
Jinno, J., Kamada, N., Miyake, M., Yamada, K., Mukai, T., Odomi, M., Toguchi, H., Liversidge, G.G., Higaki, K., Kimura, T., 2006. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. Journal of Controlled Release 111, 56–64.
Jinno, J., Kamada, N., Miyake, M., Yamada, K., Mukai, T., Odomi, M., Toguchi, H., Liversidge, G.G., Higaki, K., Kimura, T., 2008. *In vitro–in vivo* correlation for wet-milled tablet of poorly water-soluble cilostazol. Journal of Controlled Release 130, 29–37.
Joshi, H.N., Tejwani, R.W., Davidovich, M., Sahasrabudhe, V.P., Jemal, M., Bathala, M.S., Varia, S.A., Serajuddin, A.T., 2004. Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol-polysorbate 80 mixture. International Journal of Pharmaceutics 269, 251–258.
Jounela, A.J., Pentikainen, P.J., Sothmann, A., 1975. Effect of particle size on the bioavailability of digoxin. European Journal of Clinical Pharmacology 8, 365–370.
Jung, M.S., Kim, J.S., Kim, M.S., Alhalaweh, A., Cho, W., Hwang, S.J., Velaga, S.P., 2010. Bioavailability of indomethacin-saccharin cocrystals. The Journal of Pharmacy and Pharmacology 62, 1560–1568.
Kai, T., Akiyama, Y., Nomura, S., Sato, M., 1996. Oral absorption improvement of poorly soluble drug using solid dispersion technique. Chemical & Pharmaceutical Bulletin 44, 568–571.
Kaushal, A.M., Gupta, P., Bansal, A.K., 2004. Amorphous drug delivery systems: molecular aspects, design, and performance. Critical Reviews in Therapeutic Drug Carrier System 21, 133–193.
Kawabata, Y., Yamamoto, K., Debari, K., Onoue, S., Yamada, S., 2010. Novel crystalline solid dispersion of tranilast with high photostability and improved oral bioavailability. European Journal of Pharmaceutical Sciences 39, 256–262.
Kennedy, M., Hu, J., Gao, P., Li, L., Ali-Reynolds, A., Chal, B., Gupta, V., Ma, C., Mahajan, N., Akrami, A., Surapaneni, S., 2008. Enhanced bioavailability of a poorly soluble VR1 antagonist using an amorphous solid dispersion approach: a case study. Molecular Pharmaceutics 5, 981–993.
Kesisoglou, F., Panmai, S., Wu, Y., 2007. Nanosizing—oral formulation development and biopharmaceutical evaluation. Advance Drug Delivery Review 59, 631–644.
Kohli, K., Chopra, S., Dhar, D., Arora, S., Khar, R.K., 2010. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discovery Today 15, 958–965.
Kohri, N., Yamayoshi, Y., Xin, H., Iseki, K., Sato, N., Todo, S., Miyazaki, K., 1999. Improving the oral bioavailability of albendazole in rabbits by the solid dispersion technique. The Journal of Pharmacy and Pharmacology 51, 159–164.
Kondo, N., Iwao, T., Hirai, K., Fukuda, M., Yamanouchi, K., Yokoyama, K., Miyaji, M., Ishihara, Y., Kon, K., Ogawa, Y., et al., 1994. Improved oral absorption of enteric coprecipitates of a poorly soluble drug. Journal of Pharmaceutical Sciences 83, 566–570.
Kondo, N., Iwao, T., Masuda, H., Yamanouchi, K., Ishihara, Y., Yamada, N., Haga, T., Ogawa, Y., Yokoyama, K., 1993. Improved oral absorption of a poorly water-soluble drug, HO-221, by wet-bead milling producing particles in submicron region. Chemical & Pharmaceutical Bulletin 41, 737–740.
Kranz, H., Guthmann, C., Wagner, T., Lipp, R., Reinhard, J., 2005. Development of a single unit extended release formulation for ZK 811 752, a weakly basic drug. European Journal of Pharmaceutical Sciences 26, 47–53.
Ku, M.S., 2008. Use of the biopharmaceutical classification system in early drug development. The AAPS Journal 10, 208–212.
Ku, M.S., Dulin, W., 2010. A biopharmaceutical classification-based Right-First-Time formulation approach to reduce human pharmacokinetic variability and project cycle time from First-In-Human to clinical Proof-Of-Concept. Pharmaceutical Development & Technology, 1–18.
Kubo, Y., Terashima, Y., Yagi, N., Nochi, H., Tamoto, K., Sekikawa, H., 2009. Enhanced bioavailability of probucol following the administration of solid dispersion systems of probucol-polyvinylpyrrolidone in rabbits. Biological & Pharmaceutical Bulletin 32, 1880–1884.
Kushida, I., Ichikawa, M., Asakawa, N., 2002. Improvement of dissolution and oral absorption of ER-34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenase inhibitor with anti-inflammatory activity by preparing solid dispersion. Journal of Pharmaceutical Sciences 91, 258–266.
Lakshman, J.P, Cao, Y., Kowalski, J., Serajuddin, A.T., 2008. Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. Molecular Pharmaceutics 5, 994–1002.
Law, D., Schmitt, E.A., Marsh, K.C., Everitt, E.A., Wang, W., Fort, J.J., Krill, S.L., Qiu, Y., 2004. Ritonavir-PEG 8000 amorphous solid dispersions: in vitro and in vivo evaluations. Journal of Pharmaceutical Sciences 93, 563–570.
Li, S., Wong, S., Sethia, S., Almoazen, H., Joshi, Y.M., Serajuddin, A.T., 2005. Investigation of solubility and dissolution of a free base and two different salt forms as a function of pH. Pharmaceutical Research 22, 628–635.
Lipinski, C.A., 2000. Drug-like properties and the causes of poor solubility and poor permeability. Journal of Pharmacological and Toxicological Methods 44, 235–249.
Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 2001. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews 46, 3–26.
Liu, C., Wu, J., Shi, B., Zhang, Y., Gao, T., Pei, Y., 2006. Enhancing the bioavailability of cyclosporine a using solid dispersion containing polyoxyethylene (40) stearate. Drug Development and Industrial Pharmacy 32, 115–123.
Liversidge, G.G., Cundy, K.C., 1995. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. International Journal of Pharmaceutics 125, 91–97.
Lobenberg, R., Amidon, G.L., 2000. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. European Journal of Pharmaceutics and Biopharmaceutics 50, 3–12.

Loftsson, T., Brewster, M.E., 1996. Pharmaceutical applications of cyclodextrins. 1: Drug solubilization and stabilization. Journal of Pharmaceutical Sciences 85, 1017–1025.
Müller, R.H., Peters, K., 1998. Nanosuspensions for the formulation of poorly soluble drugs: I. Preparation by a size-reduction technique. International Journal of Pharmaceutics 160, 229–237.
McNamara, D.P., Childs, S.L., Giordano, J., Iarriccio, A., Cassidy, J., Shet, M.S., Mannion, R., O'Donnell, E., Park, A., 2006. Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. Pharmaceutical Research 23, 1888–1897.
Mosharraf, M., Nyström, C., 1995. The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. International Journal of Pharmaceutics 122, 35–47.
Mueller, E.A., Kovarik, J.M., van Bree, J.B., Tetzloff, W., Grevel, J., Kutz, K., 1994. Improved dose linearity of cyclosporine pharmacokinetics from a microemulsion formulation. Pharmaceutical Research 11, 301–304.
Newa, M., Bhandari, K.H., Kim, J.O., Im, J.S., Kim, J.A., Yoo, B.K., Woo, J.S., Choi, H.G., Yong, C.S., 2008. Enhancement of solubility, dissolution and bioavailability of ibuprofen in solid dispersion systems. Chemical & Pharmaceutical Bulletin 56, 569–574.
Ni, N., Sanghvi, T., Yalkowsky, S., 2002. Solubilization and preformulation of carbendazim. International Journal of Pharmaceutics 244, 99–104.
Onoue, S., Sato, H., Ogawa, K., Kawabata, Y., Mizumoto, T., Yuminoki, K., Hashimoto, N., Yamada, S., 2010a. Improved dissolution and pharmacokinetic behavior of cyclosporine A using high-energy amorphous solid dispersion approach. International Journal of Pharmaceutics 399, 94–101.
Onoue, S., Takahashi, H., Kawabata, Y., Seto, Y., Hatanaka, J., Timmermann, B., Yamada, S., 2010b. Formulation design and photochemical studies on nanocrystal solid dispersion of curcumin with improved oral bioavailability. Journal of Pharmaceutical Sciences 99, 1871–1881.
Onoue, S., Uchida, A., Takahashi, H., Seto, Y., Kawabata, Y., Ogawa, K., Yuminoki, K., Hashimoto, N., Yamada, S., 2011. Development of high-energy amorphous solid dispersion of nanosized nobiletin, a citrus polymethoxylated flavone, with improved oral bioavailability. Journal of Pharmaceutical Sciences 100, 3793–3801.
Pudipeddi, M., Serajuddin, A.T., 2005. Trends in solubility of polymorphs. Journal of Pharmaceutical Sciences 94, 929–939.
Rajewski, R.A., Stella, V.J., 1996. Pharmaceutical applications of cyclodextrins. 2: In vivo drug delivery. Journal of Pharmaceutical Sciences 85, 1142–1169.
Rodriguez-Spong, B., Price, C.P., Jayasankar, A., Matzger, A.J., Rodriguez-Hornedo, N., 2004. General principles of pharmaceutical solid polymorphism: a supramolecular perspective. Advanced Drug Delivery Reviews 56, 241–274.
Scholz, A., Abrahamsson, B., Diebold, S.M., Kostewicz, E., Polentarutti, B.I., Ungell, A.L., Dressman, J.B., 2002. Influence of hydrodynamics and particle size on the absorption of felodipine in labradors. Pharmaceutical Research 19, 42–46.
Schultheiss, N., Newman, A., 2009. Pharmaceutical cocrystals and their physicochemical properties. Crystal Growth Design 9, 2950–2967.
Serajuddin, A.T., 2007. Salt formation to improve drug solubility. Advanced Drug Delivery Reviews 59, 603–616.
Shegokar, R., Muller, R.H., 2010. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. International Journal of Pharmaceutics 399, 129–139.
Sinha, S., Ali, M., Baboota, S., Ahuja, A., Kumar, A., Ali, J., 2010. Solid dispersion as an approach for bioavailability enhancement of poorly water-soluble drug ritonavir. AAPS PharmSciTech 11, 518–527.
Stella, V.J., Nti-Addae, K.W., 2007. Prodrug strategies to overcome poor water solubility. Advance Drug Delivery Review 59, 677–694.
Stephenson, G.A., Aburub, A., Woods, T.A., 2011. Physical stability of salts of weak bases in the solid-state. Journal of Pharmaceutical Sciences 100, 1607–1617.
Streubel, A., Siepmann, J., Dashevsky, A., Bodmeier, R., 2000. pH-independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets. Journal of Controlled Release 67, 101–110.
Sugano, K., Nabuchi, Y., Machida, M., Aso, Y., 2003. Prediction of human intestinal permeability using artificial membrane permeability. International Journal of Pharmaceutics 257, 245–251.
Sun, Y., Rui, Y., Wenliang, Z., Tang, X., 2008. Nimodipine semi-solid capsules containing solid dispersion for improving dissolution. International Journal of Pharmaceutics 359, 144–149.
Sylvestre, J.P., Tang, M.C., Furtos, A., Leclair, G., Meunier, M., Leroux, J.C., 2011. Nanonization of megestrol acetate by laser fragmentation in aqueous milieu. Journal of Controlled Release 149, 273–280.
Takagi, T., Ramachandran, C., Bermejo, M., Yamashita, S., Yu, L.X., Amidon, G.L., 2006. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Molecular Pharmaceutics 3, 631–643.
Tatavarti, A.S., Hoag, S.W., 2006. Microenvironmental pH modulation based release enhancement of a weakly basic drug from hydrophilic matrices. Journal of Pharmaceutical Sciences 95, 1459–1468.
Thanou, M., Verhoef, J.C., Junginger, H.E., 2001. Chitosan and its derivatives as intestinal absorption enhancers. Advanced Drug Delivery Reviews 50 (Suppl. 1), S91–S101.
Tonnesen, H.H., Masson, M., Loftsson, T., 2002. Studies of curcumin and curcuminoids, XXVII. Cyclodextrin complexation: solubility, chemical and photochemical stability. International Journal of Pharmaceutics 244, 127–135.
Tran, P.H., Tran, T.T., Lee, K.H., Kim, D.J., Lee, B.J., 2010. Dissolution-modulating mechanism of pH modifiers in solid dispersion containing weakly acidic or basic drugs with poor water solubility. Expert Opinion on Drug Delivery 7, 647–661.
Van Eerdenbrugh, B., Van Speybroeck, M., Mols, R., Houthoofd, K., Martens, J.A., Froyen, L., Van Humbeeck, J., Augustijns, P., Van den Mooter, G., 2009. Itraconazole/TPGS/Aerosil200 solid dispersions: characterization, physical stability and in vivo performance. European Journal of Pharmaceutical Sciences 38, 270–278.
Vasconcelos, T., Sarmento, B., Costa, P., 2007. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today 12, 1068–1075.
Vaughn, J.M., McConville, J.T., Crisp, M.T., Johnston, K.P., Williams 3rd, R.O., 2006. Supersaturation produces high bioavailability of amorphous danazol particles formed by evaporative precipitation into aqueous solution and spray freezing into liquid technologies. Drug Development and Industrial Pharmacy 32, 559–567.
Volpe, D.A., 2008. Variability in Caco-2 and MDCK cell-based intestinal permeability assays. Journal of Pharmaceutical Sciences 97, 712–725.
Wahlang, B., Pawar, Y.B., Bansal, A.K., 2011. Identification of permeability-related hurdles in oral delivery of curcumin using the Caco-2 cell model. European Journal of Pharmaceutics and Biopharmaceutics 77, 275–282.
WHO, 2006. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Annex. 7, WHO Technical Report Series 937. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf (Last accessed 13 April 2011).
Wu, C.Y., Benet, L.Z., 2005. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharmaceutical Research 22, 11–23.
Wu, Y., Loper, A., Landis, E., Hettrick, L., Novak, L., Lynn, K., Chen, C., Thompson, K., Higgins, R., Batra, U., Shelukar, S., Kwei, G., Storey, D., 2004. The role of biopharmaceutics in the development of a clinical nanoparticle formulation of MK-0869: a Beagle dog model predicts improved bioavailability and diminished food effect on absorption in human. International Journal of Pharmaceutics 285, 135–146.
Xia, D., Cui, F., Piao, H., Cun, D., Jiang, Y., Ouyang, M., Quan, P., 2010. Effect of crystal size on the in vitro dissolution and oral absorption of nitrendipine in rats. Pharmaceutical Research 27, 1965–1976.
Yamashita, K., Nakate, T., Okimoto, K., Ohike, A., Tokunaga, Y., Ibuki, R., Higaki, K., Kimura, T., 2003. Establishment of new preparation method for solid dispersion formulation of tacrolimus. International Journal of Pharmaceutics 267, 79–91.
Yoshizuka, K., Ohta, H., Inoue, K., Kitazaki, H., Ishimaru, M., 1996. Selective separation of flavonoids with a polyvinyl alcohol membrane. Journal of Membrane Science 118, 41–48.
Zerrouk, N., Chemtob, C., Arnaud, P., Toscani, S., Dugue, J., 2001. In vitro and in vivo evaluation of carbamazepine-PEG 6000 solid dispersions. International Journal of Pharmaceutics 225, 49–62.
Zhang, G.G., Henry, R.F., Borchardt, T.B., Lou, X., 2007. Efficient co-crystal screening using solution-mediated phase transformation. Journal of Pharmaceutical Sciences 96, 990–995.
Zhang, G.G., Law, D., Schmitt, E.A., Qiu, Y., 2004. Phase transformation considerations during process development and manufacture of solid oral dosage forms. Advanced Drug Delivery Reviews 56, 371–390.
Zheng, X., Yang, R., Zhang, Y., Wang, Z., Tang, X., Zheng, L., 2007. Part II: bioavailability in beagle dogs of nimodipine solid dispersions prepared by hot-melt extrusion. Drug Development and Industrial Pharmacy 33, 783–789.