

Expert Opinion

1. Introduction
2. Formulation strategies
3. Conclusion
4. Expert opinion

Oral formulation strategies to improve solubility of poorly water-soluble drugs

Abhishek Singh, Zelalem Ayenew Worku & Guy Van den Mooter[†]

[†]Laboratory of Pharmaceutics and Biopharmacy, Katholieke Universiteit Leuven, Leuven, Belgium

Introduction: In the past two decades, there has been a spiraling increase in the complexity and specificity of drug–receptor targets. It is possible to design drugs for these diverse targets with advances in combinatorial chemistry and high throughput screening. Unfortunately, but not entirely unexpectedly, these advances have been accompanied by an increase in the structural complexity and a decrease in the solubility of the active pharmaceutical ingredient. Therefore, the importance of formulation strategies to improve the solubility of poorly water-soluble drugs is inevitable, thus making it crucial to understand and explore the recent trends.

Areas covered: Drug delivery systems (DDS), such as solid dispersions, soluble complexes, self-emulsifying drug delivery systems (SEDDS), nanocrystals and mesoporous inorganic carriers, are discussed briefly in this review, along with examples of marketed products. This article provides the reader with a concise overview of currently relevant formulation strategies and proposes anticipated future trends.

Expert opinion: Today, the pharmaceutical industry has at its disposal a series of reliable and scalable formulation strategies for poorly soluble drugs. However, due to a lack of understanding of the basic physical chemistry behind these strategies, formulation development is still driven by trial and error.

Keywords: mesoporous inorganic carriers, nanocrystals, poorly water-soluble drugs, self-emulsifying drug delivery system, solid dispersions, soluble complexes

Expert Opin. Drug Deliv. (2011) 8(10):1361–1378

1. Introduction

Poor aqueous solubility of the active pharmaceutical ingredient (API) (< 1 µg/ml) is a persistent problem since many years only to be intensified by the advances in drug design techniques [1]. This issue is relevant for Biopharmaceutics Classification System (BCS) class II and class IV drugs. Interestingly, the paradigm of this long existing problem is now shifting to a point where some of the new chemical entities (NCE) have both poor 'aqueous and organic' solubilities [2]. The foundation stone of dissolution rate/solubility improvement is the Nernst-Brunner equation (also called 'modified Noyes–Whitney equation').

$$\frac{dM}{dt} = \frac{AD(C_s - C_t)}{h}$$

It relates dissolution rate dM/dt to saturation solubility (C_s), concentration of the drug in the medium (C_t) at time (t), surface area available for dissolution (A), diffusion coefficient of the compound (D) and thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound (h) [3]. Saturation solubility and surface area can be feasibly manipulated within the gastrointestinal tract (GIT) to

informa
healthcare

Article highlights.

- The paradigm of the long existing problem of poor solubility is now shifting to a point where some of the new chemical entities have poor 'aqueous and organic' solubilities.
- The choice of a particular strategy to improve solubility is based on multifarious factors, viz scope of the R&D program of a company, commercial factors and patentability.
- It remains difficult, if possible at all, to predict which strategy will be the best for a given poorly water-soluble drug based on its physicochemical profile.
- In spite of selection of a carrier with high T_g , thermodynamic unsteadiness together with improper kinetic stabilization lies in the crux of time-dependent physical instability of the solid dispersions.
- The performance parameters of a lipid-based system vary quite distinctly between different physiological environments as their performance is dependent on *in situ* factors too.
- Positive effects of nanocrystals can be obtained for wide range of active pharmaceutical ingredients (APIs) having diverse structure, molecular weight, steric groups and solubilities.
- Nanocrystal approach can be further coupled with other conventional approaches to possibly manipulate the spatial and temporal fate of the API.
- Mesoporous inorganic carriers can enhance the dissolution rate/solubility relatively independent of the physicochemical properties of the hydrophobic API.

This box summarizes key points contained in the article.

achieve faster dissolution rates and various Drug delivery systems (DDS) utilize this approach [4].

The choice of a particular strategy to improve solubility is based on multifarious factors, viz scope of the R&D program of a company, commercial factors and patentability. Success of a particular strategy is reflected by the number of products in the market utilizing that approach. Table 1 gives examples of oral marketed formulations of some of the strategies discussed in subsequent sections. Mesoporous inorganic carriers are still under development and hence there is no marketed product. Salt forms have not been discussed as they can be considered as NCE. Similarly, using co-crystals is not considered as a true/classical formulation strategy and so not included. Table 2 summarizes recent *in vitro* and *in vivo* studies representative of the various strategies discussed in this review.

2. Formulation strategies

2.1 Solid dispersions

Solid dispersions are solid state microfines or molecular dispersions of a drug in an inert/biocompatible crystalline or amorphous carrier. Strictly speaking, the term 'molecular dispersions' is not applicable for all the cases as the drug might be present as amorphous, crystalline or nanocrystalline precipitates.

Several types of solid dispersions have been reported, based on their physical structure. Solid dispersions can be classified as simple eutectic mixtures, solid solutions, amorphous precipitates (in crystalline, semi-crystalline or amorphous carriers) and glass solutions [5]. Simple eutectic systems are a mixture of two components that are miscible in liquid state but immiscible in solid state. The increase in dissolution is due to the formation of fine crystals of the drug dispersed in a crystalline water-soluble carrier that facilitates the liquid-solid contact between the poorly soluble API and the dissolution medium. Solid solutions are comparable with liquid solutions consisting of just one phase irrespective of the number of components and explain solid solubility of one compound into the other either at extreme compositions (discontinuous) or any composition ratio (continuous) of drug and a crystalline carrier. As the drug (solute) is not present in crystal structure, no lattice energy is required during dissolution, which ultimately leads to better saturation solubility and dissolution rate. Among solid dispersions, glass solutions are currently applied the most and differ from solid solutions in the nature of the carrier system used. They comprise a drug that is either molecularly dispersed or forms an amorphous precipitate into the amorphous carrier [4,6].

Originally designed to increase the solubility of poorly water-soluble drugs (PWSD), the applications of solid dispersions have been extended to achieve controlled release of the API. However, most of the research has been dedicated to explore the possibility of solubility augmentation. Solid dispersions do so by presenting the drug to the dissolving medium as small-sized particles, improving wetting and reducing agglomeration. In solid solutions and glass solutions where the drug is molecularly dispersed in the carrier, there is no energy obligation to disrupt the crystal lattice thus aiding the process of dissolution [7]. Alteration in the degree of crystallinity and polymorphic form might also advantageously affect the solubility of the drug [8]. Further, carrier properties can itself aid in solubility enhancement by improving wettability and inhibiting drug nucleation/precipitation from supersaturated solution [5,9-10].

The physicochemical properties of the solid dispersions and hence their performance are an interplay of the individual properties of the drug and carrier and their mutual interaction. The method of preparation is an important factor that can alter these properties. Solid dispersions can be prepared by either fusion [11] or solvent method [12]. The fusion method involves the melting/liquefaction of a drug-carrier mixture. The resulting mixture is cooled and solidified before it can be further processed to form capsules or tablets. However, the API and carrier should be mutually miscible in molten/liquid form and thermostable. This can possibly lead to attrition of many potential candidates. Hot melt extrusion is applicable to such API as the residence time is low. Calendarling following extrusion allows direct formation of tablets leading to reduction in further downstream processing steps. The solvent method involves evaporation of a common solvent

Table 1. Examples of oral marketed formulations (tablets and capsules) based on different drug delivery systems to improve solubility of poorly water-soluble drugs (PWSD).

Brand name	Company	Drug and BCS classification	Main ingredients*	Dosage form/strength
<i>Nanocrystals</i>				
Rapamune®	Wyeth Pharmaceuticals	Sirolimus (BCS class II)	PEG8000, PEG 20000, PVP K29/32, Polaxomer 188, Glyceryl Monooleate, Carnauba Wax HPC, SLS	Tablet (0.5, 1 and 2 mg)
Emend®	Merck & Co.	Aprepitant (BCS class IV)		Hard gelatin capsule (40, 80 and 125 mg)
Tricor®	Abbott	Fenofibrate (BCS class II)	Docusate sodium, SLS, Crospovidone, HPMC (3 cps)	Tablet (48 and 145 mg)
Triglide®	Sciele Pharma, Inc.	Fenofibrate (BCS class II)	Crospovidone, sodium CMC, egg lecithin, SLS	Tablet (50 and 160 mg)
<i>Solid dispersions</i>				
Gris-PEG®	Pedinal Pharmacal, Inc.	Griseofulvin (BCS class II)	PEG 6000/(PEG 400, PEG 8000)	Tablet (125 and 250 mg)
Cesamet®	Valeant Pharmaceuticals	Nabilone	PVP	Hard gelatin capsule (1 mg)
Kaletra®	Abbott	Lopinavir (BCS class II/IV), Ritonavir (BCS class IV)	PVPVA	Tablet (200 mg lopinavir/50 mg ritonavir)
Sporanox®	Janssen Pharmaceutica	Itraconazole (BCS class II)	HPMC/PEG	Hard gelatin capsule (100 mg)
Intelence®	Tibotec	Etravirine (BCS class II)	HPMC	Tablet (100 mg)
Certican®	Novartis	Everolimus	HPMC	Tablets (0.25, 0.5, 0.75, 1 mg)
Isoptin SR-E®	Abbott	Verapamil (BCS class II)	HPC/HPMC	Tablets (120, 180 and 240 mg)
Nivadil®	Fujisawa Pharmaceutical Co., Ltd	Nivaldipine	HPMC	Hard gelatin capsules (8, 16 mg)
Prograf®	Astellas Pharma US, Inc.	Tacrolimus	HPMC	Hard gelatin capsules (0.5, 1 and 5 mg)
Rezulin®	Warner-Lambert Co.	Troglitazone	PVP	Tablets (200, 300 and 400 mg)
<i>Self-emulsifying drug delivery systems</i>				
Neoral®	Novartis	Cyclosporine (BCS class II)	PG, corn oil-mono-di-triglycerides, Cremophor RH40, DL- α -tocopherol	Soft gelatin capsules (25 and 100 mg)
Panimum Bioral®	Panacea Biotech	Cyclosporine	PG, Cremophor RH40, Labrafil M1944, Triacetin	Hard gelatin capsule (50 and 100 mg)
Gengraf®	Abbott	Cyclosporine A (BCS class IV)	PEG, Cremophor EL, Polysorbate 80, PG, Sorbitan Monooleate	Hard gelatin capsule (25 and 100 mg)
Sandimmune®	Novartis	Cyclosporine A (BCS class IV)	Corn oil, Labrafil M 2125CS, gelatin, glycerol	Soft gelatin capsule (25, 50 and 100 mg)
Agenerase®	GlaxoSmithKline	Amprenavir (BCS class II)	D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS), PEG 400, PG	Soft gelatin capsule (50 mg),
Norvir®	Abbott	Ritonavir	Oleic Acid, Cremophor EL, BHT	Soft gelatin capsule (100 mg)
Aptivus®	Boehringer Ingelheim	Tipranavir (BCS class II)	Cremophor EL, PG, mono-/di-glycerides of caprylic/capric acid	Soft gelatin capsule (250 mg)

*Main ingredients for nanocrystals (potential stabilizers), solid dispersions (carrier), SEDDS (lipidic vehicle, surfactant), soluble complexes (cyclodextrin type).

BCS: Biopharmaceutics classification system; BHA: Butylated hydroxyanisole; BHT: Butylated hydroxytoluene; HPC: Hydroxypropyl cellulose; HPMC: Hydroxypropyl methylcellulose; SLS: Sodium lauryl sulfate;

PEG: Polyethylene glycol; PVP: Polyvinylpyrrolidone; vinyl acetate; SEDDS: Self-emulsifying drug delivery systems; TPGS: Tocopheryl polyethylene glycol 1000 succinate.

Table 1. Examples of oral marketed formulations (tablets and capsules) based on different drug delivery systems to improve solubility of poorly water-soluble drugs (PWSD) (continued).

Brand name	Company	Drug and BCS classification	Main ingredients*	Dosage form/strength
Fortavase®	Hoffmann La Roche, Inc.	Saquinavir (BCS class IV)	Medium chain mono- and diglycerides, PVP, DL- α -tocopherol, glycerol	Soft gelatin capsule (200 mg)
Vesanoid®	Hoffmann La Roche, Inc.	Tretinoin	Beeswax, BHA, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils and soybean oil	Soft gelatin capsule (10 mg)
Accutane®	Hoffmann La Roche, Inc.	Isotretinoin	Beeswax, BHA, Edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil	Soft gelatin capsule (10, 20 and 40 mg)
<i>Soluble cyclodextrin complexes</i>				
Opalmon®	Ono Pharmaceutical Co., Ltd	Limaprost	α -Cyclodextrin	Tablet (5 μ g)
Pansporin T®	Takeda	Cefotiam hydrochloride	α -Cyclodextrin	Tablet (100 and 200 mg)
Meiact®	Meiji Seika Kaisha Ltd	Cefditoren (BCS class IV)	β -Cyclodextrin	Tablet (100 mg)
Mobilit®	Medical Union Pharmaceuticals	Meloxicam (BCS class II)	β -Cyclodextrin	Tablet (7.5 and 15 mg)
Nicorette®	Pfizer	Nicotine	β -Cyclodextrin	Sublingual tablet (2 mg)
Nimedx®	Novartis	Nimesulide (BCS class II)	β -Cyclodextrin	Tablet (400 mg)
Nitrophen®	Nippon Kayaku	Nitroglycerin	β -Cyclodextrin	Sublingual Tablet (0.3 mg)
Omebeta®	Betafarm	Omeprazole	β -Cyclodextrin	Tablet (20 mg)
Prostarmon E®	Ono	PGE2	β -Cyclodextrin	Sublingual Tablet (0.5 mg)
Brexin®	Chiesi	Piroxicam (BCS class II)	β -Cyclodextrin	Tablet (20 mg)
Surgamyl®	Sanofi-Aventis, Roussel-Maestrelli	Tiaprofenic acid	β -Cyclodextrin	Tablet (300 mg)

*Main ingredients for nanocrystals (potential stabilizers), solid dispersions (carrier), SEDDS (lipidic vehicle, surfactant), soluble complexes (cyclodextrin type).

BCS: Biopharmaceutics classification system; BHA: Butylated hydroxyanisole; BHT: Butylated hydroxytoluene; HPC: Hydroxypropyl cellulose; HPMC: Hydroxypropyl methylcellulose; SLS: Sodium lauryl sulfate; PEG: Polyethylene glycol; PVP: Polyvinylpyrrolidone; vinyl acetate; SEDDS: Self-emulsifying drug delivery systems; TPGS: Tocopheryl polyethylene glycol 1000 succinate.

Table 2. Pharmacokinetics and release studies of different formulation strategies.

Drug name	Study detail	Results	Core claims*	Ref.
<i>Solid dispersions</i> Tranilast (TL)	Bioavailability and photostability comparison of crystalline solid dispersion of TL (CSD/TL), amorphous solid dispersion of TL (ASD/TL) and crystalline TL (C/TL)	CSD/TL showed significantly higher bioavailability and photostability than C/TL and ASD/TL respectively	Crystalline SD compared with amorphous SD could be a viable formulation option for chemically unstable PWSD drugs	[87]
Cyclosporine A (CsA)	Pharmacokinetic and dissolution behavior of amorphous SDs of CsA with eight hydrophilic polymers	CsA and HPC (SSL) SD improved bioavailability with decreasing variation compared with amorphous CsA	The amorphous SD prepared by wet-milling technology could be effective	[88]
Esomeprazole zinc (EZ)	Release study of different ratios of EZ to PEG4000 SDs	EZ/PEG4000 = 1/8, w/w significantly higher dissolution rate than EZ but SD-EZ in enteric capsule showed a lower absorption rate than Nexium (esomeprazole magnesium enteric-coated tablet)	-	[89]
Ibuprofen	Evaluation of <i>in vitro</i> release and oral bioavailability of different ratio of Ibuprofen-Poloxamer 188 (P 188) binary SDs	A significant increase in bioavailability of ibuprofen -P 188 SDs compared with ibuprofen and physical mixtures	Relatively easy, simple, quick, inexpensive and reproducible low temperature melting method to prepare SD	[90]
<i>Soluble complex</i> Saqueinavir (SQV – a weak base)	Investigation of the combined effect of pH control and methyl- β -cyclodextrin (M- β -CD) complexation on SQV solubilization and bioavailability	SQV-M- β -CD showed an enhanced bioavailability and a reduced variability in absorption by increasing solubility and inhibition of P-gp-mediated efflux compared with SQV	Integration of pH adjustment and CD complexation can be used for improving the CD solubilizing power of an ionizable drug.	[91]
Flurbiprofen (Flu)	Investigation of the effect of cinnarizine (CN) on oral bioavailability (BA) Flu and Flu/ β -CD	Flu/ β -CD with CN showed higher mean plasma level than Flu/ β -CD, Flu with CN and Flu	A competing agent such as cinnarizine can increase free drug concentration at the absorption site	[92]
Raloxifene	Evaluation of the pharmacokinetics of raloxifene-hydroxybutenyl- β -cyclodextrin (HBen- β -CD) in comparison with formulation devoid of HBen- β -CD	Significant increase in oral BA of raloxifene-HBen- β -CD relative to formulations that did not contain HBen- β -CD	Hydroxybutenyl- β -cyclodextrin, a novel solubility enhancer, was effective to improve oral BA	[93]
<i>Ordered mesoporous silica</i> Celecoxib	A silica-lipid hybrid (SLH) microcapsule system and its physicochemical and biopharmaceutical comparison	SLH microcapsule showed significantly higher fasted-state bioavailability than aqueous suspension, lipid solution, o/w and dry emulsion and Celebrex®	SLH microcapsule combine the solubilizing effect of lipids and stabilizing effect of silica nanoparticles	[94]
<i>Self-emulsifying drug delivery systems</i> Coenzyme Q10 (CoQ10)	Developing SEDDS (6% (w/v) CoQ10) and comparative assessment of release profile and bioavailability compared with the powder	SEDDS showed optimum drug release profile and significantly higher bioavailability than CoQ10 powder	Optimization of SEDDS formulation using pseudo-ternary phase diagram, particle size, drug release, solubility and pharmacokinetics	[95]

*Special features, advantages and novelty claimed by investigators.

P-gp: P-glycoprotein; PWSD: Poorly water-soluble drugs; SEDD: Self-emulsifying drug delivery; SEDDS: Self-emulsifying drug delivery systems; SSL: Super special low.

Table 2. Pharmacokinetics and release studies of different formulation strategies (continued).

Drug name	Study detail	Results	Core claims*	Ref.
Dexibuprofen	Pharmacokinetics study of spray-dried solid form of SEDDS prepared from liquid SEDDS with Aerosil 200 and pure drug	SEDDS showed significantly higher plasma concentration than dexibuprofen powder	Solid SEDDS as a novel option for oral solid dosage forms	[96]
Phenytoin	<i>In vitro</i> and <i>in vivo</i> assessment of SEDD in comparison with Dilantin® (commercial suspension)	SEDDS (chemically and physically stable under stressed conditions for at least a year) showed significantly higher relative bioavailability	-	[97]
Nitrendipine	Solid self-emulsifying (SSE) pellets prepared via extrusion/spheronization technique using liquid SEDDS, adsorbents, microcrystalline cellulose and lactose	SSE pellets showed equivalent and significantly high oral BA compared with liquid SEDDS and conventional tablets respectively	Illustrating application of extrusion/spheronization technique for large-scale production of self-emulsifying pellets	[98]
Nanocrystals Curcumin	Comparative bioavailability assessment of amorphous solid dispersion (ASD), nanoemulsion (NE) and nanocrystal solid dispersion (NCSD) Pharmacokinetics study of nanosuspensions prepared by precipitation-ultrasonication method and commercial tablet	All showed significant increase of oral BA (ASD > NCSD > NE) Dissolution rate and bioavailability are significantly higher than the commercial tablet	Nanocrystal solid dispersion improved photostability as well as bioavailability of curcumin Ease and simplicity of precipitation-ultrasonication method for preparing nanosuspension	[99] [100]

*Special features, advantages and novelty claimed by investigators.

P-gp: P-glycoprotein; PWSD: Poorly water-soluble drugs; SEDD: Self-emulsifying drug delivery, SEDDS: Self-emulsifying drug delivery systems; SSL: Super special low.

in which API and carrier are dissolved. This method warrants organic solubility of the API and carrier, involves additional solvent-removal step from the end product and processes the exhaust air for solvent recovery for environmental and economic concerns. Spray drying is one such solvent-based method.

Although exhibiting immense potential to enhance solubility and dissolution rate, solid dispersions are an 'under-realized' tool, which can undoubtedly be attributed to physical stability problems faced in dosage form development and its subsequent scale-up. In spite of selection of a carrier with high T_g (glass transition temperature), thermodynamic unsteadiness together with improper kinetic stabilization lies in the crux of time-dependent physical instability. Although kinetic immobilization of the supersaturated drug concentrations into a highly viscous matrix should prevent phase separation and crystallization, this is not the case for infinite time. Phase separation and crystallization problems are faced with ageing, even more where drug-carrier solubility is not appreciable [6]. The processes involved in the conversion of solid dispersions to tablets might be detrimental to the *in vitro* as well as *in vivo* performance. Wet granulation and compaction can result in consolidation of the tablet structure at micro-level leading to unacceptable drug release rates [13].

The dissolution rate of a solid dispersion can be carrier controlled or drug controlled. In the case of carrier-controlled dissolution, selection of a suitable carrier is crucial [8]. Two important factors to be considered while choosing a carrier are drug-carrier solubility and compatibility. Lack of drug-carrier solubility might result in phase separation in the form of amorphous or crystalline drug precipitates and drug-carrier incompatibility in formulation failure. The main carriers used in modern formulation practice include organic polymers (polyethylene glycol (PEG), polyvinyl alcohol (PVA) and their derivatives), cellulose derivatives (hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC) and hydroxypropyl methyl cellulose phthalate (HPMCP)), polyacrylates and polymethacrylates, sugars (sucrose, dextrose and galactose), surfactant carriers (Gelucire 44/14, vitamin E TPGS, Polysorbate 80 and Polyoxyl 35 Castor oil) and others such as Gelita collagel [4]. A lot of research has been conducted using these polymers alone or in combination and influence of chain length, drug/polymer ratio has been studied.

2.2 Soluble cyclodextrin complexes

Right from being discovered by Villiers in 1891 [14], there has been an ever-increasing interest in cyclodextrins (CDs) as pharmaceutical excipients. These versatile, crystalline complexing agents have the ability of increasing the solubility, bioavailability and stability of API [15-17]. They also help in odor/taste masking in addition to preventing gastrointestinal and ocular irritation [18,19]. These varied applications are possible because the API is partially encaged in the hydrophobic cavity of CD thereby experiencing a new physical and chemical microenvironment.

Originally derived from starch, CDs are truncated cone-shaped cyclic oligosaccharides containing α -D-glucopyranose units that are connected to each other by α -(1,4) glycosidic bonds. In pharmaceutically relevant natural CDs, that is, α -CD, β -CD and γ -CD, the numbers of α -D-glucopyranose units are 6, 7 and 8, respectively [20]. The cavity of the truncated cone-shaped CD is lined with skeletal carbons and etheral oxygen of the glucose residues making it slightly hydrophobic as compared with the exterior that bears the primary and secondary hydroxyl groups. Because of this structure, PWSD can enter the CD cavity by replacing the water molecules and form an inclusion complex. The presence of hydroxyl groups on the external surface of the CD molecule increases the possibility of hydrogen bonding with the drug molecules resulting in the formation of non-inclusion complexes as well [21].

The progression of drug molecule interaction with the CD moiety is a complicated one, subject to many factors and should be thermodynamically favorable. A key factor is the size of the CD cavity. Even though the CDs have the same torus height of 7.9 Å, the cavity size of α -CD, β -CD and γ -CD is different, that is, 4.7 – 5.3 Å, 6.0 – 6.5 Å and 7.5 – 8.3 Å, respectively. α -CD is not able to accommodate many drugs due to its small cavity size [20]. Larger molecules such as steroids can be accommodated by γ -CD while complex aromatics and heterocyclics fit into β -CD [22]. The stability of the complex formed is determined by the apparent stability constant, which in turn is affected by one or more of a range of factors such as charge on the drug and CD, temperature and the addition of water-soluble polymers [23-25]. The binding constants for drug:CD complex range from 0 to 10^5 M^{-1} . In a review by Carrier and co-workers, 28 studies were examined and it was found that most of them had moderate binding constant ($< 5000 \text{ M}^{-1}$) [26]. Too high a binding constant can reduce the drug bioavailability as the free drug concentration may be smaller at the absorption site as compared with the un-complexed drug alone [27,28].

Use of natural CDs to enhance solubility is constrained by their low aqueous solubility due to a strong crystal lattice. The aqueous solubility of β -CD (18.5 mg/ml) is the lowest among all the natural CDs (α -CD – 145 mg/ml, γ -CD – 232 mg/ml) due to an additional intramolecular hydrogen bond formation [29]. Since hydroxyl groups are present at the exterior of the CD molecule, it is possible to substitute them with organic moieties. It results in significant enhancement of aqueous solubility as compared with the natural CDs, which is due to the conversion of crystalline natural analogs to amorphous mixtures of isomeric derivatives [30]. The inclusion complex formation is also influenced by the type of substituent and the degree of substitution [21,31].

The aqueous solubility of PWSD whose absorption is dissolution rate limited can be increased by CDs. The nature of interaction between API and CD is non-covalent and may be a combination of electrostatic interactions, Van der Waals forces, hydrogen bonding and charge-transfer

interaction. Other contributing forces that play a lesser role in complex formation result from the removal of structured water from the CD cavity and attenuation of conformational strain [32]. As the CD molecule itself has a significantly greater solubility than the critical solubility of 0.1 mg/ml for drugs whose absorption is dissolution rate limited [33], CDs can significantly assist in formulating these drugs in aqueous vehicles and enhancing their absorption. The CD molecule carries the hydrophobic API in its cavity by forming an inclusion complex and presents it at the site of absorption in the dissolved form. As the free API and the API-CD complex are in equilibrium, the free API that permeates is replenished by the dissociation of the complex. Since no covalent bonds are involved in the API-CD complex, the rate of complex formation and dissociation is almost similar to diffusion-controlled limits [34]. This is an improvement over the non-complexed API, where the drug concentration at the site of absorption is replenished very slowly after absorption. Importantly, the solubility enhancement by CDs and their derivatives is not solely because of inclusion complex formation. The formation of nanoscale aggregates of CD, their aggregates and complexes has also been suggested to contribute in solubility enhancement. These 10 – 100 nm aggregates enhance solubility until about 5 – 10 % (w/v) when the solubility enhancement of drug-CD complex can be solely attributed to self-aggregation [35]. In another study, dynamic light scattering showed that self-aggregation of the CDs was absent in the danazol HP- β -CD system up to a CD concentration of 10% and in the danazol HP- γ -CD system up to a CD concentration of 5% [36].

Based on the dependence of solubility on ligand concentration, complexation phenomena/complexes are classified into type A and type B (Figure 1). In type A phase diagrams, the complex solubility increases with ligand concentration and it is further classified into A_L (a linear increase), A_P (positive deviation from linearity) and A_N (negative deviation from linearity). In type B phase diagrams, the complex precipitates at a critical ligand concentration and it is classified into B_I and B_S phase diagrams. In B_S -type phase diagram, the drug solubility initially increases followed by a plateau and finally the total drug solubility decreases with an increase in ligand concentration. However, B_I -type is devoid of the initial stage (i.e., increase in drug solubility) of B_S type [37].

CD inclusion complexes can be prepared by various methods such as co-precipitation, kneading, damp mixing and heating, extrusion and dry mixing. As distinct preparation methodology can result in disparate extent of complexation and amorphicity, choice of the preparation method is crucial [26].

When taking into account toxicology and kinetics of solubility enhancement, CDs have a clear advantage over the use of organic solvents as solubilizers, so called co-solvency principle. CDs solubilize compounds as a linear function of their concentration thus reducing the chances of precipitation as opposed to organic solvents that solubilize compounds often

as a logarithmic function of their concentration resulting in rapid loss of their solubilizing power on introduction into aqueous environment [38,39]. This is conform to Le Chatelier's principle, which states that if a chemical system at equilibrium experiences a change in concentration (or temperature, volume or partial pressure), then the equilibrium shifts to counteract the imposed change and a new equilibrium is established. A major limitation associated with formulation of oral solid dosage forms utilizing CDs is the size of the dose. This can make the accommodation of the required amount of CD to elicit beneficial effect on the formulation very tough if the drug loading is moderately high to high [26,40].

CDs and their derivatives are undoubtedly useful pharmaceutical aids; however, from the perspective of toxicology, they still have not achieved complete confidence of the formulators and regulatory authorities. The presence of hydroxyl groups, molecular mass ranging between 1000 and 2000 Da and very low octanol/water partition coefficient result in negligible absorption of CDs from across the biological membranes [17] thereby reducing their toxicity potential. All of the natural CDs are safe when administered orally and parenterally except for β -CD, which is not administered parenterally due to its low aqueous solubility (18.5 mg/ml; lowest among all CDs and their derivatives) and nephrotoxicity caused by it. Due to enhanced lipophilicity, safety of randomly methylated CD derivatives after oral and parenteral administration is questionable [21].

2.3 Self-emulsifying drug delivery systems

Lipid-based DDS result in enhanced and normalized drug absorption along with added benefits of inhibition of P-glycoprotein-mediated drug efflux and pre-absorptive metabolism, promotion of lymphatic transport thus preventing hepatic first-pass metabolism, GI permeability enhancement, taste masking and for sustained delivery [41]. In general, lipid-based formulations have been classified into four groups (Table 3) based on composition, dilution and digestion effects. Among these, type II and type III formulations are referred to as self-emulsifying drug delivery systems (SEDDS) and self-micro-emulsifying drug delivery systems (SMEDDS) [42]. SEDDS are an isotropic solution of PWSD, surfactant, lipid and often a co-solvent, which results in entropy-favored spontaneous emulsification on *in situ* exposure [41,42]. The ensuing oil-in-water emulsion may have droplet size ranging from $< \sim 150$ nm to as low as 10 – 20 nm [43]. However, it is very complicated to assign a specific value for the emulsion particle size to fall under the category of SMEDDS or self-nano-emulsifying drug delivery systems (SNEDDS) and the authors would prefer to stick to the size range mentioned in the lipid formulation classification system by Pouton [44]. An important problem associated with lipid-based DDS is the food effect. It was found in a study that administration of even 2-g lipid – a quantity that might easily reach GIT in two doses of a lipid-based formulation – can result in elevated

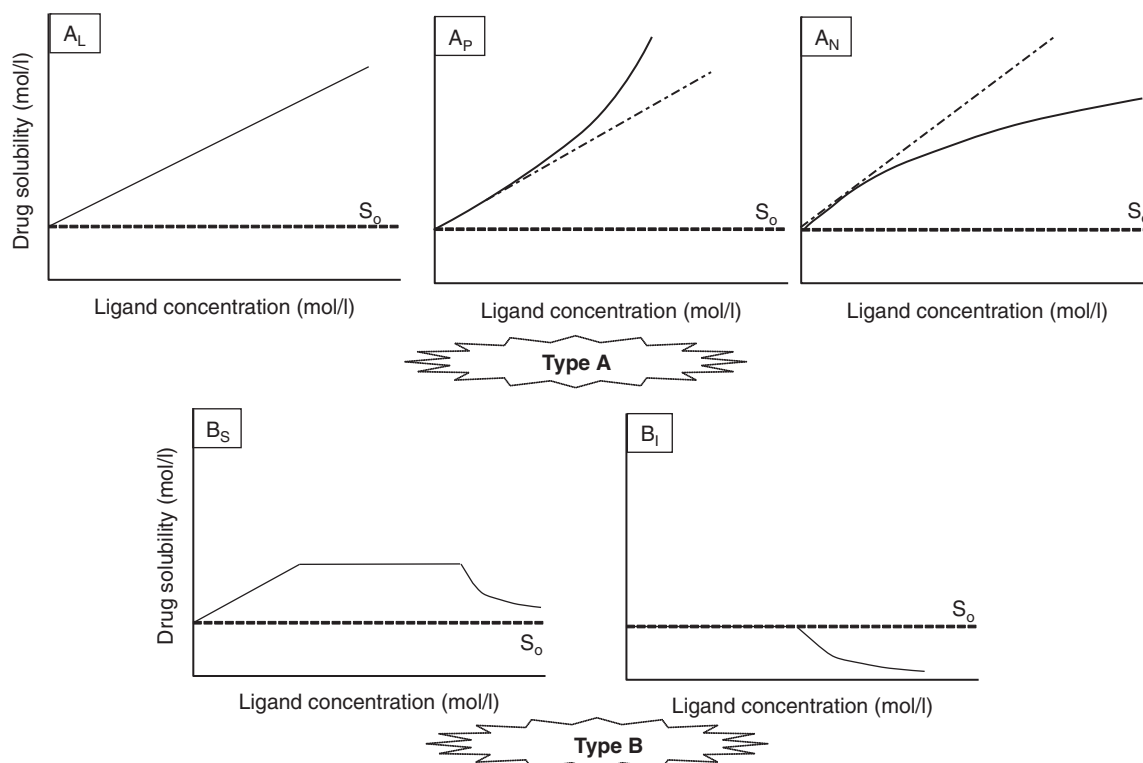


Figure 1. Higuchi and Connors classification of drug-ligand phase solubility diagram (S_0 is solubility of pure active pharmaceutical ingredient) [37].

bile levels [45]. This may result in significant variation in *in vivo* API concentration between the fed and the fasted state. The rationale for developing SEDDS is that unlike other lipid formulations, SEDDS do not depend on GI conditions for pre-absorptive emulsification and hence food effect is comparatively less/non-existent. Moreover, amphiphilic formulation components of SEDDS provide for an increased drug loading capacity of PWSD having intermediate partition coefficient, that is, $2 < \log P < 4$ [44]. Although the size of the droplets produced as a result of emulsification of SEDDS is smaller thereby increasing the surface area of the interface available for drug partitioning, a larger API absorption cannot be definitely predicted [41]. This can be ascribed to the involvement of many variables apart from emulsion droplet size in determining the final performance of a lipid-based DDS such as choice of formulation components (chemical nature, digestibility, solubility, miscibility), component ratio and the endogenous solubilizing species concentration [42].

When administered orally, SEDDS reach the GIT only to encounter aqueous GI milieu along with gentle agitation. Dilution of the formulation under these conditions coupled with the characteristics of the formulation components, that is, allowing rapid water uptake in appreciable quantities, results in self-emulsification at micro-/nanoscale, which presents the API to the intestinal glycocalyx [46]. On reaching

the duodenum, these exogenous lipids further stimulate the secretion of biliary lipids ultimately providing a continuum of lipidic microenvironment from the dosage form to emulsion droplets to the core of vesicular and micellar phases into which co-administered API may partition [47-50]. The emulsion droplets containing the API act as a reservoir from which absorption takes place either through aqueous pathway or equilibrating with, or mimicking, the endogenous intestinal surfactants comprising bile acid/bile acid mixed micelle system [43].

General choice of SEDDS formulation components at industrial scale is based chiefly on their regulatory status, solvent capacity (toward API), miscibility (with API, surrounding formulation components, GI environment), digestibility (mainly of lipid additives), capsule compatibility, chemical stability and purity [46]. In order to facilitate absorption, the API should be retained in the micellar system for which it is necessary that its $\log P$ value should not be less than 2 [43]. In addition, API mutual solubility and interaction with other formulation components such as lipid vehicle, surfactant and co-solvent are major determining factors. Lipid characteristics such as the nature of the lipid used, fatty acid chain length, the degree of unsaturation and the lipid class (fatty acid, monoglyceride, diglyceride and triglyceride) make the choice of appropriate vehicle a tricky task. Additionally, lipid carriers used may be either digestible or

Table 3. Lipid formulation classification system [46].

Attribute	Category			
	Type I	Type II	Type III	Type IV
Composition	+	+	+	-
	Oils			
	Surfactants	+	+	-
	Water insoluble			
	Water soluble	-	+	+
Characteristics	-	-	+	+
	Co-solvents			
Advantage	-	Non-dispersing, requires digestion by pancreatic lipase/co-lipase in the GIT	SEDSS/SMEDDS formed with water-soluble components	Formulation disperses typically to form a micellar solution
		GRAS status; simple; excellent capsule compatibility	Clear or almost clear dispersion;	Formulation has good solvent capacity for many drugs
Disadvantage	Formulation has poor solvent capacity unless drug is highly lipophilic	capacity on dispersion	Possible loss of solvent capacity on dispersion; less easily digested	Likely loss of solvent capacity on dispersion; may not be digestible

+Excipients that are part of the formulation.

Excipients that are not part of the formulation.

GIT: Gastrointestinal tract; GRAS: generally recognized as safe; SEDDS: Self-emulsifying drug delivery systems; SMEDDS: Self-micro-emulsifying drug delivery systems; SNEDDS: Self-nano-emulsifying drug delivery systems.

indigestible. Lipid-based DDS containing indigestible lipids might serve to reduce drug absorption as some part of API dose may be retained in its undigested part [51,52]. Surfactants used in SEDDS are generally water soluble [1,53], used at concentration above 25% (w/w) [42]. They help in solubilizing the API in SEDDS and *in situ* generation of the o/w emulsion. A number of lipids and surfactants produce highly reactive peroxide species on oxidation, which can in turn interact with the API and gelatin shell of capsule resulting in destabilization of the formulation [41]. Co-solvents such as ethanol, propylene glycol and polyethylene glycol are added to SEDDS to solubilize PWSD, which do not have appreciable lipid solubility [42]. On dilution in GI fluids, co-solvents tend to lose their solubilizing capacity. On the other hand, loss of the same property on aqueous dilution of water-soluble surfactants is less and hence the latter might be a better alternative to increase solubility of API in SEDDS [46]. However, the addition of surfactants at very high concentrations can lead to toxicity and in some cases result in the formation of viscous liquid crystalline gels at the o/w interface thereby compromising the emulsification process [42].

Not many SEDDS formulations have entered into the market due to the lack of effective *in vitro* tests that are representative of actual *in vivo* performance [42]. The performance parameters of a lipid-based system vary quite distinctly between different physiological environments as the performance of SEDDS is also dependent on *in situ* factors. Final SEDDS component mixtures may be in a liquid or semisolid state. The liquid SEDDS can be enclosed in hard/soft gelatin capsules or transformed into S-SEDDS (solid SEDDS), which can be compressed as tablets [54].

Generally, some problems are encountered with liquid SEDDS formulated as solutions or as capsules when making the laboratory to production scale transition. One of the major concerns is the questionable stability of the API and other formulation constituents in liquid phase even when it is enclosed in soft/hard gelatin shell, especially at high temperature. High ratio of the added surfactants (30 – 60%) might cause GI irritation [55]. Capsule integrity might also be compromised by some surfactants or by penetration of low molecular weight polar compounds such as propylene glycol and related co-solvents, thereby, limiting their use and warranting thorough compatibility studies between various SEDDS components and the capsule shell, especially in the case of liquid SEDDS where migration of the components is easy [46]. Hence, the alternative approach of converting liquid SEDDS into their solid counterparts opens the door of opportunities for the formulators. They also provide added advantage of convenient process control [55]. Solid SEDDS can be prepared using spray drying, spray congealing, adsorption onto solid carriers, melt granulation and hot-melt extrusion. The resultant solid particles (powder, granules, spheroids or pellets) can be formulated into tablets with acceptable content uniformity [54,55].

2.4 Nanocrystals

The nanocrystal technology for formulating PWSD has achieved commercial success in relatively short span of time, currently having five marketed products. Efficiency of these DDS is exemplified by the fact that Rapamune® tablets shows 21 % higher bioavailability than the solution form of the drug. Principally, nanocrystals are particles composed of 100% API, devoid of any carrier and form an ultrafine dispersion (nanosuspension) in liquid media [56-58]. The term 'nanocrystal' is a misnomer, as these particles can exist not only in crystalline state but also in the amorphous state, formation of which depends on the methodology of manufacturing and process conditions used [56]. On administration of a nanocrystal, formulation particles are released in the nanorange, which is of paramount importance in imparting many advantages to the nanocrystals, *viz* fast dissolution, increased kinetic saturation solubility and adhesion to biological membranes, which ultimately results in enhanced solubility and permeability [58]. Therefore, nanocrystals can be used to deliver BCS class II and class IV drugs, but are not limited to them. Positive effects of nanocrystals can be obtained for a wide range of APIs having diverse structure, molecular weight, steric groups and solubilities. Fast dissolution of nanocrystals facilitates its use for API where the absorption window is quite narrow, as the drug will dissolve quickly and in doing so avoid unsuitable environment for API absorption or stability. Other related positive factors include dosing and patient-related factors, *viz* possible dose reduction or escalation; improved dose proportionality and reproducibility; and enhanced dose tolerance, compliance and reduction in food effects [56,58]. Nanocrystal approach can be further coupled with other conventional approaches to possibly manipulate the spatial and temporal fate of the API.

Nanonization of the particles results in a decreased particle size thereby increasing surface area that ultimately leads to a substantial augmentation in both, the curvature of the particle and interface available for interaction with the surroundings. Increased curvature results in higher dissolution pressure (Kelvin equation), which favors the dissolution of the molecules at the crystal surface, consequentially increasing kinetic saturation solubility [56,58-59]. Both of the above factors result in increased flux across the gut lumen and to the blood. This is also fostered by the adhesive nature of nanoparticles due to increased Van der Waals interactions with the biological membrane/gut wall [57], which not only facilitates permeation but also assists in reducing food effects [56].

Nanocrystals can be manufactured using bottom-up or top-down approaches. Bottom-up methods include building up the crystals from a molecular level, that is, precipitation. This method involves precipitation of the API from its solution by the addition of an anti-solvent. The precipitate is separated and dried to remove residual solvent [60-62]. The resultant product can be crystalline or amorphous depending on the conditions of precipitation [56]. Even though the process involves low-cost equipment and is easy to scale up [57], presently there are no commercial products developed using the

bottom-up approach. The plausible reasons are the API insolubility in both aqueous and non-aqueous solvents, strict control of process parameters, residual solvent and most importantly nanocrystal growth to the micro-range [56,58]. Nonetheless, it is anticipated that, in future, commercial products involving amorphous nanoparticles would also enter the market. This is in lieu of the fact that technology for producing amorphous nanoparticles is already available (Nanomorph®, Abbott GmbH & Co. KG, Ludwigshafen) and can in theory provide highest increase in saturation solubility by virtue of the specific solid state properties and extremely small size [58,63], but they will need stabilization [56]. Top-down methods are the ones that have been utilized on an industrial scale, which includes milling and homogenization. Bead/pearl milling (Nanocrystals®) is one of the most widely applied technologies, in which reduction of particle size takes place when the charge (API, dispersion medium, stabilizer) in the milling chamber shears against the milling media. Even though it is a low-energy milling technique, some attrition of the milling media might take place leading to product contamination [57]. Homogenization involves high-energy techniques, *viz* Microfluidizer technology (IDD-P™ technology), piston-gap homogenization in water (Dissocubes® technology) and in aqueous mixtures or in nonaqueous media (Nanopure® technology) [56,58]. Microfluidizer technology involves jet stream homogenizers wherein collision of fluid streams in Y- or Z-shaped chambers takes place under pressure (up to 1700 bars) [56]. In Dissocubes technology, the aqueous drug dispersion is forced through the tiny opening of piston-gap homogenizers under pressure (up to 4000 bars) resulting in turbulent flow. In both of these techniques, particle size diminution is a result of high shear and cavitation forces [56]. Nanopure technology too utilizes piston-gap homogenizers; however, in this case, the API is dispersed in non-aqueous liquids, for example, oils, liquid and solid (melted) PEG, or water-reduced media (e.g., glycerol-water, ethanol-water mixtures), which makes it suitable for water-sensitive candidates. It also has extended application for thermolabile API due to the option of homogenization at low temperature. Notably, cavitation is not responsible for nanonization in Nanopure technology [58]. NANOEDGE™ technology, combination of bottom-up and top-down approach, involves precipitation followed by high-pressure homogenization and claims to prevent the growth of nanocrystals [57,58].

The methods mentioned above belong to the first-generation techniques for producing nanocrystals. Next-generation innovations to facilitate further improvements involve combinations of different processes that have been capped under the SmartCrystal® technology (Abbott GmbH & Co. KG, Ludwigshafen) [58]. These combinations can be used to facilitate faster production of nanocrystals [64]. They are better than the nanocrystals prepared by first-generation production techniques in terms of reduced size [65], enhanced physical stability and improved *in vivo* performance [66].

In addition to particle size, the stability of the formulation, *in vitro* and in turn *in vivo* fate of the nanocrystal, is also a function of its size distribution and morphology. As evident, decreasing the particle size increases the interface available to interact with the surroundings. The Gibbs free energy change is positive resulting in a thermodynamically unstable system, trying to shed this energy by agglomeration/aggregation [67]. If this happens, it would put at risk the very basic idea of nanonizing. Amorphous systems are even more problematic having a propensity to crystallize over time. In order to ensure that highly stabilized nanocrystals are obtained, stabilizers are added to the system. These stabilizers provide either electrostatic or steric barriers or both thus increasing the activation energy of the agglomeration process [68,69]. Uniform particle size distribution below 1 μm is also important as it reduces the chances of Ostwald ripening by virtue of improved homogeneity [57]. Conversion of nanocrystals into orally administrable solid dosage form is feasible using techniques such as spray drying, freeze drying, extrusion, granulation or direct filling into capsules [57,69]. However, in the marketed formulations, the API content is kept low. For example, the API content in Rapamune marketed formulation is 1 mg as compared with the total tablet weight of 365 mg. There is an upper limit to the amount of API that can be incorporated, that is, 30% of the tablet weight. On increasing the API content, there is more probability that the API particles come in contact with each other and form aggregates during compression. Using techniques such as extrusion to produce tablets where less forces are involved might be beneficial [57].

Unfortunately, the extremely small size of nanocrystals can impart many undesirable properties to the API such as inflammatory potential. There is a lot of ongoing research related to evaluation of cytotoxic potential of synthetic nanoparticles; however, there are only a limited number of reports of pharmaceutical nanocrystals. In future, as the drug categories being formulated as nanocrystals increase, a new kind of problem, that is, cytotoxicity, might emerge and relevant cytotoxicity studies will be the need of the hour.

2.5 Ordered mesoporous silica

If poorly soluble drugs can be confined in the pores of a carrier, the drug can not only be delivered at the site of absorption but also be targeted to a specific site while being saved from any unwarranted degradation. Ordered mesoporous silica (OMS) composed of silica network is one such carrier and is an emerging strategy to formulate PWSD. It can be used for many applications such as formulating PWSD for oral administration, controlled drug delivery, stimuli responsive drug delivery and osseous regeneration. OMS is biocompatible, less toxic and gives high dissolution rates of the PWSD by virtue of their structural features such as high porosity, large surface area, uniform pore shape and dimensions (pore diameter of 2 – 50 nm). High surface area allows Van der Waals interactions between the drug molecule and the carrier thereby resulting in the adsorption of API. In addition, the small

pore diameter does not allow crystallization, ensuring that the API is in non-crystalline state. As the silanol groups are present at both the external and internal surface of the pores, adsorption might occur at any one of these surfaces, which can be identified using nitrogen adsorption analysis. The presence of these silanol groups also allows extensive modifications in the chemical structure of the OMS. This is crucial in light of the fact that the interactions between the OMS and physiological fluids are governed by the chemical groups of the OMS [70].

The adsorption of API into the pores or in other words the type and amount of API retained is dependent on many variables such as pore diameter [71,72], surface area [73,74], pore volume [75,76], OMS particle size and functionalization [70]. Pore size [77,78], particle size of OMS [73,79] and functionalization also influence the drug release. This aspect is quite clear from the fact that drug release rate from OMS can be varied from the normally observed first-order kinetics by functionalizing the silica surface [80,81]. As mentioned above, the API molecules are adsorbed onto the relatively hydrophilic OMS pore walls, and on exposure to the aqueous GI environment, the water molecules displace the adsorbed API, which then diffuse across the solvent-filled pores to the bulk release medium, culminating in enhanced absorption. It should be noted that even though the release is pH independent [82], the ultimate fate of the API would rest on the pH of the bulk release medium – whether the drug remains in the supersaturated solution or is precipitated. The release mechanism of the API from OMS is generally diffusion controlled (Higuchi model) [83], and deviation is observed on functionalization of OMS. Drug release from functionalized OMS is not purely diffusion controlled and is described by the Korsmeyer-Peppas model [84].

The OMS carrier can be loaded with the drug by the soaking method, incipient wetness process [76] or melt adsorption [85]. However, since this formulation strategy is relatively new, there are no reports of the scaling-up of drug-loading procedures to our knowledge. It can be anticipated that there would certainly be some hurdles in developing and subsequent scaling-up of the formulation process. It is pertinent to mention here that whatever method is chosen for downstream processing, intactness of the ordered mesoporous structure would be of prime importance. On applying increasing pressures for compression of the OMS materials SBA-15 and COK-12, partial structural failure of pores has been observed. This is manifested by a decrease in pore volume, surface area and drug release, which is comparatively more in the case of SBA-15. Nonetheless, drug release can be partially salvaged by addition of microcrystalline cellulose before compressing the drug-loaded mesoporous carrier [86].

3. Conclusion

The playground for a formulation scientist to improve solubility/dissolution rate is to a large extent limited to the

Nernst-Brunner equation variables leaving him with limited options.

Solid dispersions have been studied extensively but have a scope for improvement in stability. Soluble complexes led to several marketed products but have limitations on the size of API molecule that can be accommodated. Drug-loaded OMS is a strategy in nascent stages, which appreciably exhibits consistent release behavior resulting in less inter-subject variation unlike solid dispersions and salt forms. Nanocrystals clearly exhibit the advantages of micro- to nano-size transition of the particle size. However, they are placed at low ranks in the formulators' decision tree. SEDDS overcome the shortcomings of other lipid-based systems in reducing the need for pre-absorptive metabolism and alleviating the need for pre-absorptive digestion for emulsification.

Future investigations can be expected to improve on the potential pitfalls for each approach thereby improving the success rate of the overall drug development process.

4. Expert opinion

One of the implications of combinatorial chemistry and *in silico* drug design used during the drug discovery phase is the increased molecular complexity leading to potent and selective compounds often with aqueous solubility that is too low to allow the development to a marketable drug. The number of pharmacologically active molecules with poor physicochemical and biopharmaceutical properties has increased steadily over the past 15 – 20 years. Currently more than 50% of all new drug candidates entering the development pipeline fail because of non-optimal physicochemical and biopharmaceutical properties. Hence, it is crucial to evaluate the potential of a compound to develop into a marketable formulation with adequate and reproducible systemic exposure as soon as possible in the drug discovery/development process. Fortunately, physicochemical profiling has currently become a part of the activities during lead optimization and candidate selection in many pharmaceutical companies.

There exist a wide variety of possible formulation strategies, each with their specific advantages and disadvantages. A SWOT (Strength, Weakness, Opportunity, Threat) analysis of the different strategies is presented in Table 4. Their aim is to improve bioavailability and stability, but the formulation process of poorly soluble compounds is still driven by trial and error. It remains difficult, if possible at all, to predict which strategy will be the best for a given PWS based on its physicochemical profile. This makes formulation development a time-consuming process since all possible formulation strategies need to be explored, without guarantee for eventual success. This is a serious threat for the pharmaceutical industry and in turn the patient.

Despite their unfavorable physical stability profile, solid dispersions have been widely investigated as a formulation strategy mainly because of their significant solubility/dissolution rate enhancement compared with crystalline

forms. The first scientific report on the use of solid dispersions as a tool to improve the solubility and dissolution rate of poorly soluble drugs was already published in 1961 by Sekiguchi and Obi [11]. In spite of the extensive research and the number of scientific papers and patents that were published during the past 50 years, few products relying on solid dispersion technology have reached the market. A whole array of excipients (carriers) can be used to stabilize the amorphous form, but it is not completely clear why a certain carrier is suitable where another one fails or why some polymeric carriers maintain the supersaturated state of the API after dissolution, while others do not. Although some general rules can be used such as selection of carriers with high T_g , it illustrates the necessity to improve our knowledge about the physics of amorphous materials. While high- and semi-throughput systems enable to empirically select carriers based on their solid dispersion potential (kinetic solubility or miscibility) and dissolution improvement, physical models to predict solid state solubility/miscibility and stability are still lacking and limit a complete breakthrough of solid dispersion technology. Selection of suitable excipients such as surfactants, lipids and co-solvents is probably more straightforward in the case of SEDDS formulations since this can be based on experimental equilibrium (thermodynamic) solubility of the API in the liquid excipients, a procedure which is currently performed using high-throughput technology.

One of the recent formulation strategies is the loading of hydrophobic drugs in mesoporous silica. It is a promising technology since it seems to be relatively independent of the physicochemical properties of the API. At present, mainly *in vitro* data are available, very few animal data and, importantly, no human data exist. Despite the encouraging *in vitro* drug release data, other hurdles will need to be tackled before this strategy can be considered as real alternative for the pharmaceutical industry. Downstream processing does not seem to be straightforward as recent investigations pointed to significant reduction in pore volume following compression [86].

Drug loading to mesoporous structures requires a sufficient solubility of the API in organic solvents. Due to increased complexity in molecular structure, more and more APIs suffer from low solubility in organic solvents next to poor aqueous solubility. In this case, nanonization can be a logical formulation strategy. Decreasing the API particle size leads not only to improved dissolution but also to a relevant increase in solubility for particles below ~ 100 nm. The large surface area of these systems implies surface stabilization to counteract the spontaneous agglomeration. More recently, efforts to transform nanosuspensions to solid dosage forms, thus reducing the stability hurdle, have been successfully accomplished.

Dosage form development goes along with *in vitro* dissolution/release test development. Although these tests are in place for quality control purposes, the story is different and more complicated when it comes to prediction for *in vivo* behavior. A reliable and predictive *in vitro* test does not exist yet to test

Table 4. SWOT analysis of formulation strategies to improve solubility of poorly water-soluble drugs.

<i>Solid dispersions</i>	
Strengths	Availability of carriers and manufacturing processes Versatility (oral (hot melt extrusion and spray drying), parenteral (freeze drying), pulmonary (spray drying))
Weaknesses	Poor powder flowability and low bulk density of spray-dried solid dispersions Physical stability problem and lack of suitable models to predict stability Understanding physics of amorphous materials
Opportunities	Exploring and further studies on the method of preparation (e.g., electrostatic spinning and surface active carriers)
Threats	API with poor solubility in aqueous and organic solvents for solvent-based method of preparation
<i>Nanocrystals</i>	
Strengths	Established, reproducible and scalable manufacturing technique API with poor solubility in aqueous and organic solvents can be formulated Reduced food effect High drug loading is feasible
Weaknesses	High manufacturing energy input Needs stabilizers and not suitable for cytotoxic drugs with narrow therapeutic index
Opportunities	Understanding the intracellular fate of nanocrystals Reference standard for assessing their safety and quality and valid method for their characterization
<i>SEDDS</i>	
Strengths	Reduced inter-subject variations and food effect More straightforward excipient selection
Weaknesses	Toxicity issues due to functional excipients (e.g., Cremophor vehicles)
<i>Ordered mesoporous silica</i>	
Strengths	Less affected by physicochemical properties of API Relatively high drug loading (~ 35%) with less stability problem
Weaknesses	Limited <i>in vivo</i> studies and hygroscopicity of silica
Opportunities	Exploring scalability and effect of manufacturing processes such as compression and granulation
Threats	API with poor solubility in aqueous and organic solvents
<i>Soluble CD complexes</i>	
Strengths	Comparatively better drug loading (~ 25 – 30% in case of HP- β -CD with API of molecular mass around 500 g/mol) Effectively improves BA due to high aqueous solubility of CD
Weaknesses	Constraints related to molecular shape/size of the API

API: Active pharmaceutical ingredient; BA: Bioavailability; CD: Cyclodextrin; SEDDS: Self-emulsifying drug delivery systems.

the *in vivo* potential of the different formulation strategies for PWSD. In addition, there is still debate about the type of animal to be used in preclinical testing.

Rational formulation design of PWSD requires in-depth knowledge about the physical chemistry of the API and the complex interplay with biological processes such as *in vivo* emulsification or nucleation inhibition. Today, fundamental but indispensable physicochemical and biopharmaceutical knowledge is lacking. Pharmaceutical companies know very well that in order to fill this intellectual gap, more investment in pharmaceutically oriented fundamental research is necessary. Unfortunately, companies can often

invest only in more basic research-oriented activities (alone or in collaboration with academia) when necessary, that is, when a problem related and linked to a development project comes up.

Declaration of interest

The authors state no conflict of interest. A Singh acknowledges the financial support by grant program Erasmus Mundus External Cooperation Window, Lot 13, India. ZA Worku acknowledges a PhD grant by IRO.

Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.

1. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *Eur J Pharm Sci* 2006;29(3-4):278-87
2. Muller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs-a review of drug nanocrystal technology and lipid nanoparticles. *J Biotechnol* 2004;113(1-3):151-70
3. Noyes AA, Whitney WR. The Rate of Solution of Solid Substances in their own Solutions. *J Am Chem Soc* 1897;19(12):930-4
4. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm* 2000;50:47-60
5. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci* 1971;60(9):1281-302
6. Janssens S, Van den Mooter G. Review: physical chemistry of solid dispersions. *J Pharm Pharmacol* 2009;61(12):1571-86
- **Detailed discussion of the physical chemistry and stability of the glass solutions.**
7. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm Res* 1997;14(12):1691-8
8. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int J Pharm* 2002;231:131-44
- **Review deliberating the carrier-/drug-controlled release mechanisms from the solid dispersions.**
9. Hilton JE, Summers M. The effect of wetting agents on the dissolution of indomethacin solid dispersion systems. *Int J Pharm* 1986;31(1-2):157-64
10. Usui F, Maeda K, Kusai A, et al. Inhibitory effects of water-soluble polymers on precipitation of RS-8359. *Int J Pharm* 1997;154(1):59-66
11. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem Pharm Bull (Tokyo)* 1961;9(11):866-72
12. Tachibana T, Nakamura A. A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of beta-carotene by polyvinylpyrrolidone. *Colloid Polym Sci* 1965;203(2):130-3
13. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J Pharm Sci* 1999;88(10):1058-66
14. Villiers A. Sur la fermentation de la fécule par l'action du ferment butyrique. *Compt Rend Acad Sci* 1891;112:536-8
15. Avdeef A, Bendels S, Tsinman O, et al. Solubility-excipient classification gradient maps. *Pharm Res* 2007;24(3):530-45
16. Kim CK, Park JS. Solubility enhancers for oral drug delivery: can chemical structure manipulation be avoided? *Am J Drug Deliv* 2004;2(2):113-30
17. Loftsson T, Jarho P, Masson M, et al. Cyclodextrins in drug delivery. *Expert Opin Drug Deliv* 2005;2(2):335-51
18. Szejtli J, Szenté L. Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins. *Eur J Pharm Biopharm* 2005;61(3):115-25
19. Lantz AW, Rodriguez MA, Wetterer SM, et al. Estimation of association constants between oral malodor components and various native and derivatized cyclodextrins. *Anal Chim Acta* 2006;557(1-2):184-90
20. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. *J Pharm Sci* 1996;85(10):1017-25
21. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. *Adv Drug Deliv Rev* 2007;59:645-66
- **Overview of the solubilizing effects of cyclodextrins including thermodynamics of complexation and supersaturation phenomenon.**
22. Valle EMMD. Cyclodextrins and their uses: a review. *Process Biochem* 2004;39(9):1033-46
23. Nagase Y, Hirata M, Wada K, et al. Improvement of some pharmaceutical properties of DY-9760e by sulfoethyl ether [beta]-cyclodextrin. *Int J Pharm* 2001;229(1-2):163-72
24. Zarzycki P, Lamparczyk H. The equilibrium constant of [beta]-cyclodextrin-phenolphthalein complex; influence of temperature and tetrahydrofuran addition. *J Pharm Biomed Anal* 1998;18(1-2):165-70
25. Cappello B, Carmignani C, Iervolino M, et al. Solubilization of tropicamide by hydroxypropyl-[beta]-cyclodextrin and water-soluble polymers: in vitro/in vivo studies. *Int J Pharm* 2001;213(1-2):75-81
26. Carrier RL, Miller LA, Ahmed I. The utility of cyclodextrins for enhancing oral bioavailability. *J Control Release* 2007;123(2):78-99
- **Excellent review of cyclodextrins as pharmaceutical solubilizers, evaluating critical quantitative parameters from twenty-eight selected studies.**
27. Szejtli J. Medicinal applications of cyclodextrins. *Med Res Rev* 1994;14(3):353-86
28. Bekers O, Uijtendaal E, Beijnen J, et al. Cyclodextrins in the pharmaceutical field. *Drug Dev Ind Pharm* 1991;17(11):1503-49
29. Loftsson T, Duchene D. Cyclodextrins and their pharmaceutical applications. *Int J Pharm* 2007;329(1-2):1-11
30. Pitha J, Milecki J, Fales H, et al. Hydroxypropyl-[beta]-cyclodextrin: preparation and characterization; effects on solubility of drugs. *Int J Pharm* 1986;29(1):73-82
31. Loftsson T, Duchene D. Cyclodextrins and their pharmaceutical applications. *Int J Pharm* 2007;329:1-11
32. Liu L, Guo QX. The driving forces in the inclusion complexation of cyclodextrins. *J Inclusion Phenom Macrocyclic Chem* 2002;42(1):1-14
33. Dressman J, Butler J, Hempenstall J, et al. The BCS: where do we go from here? *Pharm Technol* 2001;25(7):68-77
34. Stella VJ, Rao VM, Zannou EA, et al. Mechanisms of drug release from cyclodextrin complexes. *Adv Drug Deliv Rev* 1999;36(1):3-16

35. Jansook P, Kurkov SV, Loftsson T. Cyclodextrins as solubilizers: formation of complex aggregates. *J Pharm Sci* 2010;99(2):719-29
36. Thi TD, Nauwelaerts K, Baudemprez L, et al. Comparison between 2-hydroxypropyl-beta-cyclodextrin and 2-hydroxypropyl-gamma-cyclodextrin for inclusion complex formation with danazol. *J Inclusion Phenom Macrocyclic Chem* 2011;published online 25 January 2011; doi: DOI 10.1007/s10847-010-9917-y
37. Rao VM, Sanghvi R, Zhu HJ. Solubility of pharmaceutical solids. 1st edition. Elsevier; San Diego: 2009
38. Pitha J, Hoshino T, Torres-Labandeira J, et al. Preparation of drug: hydroxypropylcyclodextrin complexes by a method using ethanol or aqueous ammonium hydroxide as co-solubilizers. *Int J Pharm* 1992;80(1-3):253-8
39. Pitha J, Hoshino T. Effects of ethanol on formation of inclusion complexes of hydroxypropylcyclodextrins with testosterone or with methyl orange. *Int J Pharm* 1992;80(1-3):243-51
40. Miller LA, Carrier RL, Ahmed I. Practical considerations in development of solid dosage forms that contain cyclodextrin. *J Pharm Sci* 2007;96:1691-707
41. Hauss DJ. Oral lipid-based formulations. *Adv Drug Deliv Rev* 2007;59(7):667-76
- **Review discussing formulation modalities of the lipid-based formulations.**
42. Porter CJH, Pouton CW, Cuine JF, et al. Enhancing intestinal drug solubilisation using lipid-based delivery systems. *Adv Drug Deliv Rev* 2008;60(6):673-91
43. Morozowich W, Gao P. Improving the oral absorption of poorly soluble drugs using SEDDS and S-SEDDS formulations. In Qiu Y, Chen Y, Liu L, Zhang GGZ. editors. *Developing solid oral dosage forms: pharmaceutical theory and practice*. 1st edition. Elsevier: San Diego, CA 2009. p. 443-50
44. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and self-microemulsifying drug delivery systems. *Eur J Pharm Sci* 2000;11:S93-8
45. Kossena GA, Charman WN, Wilson CG, et al. Low dose lipid formulations: effects on gastric emptying and biliary secretion. *Pharm Res* 2007;24(11):2084-96
46. Pouton CW, Porter CJH. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. *Adv Drug Deliv Rev* 2008;60(6):625-37
47. Naylor LJ, Bakatselou V, Dressman JB. Comparison of the mechanism of dissolution of hydrocortisone in simple and mixed micelle systems. *Pharm Res* 1993;10(6):865-70
48. Dangi J, Vyas S, Dixit V. The role of mixed micelles in drug delivery. I. Solubilization. *Drug Dev Ind Pharm* 1998;24(7):681-4
49. Pedersen BL, Mullertz A, Brøndsted H, et al. A comparison of the solubility of danazol in human and simulated gastrointestinal fluids. *Pharm Res* 2000;17(7):891-4
50. Wiedmann TS, Kamel L. Examination of the solubilization of drugs by bile salt micelles. *J Pharm Sci* 2002;91(8):1743-64
51. Volpenhein R, Webb D, Jandacek R. Effect of a nonabsorbable lipid, sucrose polyester, on the absorption of DDT by the rat. *J Toxicol Environ Health* 1980;6:679-83
52. Rozman K, Ballhorn L, Rozman T. Mineral oil in the diet enhances fecal excretion of DDT in the rhesus monkey. *Drug Chem Toxicol* 1983;6(3):311-16
53. Hauss D. Oral lipid-based formulations: enhancing the bioavailability of poorly water soluble drugs. Informa Healthcare, Inc; New York: 2007
54. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. *Adv Drug Deliv Rev* 2008;60(6):734-46
55. Tang B, Cheng G, Gu JC, et al. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. *Drug Discov Today* 2008;13(13-14):606-12
56. Junghanns JUAH, Muller RH. Nanocrystal technology, drug delivery and clinical applications. *Int J Nanomedicine* 2008;3(3):295-310
57. Keck CM, Muller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. *Eur J Pharm Biopharm* 2006;62(1):3-16
- **Overview of top-down homogenization technique for nanocrystal production.**
58. Shegokar R, Muller RH. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. *Int J Pharm* 2010;399:129-39
59. Simonelli A, Mehta S, Higuchi W. Inhibition of sulfathiazole crystal growth by polyvinylpyrrolidone. *J Pharm Sci* 1970;59(5):633-8
60. List M, Sucker H. Pharmaceutical colloidal hydrosols for injection. GB2200048; 1988
61. Gassmann P, List M, Schweitzer A, et al. Hydrosols: alternatives for the parenteral application of poorly water soluble drugs. *Eur J Pharm Biopharm* 1994;40(2):64-72
62. Sucker H, Gassmann P. Improvements in pharmaceutical compositions. GB2269536A; 1994
63. Auweter H, Bohn H, Heger R, et al. Precipitated water-insoluble colorants in colloid disperse form. US6494924; 2002
64. Moschwitz J. Method for the production of ultrafine submicron suspensions. DE1020050117864; 2005
65. Moschwitz J, Lemke A. Method for the gentle production of ultrafine particle suspensions. DE1020050177778; 2005
66. Petersen R. Nanocrystals for use in topical cosmetic formulations and method of production thereof. WO2008058755; 2008
67. Gonzales-Caballero F, de Dios Garcia Lopez-Duran J. Suspension formulation. Marcel Dekker, Inc; New York: 2000
68. 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;63(6):427-40
69. Van Eerdenbrugh B, Van den Mooter G, Augustijns P. Top-down production of drug nanocrystals: nanosuspension stabilization, miniaturization and transformation into solid products. *Int J Pharm* 2008;364(1):64-75
- **A good review addressing aspect of nanosuspension stabilization along with examples of different stabilizing systems.**

70. Manzano M, Vallet-Regi MA. New developments in ordered mesoporous materials for drug delivery. *J Mater Chem* 2010;20:5593-604
71. Colilla M, Manzano M, Vallet-Regi M. Recent advances in ceramic implants as drug delivery systems for biomedical applications. *Int J Nanomedicine* 2008;3(4):403
72. Yiu HHP, Botting CH, Botting NP, et al. Size selective protein adsorption on thiol-functionalised SBA-15 mesoporous molecular sieve. *Phys Chem Chem Phys* 2001;3(15):2983-5
73. Qu F, Zhu G, Huang S, et al. Controlled release of Captopril by regulating the pore size and morphology of ordered mesoporous silica. *Microporous Mesoporous Mater* 2006;92(1-3):1-9
74. Balas F, Manzano M, Horcajada P, et al. Confinement and controlled release of bisphosphonates on ordered mesoporous silica-based materials. *J Am Chem Soc* 2006;128(25):8116-17
75. Schmidt-Winkel P, Lukens Jr WW, Zhao D, et al. Mesocellular siliceous foams with uniformly sized cells and windows. *J Am Chem Soc* 1999;121(1):254-5
76. Charnay C, Begu S, Tourne-Petieilh C, et al. Inclusion of ibuprofen in mesoporous templated silica: drug loading and release property. *Eur J Pharm Biopharm* 2004;57(3):533-40
77. Horcajada P, Ramila A, Perez-Pariente J, et al. Influence of pore size of MCM-41 matrices on drug delivery rate. *Microporous Mesoporous Mater* 2004;68(1-3):105-9
78. Mellaerts R, Aerts CA, Van Humbeeck J, et al. Enhanced release of itraconazole from ordered mesoporous SBA-15 silica materials. *Chem Commun* 2007(13):1375-7
79. Grun M, Unger KK, Matsumoto A, et al. Novel pathways for the preparation of mesoporous MCM-41 materials: control of porosity and morphology. *Microporous Mesoporous Mater* 1999;27(2-3):207-16
80. Song SW, Hidajat K, Kawi S. Functionalized SBA-15 materials as carriers for controlled drug delivery: influence of surface properties on matrix-drug interactions. *Langmuir* 2005;21(21):9568-75
81. Rosenholm JM, Linden M. Towards establishing structure-activity relationships for mesoporous silica in drug delivery applications. *J Control Release* 2008;128(2):157-64
82. Mellaerts R, Mols R, Kayaert P, et al. Ordered mesoporous silica induces pH-independent supersaturation of the basic low solubility compound itraconazole resulting in enhanced transepithelial transport. *Int J Pharm* 2008;357(1-2):169-79
83. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci* 1963;52(12):1145-9
84. Korsmeyer RW, Gurny R, Doelker E, et al. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm* 1983;15(1):25-35
85. Mellaerts R, Jammaer JAG, Van Speybroeck M, et al. Physical state of poorly water soluble therapeutic molecules loaded into SBA-15 ordered mesoporous silica carriers: A case study with itraconazole and ibuprofen. *Langmuir* 2008;24(16):8651-9
86. Vialpando M, Aerts A, Persoons J, et al. Evaluation of ordered mesoporous silica as a carrier for poorly soluble drugs: influence of pressure on the structure and drug release. *J Pharm Sci* 2011;published online 8 March 2011; doi:10.1002/jps.22535
- **Study of the influence of compression force on the intactness of the OMS materials for immediate release.**
87. Kawabata Y, Yamamoto K, Debari K, et al. Novel crystalline solid dispersion of tranilast with high photostability and improved oral bioavailability. *Eur J Pharm Sci* 2010;39(4):256-62
88. Onoue S, Sato H, Ogawa K, et al. Improved dissolution and pharmacokinetic behavior of Cyclosporine A using high-energy amorphous solid dispersion approach. *Int J Pharm* 2010;399:94-101
89. Xie Y, Xie P, Song X, et al. Preparation of esomeprazole zinc solid dispersion and study on its pharmacokinetics. *Int J Pharm* 2008;360(1-2):53-7
90. Newa M, Bhandari KH, Li DX, et al. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188. *Int J Pharm* 2007;343(1-2):228-37
91. Pathak SM, Musmade P, Dengle S, et al. Enhanced oral absorption of saquinavir with Methyl-Beta-Cyclodextrin-Preparation and in vitro and in vivo evaluation. *Eur J Pharm Sci* 2010;41:440-51
- **Investigation of the integrated approach of pH control and M-β-CD complexation to enhance solubilization of an ionizable drug in CD.**
92. Tokumura T, Muraoka A, Machida Y. Improvement of oral bioavailability of flurbiprofen from flurbiprofen/[beta]-cyclodextrin inclusion complex by action of cinnarizine. *Eur J Pharm Biopharm* 2009;73(1):202-4
93. Wempe MF, Wachter VJ, Ruble KM, et al. Pharmacokinetics of raloxifene in male Wistar-Hannover rats: influence of complexation with hydroxybutenyl-beta-cyclodextrin. *Int J Pharm* 2008;346(1-2):25-37
94. Tan A, Simovic S, Davey AK, et al. Silica-lipid hybrid (SLH) microcapsules: a novel oral delivery system for poorly soluble drugs. *J Control Release* 2009;134(1):62-70
95. Balakrishnan P, Lee BJ, Oh DH, et al. Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. *Int J Pharm* 2009;374(1-2):66-72
96. Balakrishnan P, Lee BJ, Oh DH, et al. Enhanced oral bioavailability of dexibuprofen by a novel solid self-emulsifying drug delivery system (SEDDS). *Eur J Pharm Biopharm* 2009;72(3):539-45
97. Atef E, Belmonte AA. Formulation and in vitro and in vivo characterization of a phenytoin self-emulsifying drug delivery system (SEDDS). *Eur J Pharm Sci* 2008;35(4):257-63
98. Wang Z, Sun J, Wang Y, et al. Solid self-emulsifying nitrendipine pellets: Preparation and in vitro/in vivo evaluation. *Int J Pharm* 2010;383(1-2):1-6
99. Onoue S, Takahashi H, Kawabata Y, et al. Formulation design and photochemical studies on nanocrystal solid dispersion of curcumin with improved oral bioavailability. *J Pharm Sci* 2010;99(4):1871-81
- **Reveals effectiveness of nanocrystal solid dispersions for PWSD with**

**photostability problems compared with
amorphous solid dispersions.**

100. Xia D, Quan P, Piao H, et al.
Preparation of stable nitrendipine
nanosuspensions using the
precipitation-ultrasonication method for
enhancement of dissolution and oral
bioavailability. *Eur J Pharm Sci*
2010;40:325-34

Affiliation

Abhishek Singh¹ BPharm,
Zelalem Ayenew Worku¹ MPharm &
Guy Van den Mooter^{†2} PhD

[†]Author for correspondence

¹Laboratory of Pharmacotechnology and
Biopharmacy,

Katholieke Universiteit Leuven,

Herestraat 49, bus 921,

B-3000 Leuven, Belgium

²Professor,

Laboratory of Pharmacotechnology and
Biopharmacy,

Katholieke Universiteit Leuven,

Herestraat 49, bus 921,

B-3000 Leuven, Belgium

Tel: +0032 16 330300; Fax: +0032 16 330305;

E-mail: Guy.Vandenmooter@pharm.kuleuven.be