Expert Opinion

Drug delivery strategies for poorly water-soluble drugs

Alfred Fahr† & Xiangli Liu
Friedrich-Schiller-Universität Jena, Institute for Pharmacy, Lessingstrasse 8, D-07743 Jena, Germany

The drug candidates coming from combinatorial chemistry research and/or the drugs selected from biologically based high-throughput screening are quite often very lipophilic, as these drug candidates exert their pharmacological action at or in biological membranes or membrane-associated proteins. This challenges drug delivery institutions in industry or academia to develop carrier systems for the optimal oral and parenteral administration of these drugs. To mention only a few of the challenges for this class of drugs: their oral bioavailability is poor and highly variable, and carrier development for parenteral administration is faced with problems, including the massive use of surface-active excipients for solubilisation. Formulation specialists are confronted with an even higher level of difficulties when these drugs have to be delivered site specifically. This article addresses the emerging formulation designs for delivering of poorly water-soluble drugs.

Keywords: cyclodextrin, emulsion, insoluble, liposomes, nanosuspension, solid dispersion, solid lipid nanoparticles

Expert Opin. Drug Deliv. (2007) 4(4):403-416

1. Introduction

The advances in automated synthesis, combinatorial chemistry and innovative high-throughput screening have led to the production of a vast number of potential drug candidates, as well as introducing more poorly water-soluble drugs in the pharmaceutical pipeline. It is estimated that > 40% of marketed drugs are poorly water-soluble [1,2]; among the US pharmacopeia, this share is > 30% [2]. The percentage of insoluble substances coming out of pharmaceutical chemical laboratories is up to 60% of the total. Based on the biopharmaceutics classification system (BCS, see also [201]), drug substances are classified into four categories according to their solubility and permeability properties, as shown in **Figure 1** [3,4]. For the drugs exhibiting low solubility but reasonable membrane permeability, which are categorised as BCS class II, the rate-limiting process of absorption is the drug dissolution step. Formulation plays a major role in determining the rate and extent of absorption of such drugs from the gastrointestinal tract. The bioavailability from conventional tablet formulations may be unacceptable for these drugs, which often have water-solubility of < 1 µg/ml [5]. A number of formulation strategies have been developed to improve the delivery of BCS class II drugs. They are based on either techniques to increase the drug dissolution rate or techniques to achieve sustained solubilisation of the drugs. For the poorly water-soluble drugs with poor membrane permeability, which belong to BCS class IV, formulation strategies can do little to improve their absorption due to the limited membrane permeability; the best solution to improve their bioavailability is to go back to the lead optimisation phase of drug discovery and modify their structures to obtain the appropriate physicochemical properties [6].

Proper formulation is of key importance to establish a successful product for the oral administration of a BCS class II drug. In general, the formulations for poorly

informa
healthcare

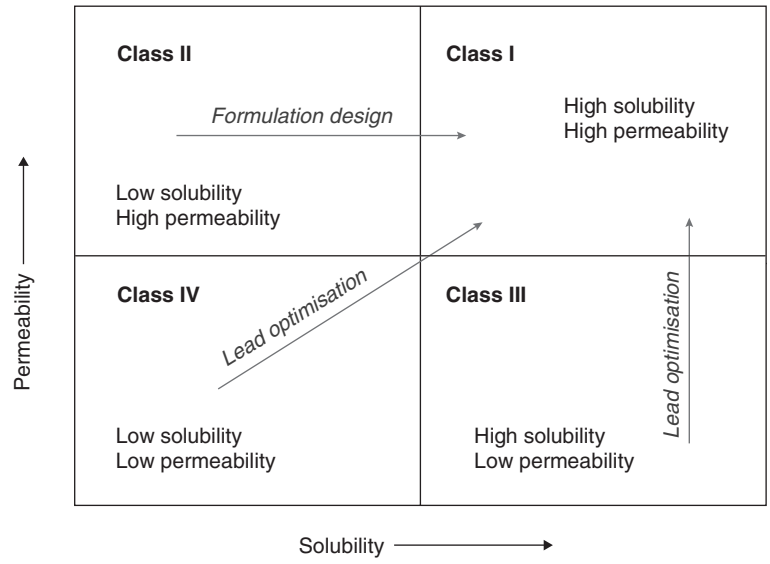

Figure 1. Biopharmaceutics classification system of drugs (modified from [5]). The absorption of BCS Class II drugs can be markedly enhanced by optimal formulation design, whereas the best solution to improve the bioavailability of BCS Class IV is to go back to the lead optimisation phase of drug discovery and modify their structures for the appropriate physicochemical properties.
BCS: Biopharmaceutics classification system.

water-soluble drugs include crystalline solid formulations, amorphous formulations and lipid formulations.

This article addresses several emerging formulation designs (**Table 1**) for the delivery of poorly water-soluble drugs (also referred to here as 'insoluble') except nanoparticulate polymer carrier systems, where a vast amount of review literature exists (e.g., [7]).

2. Solid dispersion

Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state, prepared by melting (fusion), the addition of a solvent, or the melt-solvent method, with a view to enhancing the oral bioavailability of poorly water-soluble drugs [8]. It has been demonstrated that the drug can be present in a eutectic mixture in a microcrystalline state, or molecularly dispersed in the matrix, thereby forming a solid solution [9,10]. In either case, when the solid dispersion is exposed to aqueous media and the carrier dissolved, the drug is released as very fine, colloidal particles. Due to the greatly enhanced surface area obtained this way, the dissolution rate and the bioavailability of poorly water-soluble drugs are expected to be high [11]. The bioavailability enhancement of poorly water-soluble drugs by solid dispersion compared with conventional tablets or capsules is demonstrated in **Figure 2**.

Dispersions have traditionally been formed by heating mixtures of the drug and carrier to a molten state, followed by resolidification via cooling. Alternative methods involve dissolving the components in a mutual volatile solvent followed by evaporation or dissolving the drug in a solvent such as propylene glycol and adding that to the molten carrier. A solid dispersion of nitrendipine prepared by a melt-mixing method using silica particles as carriers has showed remarkably improved dissolution properties compared with that of the original nitrendipine crystals [12]. A solid dispersion of lipophilic glyburide prepared by melt and solvent methods using PEG as a carrier has exhibited a significant increase in dissolution compared with that of pure drug [13]. The improvement of dissolution and oral absorption of a solid dispersion of ER-34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenase inhibitor, has been reported with hydroxypropylmethylcellulose as the carrier, created by a solvent method [14].

However, the melt method often requires relatively high temperatures (> 100°C), which may lead to thermal degradation of the drug. Problems with the solvent method include environmental aspects due to the use of organic solvents and health concerns because of possible residual solvents. In addition, solvent methods are time consuming and expensive because of the long processing and drying times required [8,15]. Other approaches such as melt extrusion appear to offer a number of promising features. With this method, heat is used to make thermoplastic materials pliable enough to incorporate drug particles in the polymer matrix. Intensive mixing is achieved through the shear stress created by the shear rate used. One of its advantages is that there is no need for the use of an organic solvent during the process of preparation. Moreover, a solid dispersion can be produced at a lower temperature than the melting point of the drug and the softening temperature of the polymer (carrier), preventing their decomposition. This technique has been

Table 1. Approaches to improve the solubility or to increase the available surface area for dissolution.

Physical modifications
Particle size
Micronization
Nanosuspensions
Crystal modification
Polymorphs
Pseudopolymorphs (including solvates)
Complexation / solubilization
Use of surfactants
Use of cyclodextrins
Drug dispersion in carriers
Solid dispersions (non-molecular)
Solid solutions
Eutectic mixtures

Modified from [107].

successfully used to prepare a solid dispersion of 17β-estradiol hemihydrate in 50% PVP/Gelucire 44/14 [16], itraconazole in hydroxypropylmethylcellulose [17,18] to improve the solubility and dissolution properties of these poorly water-soluble drugs.

Despite an active research interest, the commercial application of solid dispersions in dosage form design has been very limited. Only a few products, for example, a griseofulvin-in-PEG solid dispersion, Gris-PEG® (Novartis) or Lopinavir/Ritonavir tablet using a proprietary melt extrusion, Kaletra® (Soliqs) have been marketed. This low number is mainly due to the lack of a basic understanding of the properties such as the solid-state structure, the stability of dispersions in storage and *in vitro*/*in vivo* correlation [19]. Recent attempts to establish these characteristics for drug dispersion (e.g., [20]) may help to understand the dissolution profile differences due to, for example, intermolecular bonding or crystallinity.

The dissolution profile is also an issue for the compaction of solid dispersions, and is thoroughly investigated in industrial pharmaceutical laboratories. BCS class II drugs will profit from a rapid dissolution of the formulation, as this will increase permeation through the gut wall. In contrast, BCS class IV substances may not gain from fast dissolution, as a lower permeation may cause the recrystallisation of the drug after dissolution in the gut environment.

3. Cyclodextrin inclusion complex

Cyclodextrins are cyclic oligosaccharides composed of 6 – 8 dextrose units (α-, β-, γ-cyclodextrins, respectively) joined through 1 – 4 C–C bonds. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic. Cyclodextrins and their commercially available derivatives are able to incorporate apolar molecules or parts of molecules inside their hydrophobic cavity. This constitutes a true molecular encapsulation. The water-soluble inclusion complexes exhibit new physicochemical characteristics compared with the original guest molecules, such as better stability, high water solubility, increased bioavailability or decreased undesirable side effects [21]. For many years, cyclodextrins have been proposed for poorly water-soluble drug formulations, with the main objective of increasing their water solubility and, thus, their bioavailability [22]. With the first pharmaceutical applications of cyclodextrins, β-cyclodextrin, whose structure is shown in **Figure 3**, was the most widely used because it was readily available, and moreover, it provided pharmaceutically useful complexation characteristics with a wide range of drugs. However, its low aqueous solubility, together with its nephrotoxicity, enforced the development of appropriate derivatives [23,24]. At present, the most widely used cyclodextrins are 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin and sulfobutyl ether-β-cyclodextrin, due to their high water solubility and low toxicity [25,26]. Numerous researchers have reported complex formation between cyclodextrins or their derivatives and poorly water-soluble drugs to improve their aqueous solubility. The complex of praziquantel with β-cyclodextrin has shown improved dissolution profiles over that of the pure drug, and a good stability constant [27]. The oral preparation of itraconazole, containing 40% (w/v) of 2-hydroxypropyl-β-cyclodextrin, has been commercialised in the US and Europe [28]. DY-9760e, a novel cytoprotective agent, can form a very stable inclusion complex with sulfobutyl ether-β-cyclodextrin, resulting in significant improvements in aqueous solubility and the photo-stability of DY-9760e [29]. Tablets containing the 2-hydroxypropyl-β-cyclodextrin complex of ursodeoxycholic acid, starch and microcrystalline cellulose, have exhibited a much faster and more complete dissolution, as well as better bioavailability, in human volunteers, compared with those of the commercially available Ursacol® (Zambon) tablets of ursodeoxycholic acid [30]. The combined approach of cyclodextrins and liposomes, surfactants or polymers has also been applied for the solubilisation of poorly soluble drugs. The inclusion complexes between 2-hydroxypropyl-β-cyclodextrin and three water-insoluble drugs of appropriate size (dehydroepiandrosterone, retinal and dexamethasone) have been entrapped in the aqueous phase of a liposome, with the combined effect of improving water solubility and targeting [23]. It has been reported that the changes in tolbutamide solubility in the presence of β-cyclodextrin is dependent on the type and concentration of the surfactant [31]. The association of water-soluble polymer PEG4000 with glimepiride-2-hydroxypropyl-β-cyclodextrin systems has shown a greatly enhanced dissolution rate, increased duration of action and improvement of therapeutic efficacy of the drug after oral administration in diabetic rats [32,33]. There are

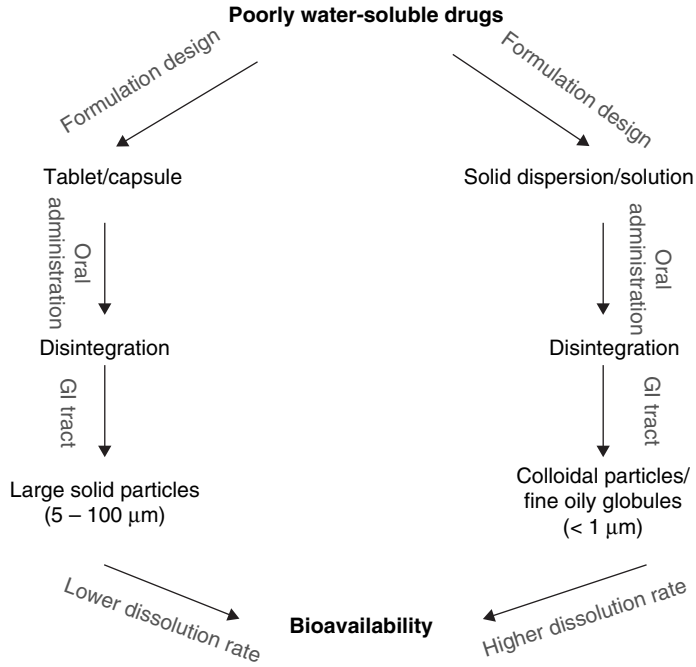

Figure 2. The bioavailability enhancement of poorly water-soluble drugs by solid dispersion compared with conventional tablet or capsule (modified from [11]).
GI: Gastrointestinal.

> 30 products containing cyclodextrin–drug complexes on the market [34].

Table 2 shows some of the marketed products arising from the cyclodextrin inclusion technique, implying its importance for pharmaceutical applications.

4. Emulsion and microemulsion

Emulsified formulations have a rather long history and have shown their ability to enhance the absorption of poorly water-soluble drugs [35]. For example, the corn oil emulsion formulation of phenytoin, after oral administration to rats, has shown an approximate 90% improvement of the maximum serum concentration of phenytoin than that of its aqueous suspension [36]. Similar trends have been observed after the administration of griseofulvin in either a solution or emulsion formulation of corn oil to rats [37]. The corn oil emulsion formulation of griseofulvin has also been evaluated in humans and showed a twofold enhancement in bioavailability compared with either an aqueous suspension or commercial tablet formulation [38]. However, emulsions are known for their thermodynamic instability. One popular way to overcome this drawback and to make their use more attractive is the transformation of emulsions into dry powdered emulsions. Solid-state emulsions, referring to the dispersion of an immiscible oil phase within a solid-state, can be obtained by removal of the aqueous phase of a liquid emulsion. One widely used technique to prepare a dry emulsion is spray-drying [39,40]. The dry emulsion formulation of vitamin E acetate prepared by spray-drying has been shown to be rapidly absorbed after its oral administration to beagle dogs, compared with an oily mixture of the drug with cottonseed oil and an oil-in-water emulsion [41]. A physically stabilised, dry emulsion dosage form of lipophilic 5-phenyl-1,2-dithiole-3-thione (5-PDTT), reforming the original emulsion after rehydration, has been developed by spray drying a liquid oil-in-water emulsion containing maltodextrin (carrier) and sodium caseinate (emulsifying agent) [42]. Incorporation of 5-PDTT into the oil phase neither affects the surface characteristics of the powder nor the reconstitution and droplet size or the drug-releasing properties. Furthermore, the dry emulsion dosage allows an improvement of 5-PDTT bioavailability in the rabbit after oral administration, compared with a cyclodextrin dosage form. However, the spray-dried powder is cohesive and bulky, causing inconvenience for oral administration. From a dosing and handling point of view, it would be advantageous if the dry emulsion powder is compressed into tablets or capsules [43]. A directly compressed dry emulsion of Lu 28 – 179 prepared by the spray drying of an oil-in-water emulsion as a tablet has shown comparable bioavailability to that of a dry emulsion powder after administration to Beagle dogs [44].

The oils typically used for pharmaceutical emulsions consist of digestible oils from the triglycerides family, including soybean oil, sesame seed oil, cottonseed oil and safflower oil. In addition, tocols (the tocopherol and tocotrienol family) are reported to be excellent solvents for water-insoluble drugs [45,46]. The tocol emulsions have numerous advantages, such as high

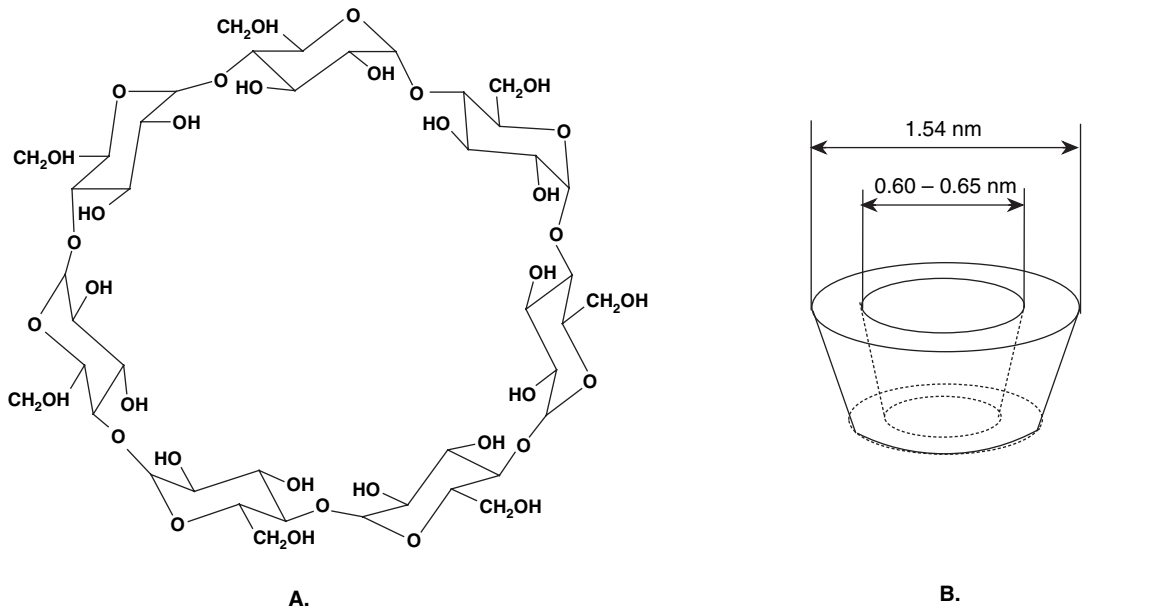

Figure 3. The chemical structure (A) and the toroidal shape (B) of β-cyclodextrin.

drug loading without increasing the toxicity and controlling the mean droplet diameter [47,48]. Surfactant(s) such as lecithin from egg yolk or soybeans is commonly used to stabilise the emulsion, and other excipients are typically added to render the emulsion more stable, biocompatible and less toxic [49].

Presently, microemulsions are of big interest to pharmaceutical scientists because of their considerable potential to act as drug delivery vehicles by incorporating a wide range of drug molecules [50]. Microemulsions are defined as 'a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution [51]'. The key differences between emulsions and microemulsions are that the former are fundamentally thermodynamically unstable and will eventually phase separate [52]. Another important difference concerns their appearance: emulsions are cloudy and microemulsions are clear and translucent. Furthermore, the preparation of an emulsion requires a large input of energy, but that of a microemulsion does not. Microemulsion systems are widely used to improve the solubility and absorption of poorly water-soluble drugs. An optimised oil-in-water microemulsion formulation for the delivery of lipophilic ciclosporin (CsA) has been reported by using Cremophor® EL (BASF) as the surfactant, Transcutol® (Gattefossé) as the cosurfactant and Captex 355® (Abitec Corp.) as the oil phase. Bioavailability enhancements of factors 3.3 and 1.25 were observed relative to the Sandimmune® (Novartis) and Sandimmune Neoral® formulations [53], and also diminished the fed-state dependency. The microemulsion formulation of *N*-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N′-[4-(*N*-benzylpiperidyl)]urea (*N*-4472), a poorly water-soluble drug, has been prepared with Gelucire 44/14, HCO-60 and sodium dodecyl sulphate, and has shown gastrointestinal stability and high oral absorption after administration to rats [54]. A novel oil-in-water microemulsion formulation has been made using medium chain fatty acid triglyceride diglyceryl monooleate, polyoxyethylene hydrogenated castor oil 40, ethanol and PBS (pH 6.8) as an oil phase, a lipophilic surfactant and a solubiliser, respectively. With this formulation, the water solubility of nine poorly water-soluble drugs, such as ibuprofen, ketoprofen, tamoxifen, testosterone, tolbutamide and other new compounds, was increased between 60- and 20,000-times. Following a single oral administration to fasted rats, the AUCs of the plasma concentration of ibuprofen in this formulation was improved 9-times to that of suspension administration, but equivalent to that of solution administration, as shown in **Figure 4** [55].

Self-microemulsifying drug delivery systems (SMEDDS) are closely related to microemulsions. A SMEDD typically comprises a mixture of surfactant, oil and drug (known as preconcentrate), which is rapidly dispersed to form droplets of approximately the same size range as those observed in the microemulsion system. Once dispersed, such a system would be expected to behave *in vivo* in much the same way as oil-in-water microemulsions. Compared with ready-to-use microemulsions, it has been shown to have an improved physical stability profile in long-term storage, and can be filled directly into soft or hard gelatine capsules for conventional drug delivery. SMEDDS have been used for the purpose of improving the solubility and absorption of poorly water-soluble drugs. The preconcentrate of flurbiprofen, consisting of 20% Capmul PG8 as the oil phase, 40% Tween 20 and 40% Cremophor EL as surfactants, has been

Table 2. A selection of marketed products arising from the cyclodextrin inclusion technique.

Drug/cyclodextrin	Market name	Company
Benexate/β-cyclodextrin	Ulgut®	Teikoku
	Lonmiel®	Shionogi
Dexamethasone glyteer/ β-cyclodextrin	Glymesason®	Fujinaga
Iodine/β-cyclodextrin	Mena-Gargle®	Kyushin
Itraconazole/ HP-β-cyclodextrin	Sporanox™	Janssen
Nitroglycerin/β-cyclodextrin	Nitropen®	Nippon Kayaku
PGE/β- cyclodextrin	Prostandin®	Ono
	Prostavasin®	Schwarz Pharma
Piroxicam/β-cyclodextrin	Brexin®	Chiesi
	Cycladol®	Masterpharm
	Brexin®	Robapharm
		Promedica
	Brexidol®	Launder

shown to generate clear microemulsions with small particle sizes (10 – 11 nm) upon dilution; the increased flurbiprofen loading did not influence the particle size. The microemulsions from preconcentrate showed stability at ambient temperature over 20 days, without significant change in the particle size with different flurbiprofen loading, implying the promise in dosage development for poorly water-soluble drugs in using SMEDDS [56]. In another study, the optimal formulation of SMEDDS containing simvastatin (high drug loading and small particle size), 37% Capryol 90, 28% Cremophor EL and 28% Cabitol, revealed that the release of simvastatin from SMEDDS was faster than that from the conventional Tablet (Zocor®; Merck & Co., Inc) *in vitro* dissolution studies. Also, SMEDDS showed significantly improved bioavailability than the conventional tablet in *in vivo* studies [57]. SMEDDS composed of solvent Green 3, a model poorly water-soluble compound, and Gelucire 44/14, have demonstrated a 1,7-fold higher bioavailability of solvent Green 3 than that with a soybean oil emulsion after oral administration to rats [58]. Commercially available drugs that use SMEDDS include CsA (Panimun Bioral; Panacea Biotec) and saquinavir (Fortovase®; Roche).

Self-emulsifying drug delivery systems (SEDDS), in contrast to SMEDDS, form fine emulsions (not necessarily transparent) in the aqueous gut lumen and consist mainly of a mixture of oil, surfactants and drug, but otherwise serve the same purpose as SMEDDS.

5. Nanosuspension

Nanosuspensions (hydrosols) for pharmaceutical application are very finely dispersed solid drug particles in an aqueous vehicle. The key difference from conventional suspensions is that the particle size distribution of the solid particles in nanosuspensions is usually < 1 μm, with an average particle size range of 200 – 600 nm [59]. Nanosuspensions can be used to formulate compounds that are insoluble in both water and oils and to reformulate existing drugs to remove toxicologically less favourable excipients [60].

Micronisation of poorly soluble drugs, a general approach used for many years, increases the dissolution rate of the drug due to the increase in surface area, but does not change the saturation solubility. At very low saturation solubility, the achieved increase in dissolution rate cannot lead to a sufficiently high bioavailability. In a nanosuspension system, the overall bioavailability is improved by an increase in surface area and saturation solubility via particle size reduction [61]. In addition, nanosuspensions overcome a number of carrier-related drawbacks, such as limitations in drug load, as well as side effects due to the matrix material of the carrier particles [62].

Nanosuspension engineering processes presently used are precipitation [63-65], pearl milling [66] and high-pressure homogenisation [67,68]. Precipitation is performed by dissolving the drug in a solvent and adding this solvent to a non-solvent (so-called '*via humida paratum*') [69]. The drawback of the simple precipitation method is that it is difficult to control nucleation and crystal growth to obtain a narrow particle size distribution. The pearl milling technique led to the product Nanocrystal® (Elan Corp.), which makes use of unusually tough milling media in aqueous suspension [70,71]. This technology can reduce crystalline particle size to ~ 100 – 250 nm. The drawback of this technique is that the milling processes often requires grinding for hours to days in order to reach the desired size range. The principle of high-pressure homogenisation to obtain nanosuspensions is the creation of cavitation forces. The drug powder is dispersed in an aqueous surfactant solution by high-speed stirring. The obtained macro-suspension is passed through a high-pressure homogeniser applying typically 1500 bar and three to ten (a maximum of 20) passes (homogenisation cycles). The suspension passes a very small gap in the homogeniser. Due to the narrowness of the gap, the streaming velocity of the suspension increases tremendously, which means the dynamic fluid pressure increases. Simultaneously, the static pressure on the fluid decreases below the boiling point of water at room temperature. Consequently, water starts boiling at room temperature due to the high pressure, and gas bubbles are formed, which implode when the fluid leaves the homogenisation gap. These cavitation forces are strong enough to break drug microparticles into drug nanoparticles [61].

One of the first successful approaches of nanosuspension (hydrosols) production by precipitation was performed by Sucker and colleagues for the intravenous administration of CsA [64]. The classic formulation for CsA contains an emulsifier, which can cause serious side effects, especially with

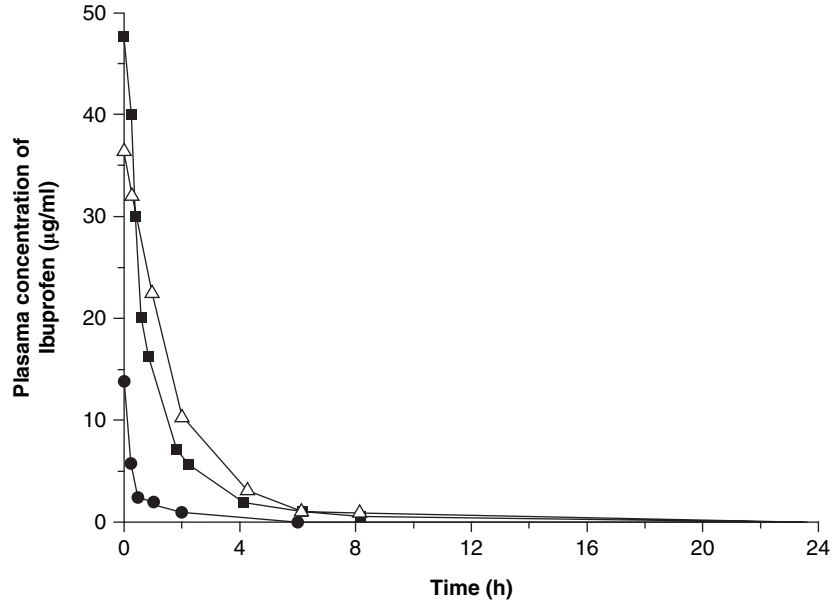

Figure 4. The plasma concentration profile of ibuprofen following a single oral administration of the drug to fasted male rats as a suspension (•), solution (Δ) and an oil-in-water microemulsion (■) at a dose of 10 mg/kg. Data are presented as mean ± SD of four animals (modified from [55]).
SD: Standard deviation.

chronic dosing [72]. The process described yields a diluted suspension stabilised by a small amount of emulsifiers, which has to be concentrated by a drying processes [64]. A convenient side effect of the drying is the increased stability of the product. The precipitation process has to be established for each drug, being a complex interplay of drug and excipient interactions, changing variables – often in a chaotic manner – such as size, colloidal stability and crystal habit. **Table 3** gives a vivid example that drugs with apparently similar physicochemical characteristics require quite different processes to yield a usable formulation.

Another example is a nanosuspension of mitotane, which possesses very poor water solubility and low bioavailability, and was prepared by emulsifying an organic solution (butyl lactate) of the drug in an aqueous solution of a stabilising agent, followed by rapid displacement of the solvent from the internal into the external phase, provoking solid particle formation. Drug particles of ~ 80 nm size were obtained. Because of the increase in available surface area, the dissolution rate of mitotane nanosuspensions increased greatly compared with the commercial product [65]. It has been demonstrated in rats that the gastric irritation induced following oral administration of naproxen was decreased by reducing the drug particle size from 20 – 30 µm to 270 nm in a roller mill. The size reduction of naproxen was also associated with an apparent increase in the rate of absorption by approximately fourfold. The increase in the rate of absorption is attributed to an increase in the surface area of the naproxen nanosuspension [66]. Amphotericin B (AmB) has been formulated in a nanosuspension for the treatment of experimental visceral leishmaniasis. AmB suspensions were produced by high pressure homogenisation, obtaining particles with a diameter of 528 nm. *In vivo* efficacy was determined in a mouse model of visceral leishmaniasis. Following oral administration, the AmB nanosuspension reduced liver parasite load by 28.6% compared with untreated controls, whereas micronised AmB did not show any curative effect. Furthermore, AmB nanosuspension proved to be stable over at least 3 weeks, indicating good shelf-life characteristics [73]. Atovaquone is an effective new drug used for the treatment of opportunistic *Pneumocystis carinii* infections in HIV patients or leishmaniasis.

Atovaquone has low water solubility combined with low absorption. The oral administration of nanosuspensions are assumed to overcome this problem because of the enhanced adhesiveness of drug particles that allows them to stick to the epithelial gut wall and prolongs the absorption time. After given orally to Leishmania-infected mice, nanosuspensions of atovaquone have been shown to significantly improve absorption compared with micronised drug, and, therefore, greatly improved its activity [61].

6. Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are particulate systems with mean particle diameters ranging 50 – 1000 nm. They are derived from oil-in-water emulsions by replacing the liquid lipid (oil) by a solid lipid. General ingredients for SLNs include solid lipid(s), emulsifier(s) and water. The lipids generally used are triglycerides, partial glycerides,

Table 3. Nanosuspensions of different drugs produced by precipitation.

Drug	Solubility (μg/ml)	Stabilizer	Drug content (mg/ml)	Drying by	Particle size	
					After preparation (nm)	After reconstitution (nm ± s)
Isradipine	< 2	Plas.	0.25	Lyophilisation	170	170
		Plas.	2.8	Spray-drying	185	220
Beclometha-sone dipropionate	< 1	Plas.	1.0	Spray-drying	190	230
Ciclosporine	23‡	Plas.	0.5	Lyophilisation.	200	225
		Plas.	1.0	Spray-drying	210	260*
		Pol.	2.5	Spray-drying	170	350
		Lec.	3.0	Spray-drying	80 ± 15	120 ± 65

Modified from [108].
The percentage of stabilizer is the concentration in the aqueous nonsolvent phase.
*Particle size of the reconstituted hydrosol after 30 min.
‡The solubility of cyclosporine in water is unusual, as the solubility decreases from 23 μg/ml at 20°C to 4.4 μg/ml at 37°C, but in a solution of 3% succinylated gelatine, the solubility diminishes to 6 μg/ml.
Lec.: Palmitoyl-oleyl-phosphatidyl-glycerol 0.06% + Poloxamer 188 0.3%; Plas.: Succinylated gelatine 3%, Plasmagelan® (B.Braun D-Melsungen) + citric acid 1%; Pol. = Poloxamer 188 (BASF, USA-Wyandotte) 0.3%.

fatty acids, steroids and waxes. All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilise the lipid dispersion. They are used not only for the controlled release and targeting of the incorporated drugs [74], but also for the modification of the dissolution rate of the poorly water-soluble drugs incorporated, and, thus, for the enhancement of bioavailability in oral administration [75,76]. The mechanisms of bioavailability enhancement by SLNs are that they possess adhesive properties that make them adhere to the gut wall and release the drug exactly where it should be absorbed [77]. In addition, the lipids are known to have properties that promote the oral absorption of lipophilic drugs and drugs in general [78,79]. SLNs have a number of advantages. First, the lipid matrix of SLNs is made from physiologically tolerated lipid components, which decreases the potential for acute and chronic toxicity [80]. It has been reported that SLNs are 10- to 100-fold less cytotoxic than their polymeric counterparts [81,82]. Second, SLN formulations have the ability to be stable for 3 years, which is of paramount importance with respect to colloidal drug carriers [83,84]. Third, SLNs can be produced on a large industrial scale by high-pressure homogenisation, which has shown excellent reproducibility [85,86].

SLN formulations have been developed for a dopaminergic drug, piribedil, which has a low aqueous solubility and a short elimination half-life [75]. The bioavailability and plasma profiles were studied following oral administration to rabbits. Incorporation of piribedil into SLNs increased the bioavailability and prolonged the plasma levels, which suggested some adhesion of the particles to the mucosal wall. The result of this study opens up the possibility of developing mucoadhesive SLNs. CsA SLNs have been prepared from warm oil-in-water microemulsion [87]. The matrix consisted of stearic acid, phosphatidylcholine and taurocholate. The average diameter of CsA-loaded SLNs was < 300 nm. Thirteen percent of CsA was incorporated – above that of commercial the microemulsion Neoral. The *in vitro* release of CsA from SLNs was < 4% in 2 h – much lower than that from the saturated solution (60%) – showing the performance of SLNs in sustained release. An oral SLN formulation has been developed for CsA for the enhancement of its bioavailability [88]. Two percent of this drug was formulated in SLNs with a mean size of 157 nm. The pharmacokinetic parameters of the SLN formulation were assessed and compared with that of drug nanocrystals and the commercial microemulsion Sandimmun Neoral/Optoral®, used as a reference after oral administration to three young pigs. The blood profiles of Sandimmun Neoral/Optoral revealed a fast absorption of drug, leading to a plasma peak > 1000 ng/ml within the first 2 h. For the drug nanocrystals, most of the blood concentrations were in the range of 30 – 70 ng/ml over a period of 14 h, and displayed huge variability both between the measuring time points and between the tested animals. In contrast, the administration of CsA-loaded SLNs led to a mean plasma profile with similarly low variations in comparison to the reference microemulsion, yet without the initial blood peak observed with Sandimmun Neoral/Optoral, which is responsible for its side effects. This study proved that SLNs can be a suitable oral delivery system to enhance the oral bioavailability of a typical low-solubility drug such as CsA.

SLN formulations have also been prepared for vinpocetine by an ultrasonic solvent emulsification technique [89]; the lipid matrix consists of a glyceryl monostearate. An oral pharmacokinetic study was conducted in male rats and the results showed that the SLN formulation provided a significant improvement in the bioavailability of vinpocetine compared with a vinpocetine solution. The amount of surfactant was also proven to have an important influence on the oral absorption of vinpocetine.

7. Liposomal formulations

Liposomes are phospholipid vesicles, comprising a phospholipid bilayer surrounding an aqueous compartment. In the lipid domain of the bilayer membrane, lipophilic drugs can be dissolved. Due to their biphasic characteristic and diversity in design, composition and construction, liposomes offer a dynamic and adaptable technology for enhancing drug solubility. It has been reported that the liposome encapsulation efficiency of lipophilic drugs depends on both the physicochemical properties of the drug, such as its lipophilicity [90], and on factors including bilayer composition and the method of preparation [91]. Since the introduction of liposomes into the world of intravenous drug delivery research [92,93], liposomal formulations for lipophilic drugs have been developed and successfully introduced to the market. Incorporation of the poorly water-soluble drug ibuprofen, into egg-phosphatidylcholine/cholesterol liposomes has been investigated [94]. Optimum drug-loading was achieved by using multi-lamellar vesicles containing 20% (total lipid) cholesterol, 9% stearylamine, or by substituting a long alkyl chain lipid for the phosphatidylcholine. It was proven that ibuprofen-loaded liposomes were structurally more resistant to destabilisation during dehydration than drug-free liposomes. The therapeutic index of vincristine, a lipophilic drug widely used in the treatment of human carcinomas, can be enhanced significantly through the use of a liposomal delivery system, with reduced toxicity [95].

Liposomes have also been developed for the improved delivery of CsA, the drug of choice in transplantation medicine. It was suggested that a parenteral liposomal formulation of CsA may keep CsA away from the patient's kidneys, as is the fear with the excipients used in the marketed formulation. However, no advantage was clearly extractable from all the available literature regarding this type of formulation [96]. Nevertheless, it became clear from pharmacokinetic studies [72,96] that CsA is not bound with high affinity to the liposomal bilayer, but does easily exchange with other binding places. Drug binding, therefore, is only governed by the law of mass action [72]. Further physicochemical studies of CsA interaction with lipid formulations revealed that CsA does not bind to lipid membranes, but is attracted to the liposomal lipid bilayer merely due to its hydrophobicity. This is supported by the fact that binding to liposomes is endothermic ($\Delta H = +10$ kcal/mole) and hence is only entropy driven [97].

The main advantage of a liposome formulation in contrast to other carrier systems is often the generally regarded as safe GRAS status of the phospholipid constituents. This concept of using liposomes just as solubilising excipients with GRAS characteristics can also be applied to other drugs [98].

Liposomal and lipidic formulations of AmB are available in different forms on the market [99], the most notable of which is Ambisome® (Gilead Sciences, Inc). The success of this liposomal formulation is inherently connected to the fact that AmB is a membrane-bound drug by nature, which can easily be seen by its chemical structure (**Figure 5**). Simply spoken, the drug, embedded in the liposomal membrane, will be 'waiting' until it 'meets' a fungal membrane, where it is attracted with high affinity by the ergosterol content of the fungal cell membranes, which is contrast to liposomal membranes without ergosterol. This drastically lowers the renal side effects otherwise observed with other solubilising systems [100], which cannot take advantage of this membrane-binding specificity.

8. Conclusions

Two techniques are known to the pharmacist to make a poorly soluble drug better available: either by increasing the (saturation) solubility in the biological medium of choice or by increasing the dissolution kinetics. The first strategy involves mostly chemical methods by adding (often not completely harmless) excipients; the second approach very often involves approaches based on physics.

By improving these conventional techniques and developing new techniques – always designed with consideration of the characteristics of the drug, new materials, as well as new formulations in drug delivery systems – the low bioavailability of poorly water-soluble drugs has been gradually overcome. However, problems such as drug leakage from the formulation, and formulation instability, still exist in some new formulation principles; for example, in solid lipid nanoparticles, which were thought to encapsulate lipophilic drugs *per se* (but this offers the possibility to use these carrier systems just as solubiliser). Often the term 'hydrophobicity' is synonymously used with the term 'lipophilicity', but this is not always the case, as has been shown for the interaction of CsA with lipid membranes.

With further investigations, the development of new materials and new technologies, more basic material science research and especially increasing numbers of basic physicochemical studies performed, the problems can be minimised because they are understood and the formulation strategy of poorly water-soluble drugs will be more promising.

9. Expert opinion

In order to rationalise the very often mysterious and 'magical' work to formulate lipophilic and water-insoluble drugs, several attempts have been made in the past to find out if drug can be solubilised by appropriate methods. In the industrial

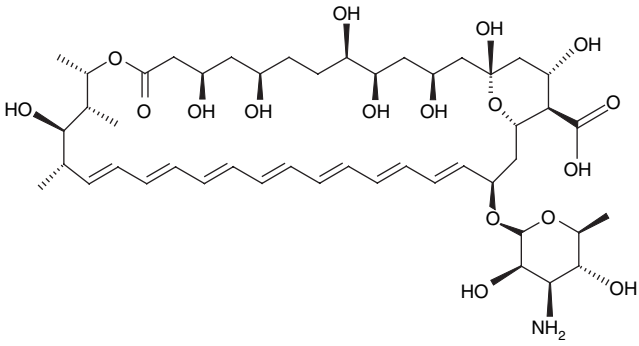

Figure 5. The structure of amphotericin B.

environment, this formulation search is often complicated by the patent environment, which very often restricts the use and also the search for adequate drug carrier system components, and by the still only partially understood physicochemical characteristics of the drug.

One of the prerequisites for a successful carrier system for the class of drug considered here (BCS class II and IV) is of course the 'carrier'-philicity of the drug. This is also often referred to by the term lipophilicity. Sometimes one can be lucky by relying of simple or more elaborate models (e.g., [101,102]) for the lipophilicity calculations to be relevant for the guidance to desired formulation. However, this basic approach does not work very often because of the high complexity of the interaction between drug and carrier system. Sometimes only a small change to the drug molecule, such as the addition of a single OH group, or even an isomerisation, drastically changes the compatibility of a drug for a specific carrier system. Therefore, elaborate (often trial-and-error) tests are necessary to get a rough guideline for the development of a proper carrier system for a drug.

Some very interesting work that provides at least some solidity in this respect has been performed by Illum *et al.* [103], who have been able to predict for their tocopherol carrier systems for certain classes of lipophilic drugs, some rules using chloroform and methanol solubility data. Drugs with a high solubility in chloroform were suitable for the carrier, whereas drugs with a high solubility in methanol were not suitable.

However, in most situations, lipophilicity or solubility will not be the only determining factors for a successful formulation of lipophilic drugs. A successful incorporation of lipophilic drugs in a carrier system may be often the only important factor for the mere purpose of solubilising the drug, whereas for retarded or targeted formulation intentions, some form of encapsulated formulation is needed.

Surprisingly, a rapid release of drug has been observed with solid lipid nanoparticles [104]. In a series of elegant works, the group of Mäder [105], has shown, principally, that there is no difference between the retardation effect of conventional SLNs and a common nanoemulsion, and also no special protection of the drug, despite the expectations of the effect of a drug embedded in a solid lipid matrix. Only a steric or electrostatic fit between the drug and lipid matrix components, as in the case of CsA SLN [87], or the use of nanostructured lipid carriers with non-crystalline domains in the matrix (e.g., [106]) will keep the drug in the solid lipid matrix for longer. This behaviour has to be elucidated in each case and could be successfully used for the oral delivery of insoluble drugs by releasing the drug with or without retardation into the gut lumen, avoiding the quite limited diffusion of nanoparticles through the mucus.

For the development of liposomal formulations, this holds as well. Drugs without a designed 'membranophily' will also be released rapidly when in contact with biological fluids, as they sit only loosely in the liquid-crystalline lipid bilayer and may even disturb the lipid bilayer [97]. However, drugs designed for membrane insertion (as in the case of AmB) can profit from a tailor-made formulation using the 'complex' with the lipid matrix.

However, the desire of pharmaceutical companies is for a fast, robust and reliable method for the delivery of insoluble drugs by using minimal amounts of solubilising agents such as emulsifiers. Nanosuspensions made by precipitation may be such a method, but this also needs prerequisites, such as an almost complete insolubility of the drug in the aqueous medium, and, ideally, an amorphous structure of the particles [20], which exhibit an often not well understood interplay between drug and excipients.

The 'nanoisation' of drug particles by physical means leads to a drastic increase in the proportion of the surface in contact with the solubilisation medium, and, hence, in the dissolution speed, which very often helps in obtaining sufficient bioavailability for oral administration or even parenteral usage. For the purpose of purely achieving solubilisation, this might even be the first strategy attempted, if the drug survives the milling process and the adherent stress sufficiently and the particles are stabilised against aggregation. An outstanding feature of the nanosuspension technology is its simplicity.

For purely achieving oral delivery, solid dispersion technology by hot melt extrusion (e.g., Soliqs' Nanomorph® technology) is becoming a widely applicable procedure for fast and promising results.

The simpler and the more generally applicable the delivery system is, the higher the chances of getting to a formulation that can be used in clinical studies. The targeting principles, or the triggered release characteristics for the drug is, in this respect, only of secondary importance. For site-directed delivery, which might be of additional benefit for the patient, a large additional workload must be undertaken in advance to establish the characteristics of the drug and its interaction with the carrier – preferably in the preclinical research phase. This is a demanding and lengthy task, and does not work at all for many drugs.

Luck will always favour the hard-working scientist, especially those in the field of pharmacy, but one cannot

rely on good fortune. Basic investigations will pay off sooner or later in the formulation development department. In contrast, searching for a needle in a haystack can be fun, but only successful in a few instances, and afterwards it will become de-motivating. Therefore, an investment in basic physicochemical science would pay off not only for gaining information for future development, but also commercially, as long as the right people are working in the commercial organisation or in contracting labs or co-operating universities. Several companies have taken such steps to investigate physicochemical characterisation and the biopharmaceutical consequences. In addition, the next step has been taken by several companies, where the formulation scientists are already participating in the lead optimisation process to obtain the best 'drugable' molecule and the appropriate delivery system.

Acknowledgment

A Fahr thanks FW Richter (Divisional Vice President, Abbott Laboratories) for stimulating discussions.

Bibliography

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

1. LIPINSKI CA, LOMBARDO F, DOMINY BW, FEENEY PJ: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* (2001) **46**:3-26.
2. GILIYAR C, FIKSTAD DT, TYAVANAGIMATT S: Challenges and opportunities in oral delivery of poorly water-soluble drugs. *Drug Deliv. Technol.* (2006) **6**:57-63.
3. LÖBENBERG R, AMIDON GL: Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. *Eur. J. Pharm. Biopharm.* (2000) **50**:3-20.
4. YU LX, AMIDON GL, POLLI JE *et al.*: Biopharmaceutics classification system: the scientific basis for biowaiver extension. *Pharm. Res.* (2002) **19**:921-925.
5. 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**:278-287.
6. KERNS EH, DI L: Pharmaceutical profiling in drug discovery. *Drug Discov. Today* (2003) **8**:316-323.
7. MOGHIMI SM: Recent developments in polymeric nanoparticle engineering and their applications in experimental and clinical oncology. *Anti-Cancer Agents in Med. Chem.* (2006) **6**:553-561.
8. CHIOU WL, RIEGELMAN S: Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* (1971) **60**:1281-1302.
9. SEKIGUCHI K, OBI N: Absorption of eutectic mixtures. 1. A comparison of the behavior of a eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem. Pharm. Bull.* (1961) **9**:866-872.
10. GOLDBERG AH, GIBALDI M, KANIG JL: Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II: Experimental evaluation of a eutectic mixture: Urea-acetaminophen system. *J. Pharm. Sci.* (1966) **55**:482-487.
11. SERAJUDDIN ATM: Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* (1999) **88**:1058-1066.

•• **A critical review on advantages and limitations of solid dispersion.**

12. WANG L, CUI FD, SUNADA H: Preparation and evaluation of solid dispersions of nitrendipine prepared with fine silica particles using the melt-mixing method. *Chem. Pharm. Bull.* (2006) **54**:37-43.
13. BETAGERI GV, MAKARLA KR: Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. *Int. J. Pharm.* (1995) **126**:155-160.
14. KUSHIDA I, ICHIKAWA M, ASAKAWA N: 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. *J. Pharm. Sci.* (2002) **91**:258-266.
15. BLOCH DW, SPEISER PP: Solid dispersions – fundamentals and examples. *Pharm. Acta Helv.* (1987) **62**:23-27.
16. HÜLSMANN S, BACKENSFELD T, KEITEL S, BODMEIER R: Melt extrusion–an alternative method for enhancing the dissolution rate of 17β-estradiol hemihydrate. *Eur. J. Pharm. Biopharm.* (2000) **49**:237-242.
17. VERRECK G, SIX K, VAN DEN MOOTER G *et al.*: Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion–Part I. *Int. J. Pharm.* (2003) **251**:165-174.

• **The solid dispersion of itraconazole was produced by melt extrusion – a method which has advantages over the traditional techniques.**

18. RAMBALI B, VERRECK G, BAERT L, MASSART DL: Itraconazole formulation studies of the melt-extrusion process with mixture design. *Drug Dev. Ind. Pharm.* (2003) **29**:641-652.
19. CRAIG DQM: The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.* (2002) **231**:131-144.
20. DOUROUMIS D, BOUROPOULOS N, FAHR A: Physicochemical characterization of solid dispersions of three antiepileptic drugs prepared by solvent evaporation method. *J. Pharm. Pharmacol.* (2007) **59**:1-9.
21. DUCHENE D, WOUESSIDJEWE D, PONCHEL G: Cyclodextrins and carrier systems. *J. Control. Release* (1999) **62**:263-268.
22. LOFTSSON T, BREWSTER ME: Pharmaceutical applications of cyclodextrin. 1. Drug solubilization and stabilization. *J. Pharm. Sci.* (1996) **85**:1017-1025.

• **A short review on the properties and pharmaceutical applications of cyclodextrins.**

23. MCCORMACK B, GREGORIADIS G: Drugs-in-cyclodextrins-in-liposomes: an approach to controlling the fate of water insoluble drugs *in vivo*. *Int. J. Pharm.* (1998) **162**:59-69.

•• **The advantages of a formulation design by the combined use of cyclodextrin and liposome were described.**

24. SZENTE L, SZEJTLI J: Highly soluble cyclodextrin derivatives: chemistry, properties, and trends in development. *Adv. Drug Deliv. Rev.* (1999) **36**:17-28.

25. RAJEWSKI RA, STELLA VJ: Pharmaceutical applications of cyclodextrins. 2. *In vivo* drug delivery. *J. Pharm. Sci.* (1996) **85**:1142-1169.

26. STELLA VJ, RAJEWSKI RA: Cyclodextrins: their future in drug formulation and delivery. *Pharm. Res.* (1997) **14**:556-567.

•• **A critical assessment of the present status of cyclodextrins in the formulation and delivery of drugs and their potential future use.**

27. BECKET G, SCHEP LJ, TAN MY: Improvement of the *in vitro* dissolution of praziquantel by complexation with α-, β- and γ-cyclodextrins *Int. J. Pharm.* (1999) **179**:65-71.

28. STEVENS DA: Itraconazole in cyclodextrin solution. *Pharmacotherapy* (1999) **19**:603-611.

29. NAGASE Y, HIRATA M, WADA K *et al.*: Improvement of some pharmaceutical properties of DY-9760e by sulfobutyl ether β-cyclodextrin. *Int. J. Pharm.* (2001) **229**:163-172.

30. PANINI R, VANDELLI MA, FORNI F, PRADELLI JM, SALVIOLI G: Improvement of ursodeoxycholic acid bioavailability by 2-hydroxypropyl-β -cyclodextrin complexation in healthy volunteers. *Pharm. Res.* (1995) **31**:205-209.

31. VEIGA MD, AHSAN F: Solubility study of tolbutamide in monocomponent and dicomponent solutions of water. *Int. J. Pharm.* (1998) **160**:43-49.

32. AMMAR HO, SALAMA HA, GHORAB M, MAHMOUD AA: Formulation and biological evaluation of glimepiride-cyclodextrin-polymer systems. *Int. J. Pharm.* (2006) **309**:129-138.

33. AMMAR HO, SALAMA HA, GHORAB M, MAHMOUD AA: Implication of inclusion complexation of glimepiride in cyclodextrin-polymer systems on its dissolution, stability and therapeutic efficacy. *Int. J. Pharm.* (2006) **320**:53-57.

34. LOFTSSON T, JARHO P, MÁSSON M, JÄRVINEN T: Cyclodextrins in drug delivery. *Expert Opin. Drug Deliv.* (2005) **2**:335-351.

35. HUMBERSTONE AJ, CHARMAN WN: Lipid-based vehicles for the oral delivery of poorly water soluble drugs. *Adv. Drug Del. Rev.* (1997) **25**:103-128.

36. CHAKRABARTI S, BELPAIRE FM: Bioavailability of phenytoin in lipid containing dosage forms in rats. *J. Pharm. Pharmacol.* (1978) **30**:330-331.

37. CARRIGAN PJ, BATES TR: Biopharmaceutics of drugs administered in lipid-containing dosage forms 1: GI absorption of griseofulvin from an oil-in-water emulsion in the rat. *J. Pharm. Sci.* (1973) **62**:1476-1479.

38. BATES TR, SEQUEIRA JA: Bioavailability of micronized griseofulvin from corn oil-in-water emulsion, aqueous suspension, and commercial tablet dosage forms in humans. *J. Pharm. Sci.* (1975) **64**:793-797.

39. CHRISTENSEN KL, PEDERSEN GP, KRISTENSEN HG: Preparation of redispersible dry emulsions by spray drying. *Int. J. Pharm.* (2001) **212**:187-194.

40. CHRISTENSEN KL, PEDERSEN GP, KRISTENSEN HG: Technical optimisation of redispersible dry emulsions. *Int. J. Pharm.* (2001) **212**:195-202.

41. TAKEUCHI H, SASAKI H, NIWA T *et al.*: Redispersible dry emulsion system as novel oral dosage form of oily drugs: *In vivo* studies in beagle dogs. *Chem. Pharm. Bull.* (1991) **39**:3362-3364.

42. DOLLO G, LE CORRE P, GUERIN A *et al.*: Spray-dried redispersible oil-in-water emulsion to improve oral bioavailability of poorly soluble drugs. *Eur. J. Pharm. Sci.* (2003) **19**:273-280.

43. HANSEN T, HOLM P, SCHULTZ K: Process characteristics and compaction of spray-dried emulsions containing a drug dissolved in lipid. *Int. J. Pharm.* (2004) **287**:55-66.

44. HANSEN T, HOLM P, ROHDE M, SCHULTZ K: *In vivo* evaluation of tablets and capsules containing spray-dried o/w-emulsions for oral delivery of poorly soluble drugs. *Int. J. Pharm.* (2005) **293**:203-211.

• **The oral bioavailability resulting from administration of a directly compressible dry emulsion as a tablet was investigated for a model drug.**

45. CONSTANTINIDES PP, TUSTIAN A, KESSLER DR: Tocol emulsions for drug solubilization and parenteral delivery. *Adv. Drug Del. Rev.* (2004) **56**:1243-1255.

46. CONSTANTINIDES PP, HAN J, DAVIS SS: Advances in the use of tocols as drug delivery vehicles. *Pharm. Res.* (2006) **23**:243-255.

• **An expert review on the drug delivery applications of tocols.**

47. VON CORSWANT C, THOREN P, ENGSTRÖM S: Triglyceride-based microemulsion for intravenous administration of sparingly soluble substances. *J. Pharm. Sci.* (1998) **87**:200-208.

48. CONSTANTINIDES PP, LAMBERT KJ, TUSTIAN AK *et al.*: Formulation development and antitumor activity of a filter-sterilizable emulsion of paclitaxel. *Pharm. Res.* (2000) **17**:175-182.

49. COLLINS-GOLD LC, LYONS RT, BARTHOLOW LC: Parenteral emulsions for drug delivery. *Adv. Drug Del. Rev.* (1990) **5**:189-208.

50. LAWRENCE MJ, REES GD: Microemulsion-based media as novel drug delivery system. *Adv. Drug Del. Rev.* (2000) **45**:89-121.

•• **A review covering a comprehensive overview of formation, characterisation and application of microemulsion as a drug delivery vehicle.**

51. DANIELSSON I, LINDMAN B: The definition of microemulsion. *Colloids and Surfaces* (1981) **3**:391-392.

52. SHINODA K, LINDMAN B: Organized surfactant system: microemulsions. *Langmuir* (1987) **3**:135-149.

53. GAO ZG, CHOI HG, SHIN HJ *et al.*: Physicochemical characterization and evaluation of a microemulsion system for oral delivery of cyclosporin A. *Int. J. Pharm.* (1998) **161**:75-86.

54. ITOH K, MATSUI S, TOZUKA Y, OGUCHI T, YAMAMOTO K: Improvement of physicochemical properties of N-4472. Part II: characterization of N-4472 microemulsion and the enhanced oral absorption. *Int. J. Pharm.* (2002) **246**:75-83.

55. ARAYA H, TOMITA M, HAYASHI M: The novel formulation design of O/W microemulsion for improving the gastrointestinal absorption of poorly water soluble compounds. *Int. J. Pharm.* (2005) **305**:61-74.

56. LI P, GHOSH A, WAGNER RF *et al.*: Effect of combined use of nonionic surfactant on formation of oil-in-water

microemulsions. *Int. J. Pharm.* (2005) **288**:27-34.

57. KANG BK, LEE JS, CHON SK *et al.*: Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *Int. J. Pharm.* (2004) **274**:65-73.
• **Concludes that SMEDDS enhanced oral bioavailability of poorly water-soluble drug, simvastatin.**
58. IWANAGA K, KUSHIBIKI T, MIYAZAKI M, KAKEMI M: Disposition of lipid-based formulation in the intestinal tract affects the absorption of poorly water-soluble drugs. *Biol. Pharm. Bull.* (2006) **29**:508-512.
59. CHANDRA SEKHARA RAO G, SATISH KUMAR M, MATHIVANAN N, BHANOJI RAO ME: Nanosuspensions as the most promising approach in nanoparticulate drug delivery systems. *Pharmazie* (2003) **59**:5-9.
60. KOCBEK P, BAUMGARTNER S, KRISTL J: Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs. *Int. J. Pharm.* (2006) **312**:179-186.
61. MÜLLER RH, JACOBS C, KAYSER O: Nanosuspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the future. *Adv. Drug Del. Rev.* (2001) **47**:3-19.
•• **A comprehensive review on the properties, pharmaceutical application and production of nanosuspensions.**
62. WESTESEN K: Novel lipid-based colloidal dispersions as potential drug administration systems – expectations and reality. *Colloid Polym. Sci.* (2000) **278**:608-618.
63. DEBUIGNE F, CUISENAIRE J, JEUNIEAU L, MASEREEL B, NAGY JB: Synthesis of nimesulide nanoparticles in the microemulsion epikuron/isopropyl myristate/water/n-butanol (or isopropanol). *J. colloid Interface Sci.* (2001) **243**:90-101.
64. GASSMANN P, LIST M, SCHWEITZER A, SUCKER H: Hydrosols – Alternatives for the parenteral application of poorly water soluble drugs. *Eur. J. Pharm. Biopharm.* (1994) **40**(2):64-72.
65. TROTTA M, GALLARATE M, PATTARINO F, MOREL S: Emulsions containing partially water-miscible solvents for the preparation of drug nanosuspensions. *J. Control. Release* (2001) **76**:119-128.
66. LIVERSIDGE GG, CONZENTINO P: Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. *Int. J. Pharm.* (1995) **125**:309-313.
•• **Concludes that particle size reduction of naproxen to 270 nm eliminated its gastric irritant effect and enhanced its absorption.**
67. PETERS K, LEITZKE S, DIEDERICHS JE *et al.*: Preparation of a clofazimine nanosuspension for intravenous use and evaluation of its therapeutic efficacy in murine *Mycobacterium avium* infection. *J. Antimicrob. Chemother.* (2000) **45**:77-83.
68. MÖSCHWITZER J, ACHLEITNER G, POMPER H, MÜLLER RH: Development of an intravenously injectable chemically stable aqueous omeprazole formulation using nanosuspension technology. *Eur. J. Pharm. Biopharm.* (2004) **58**:615-619.
69. KIPP JE: The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. *Int. J. Pharm.* (2004) **284**:109-122.
70. MERISKO-LIVERSIDGE E, SARPOTDAR P, BRUNO J *et al.*: Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs. *Pharm. Res.* (1996) **13**:272-278.
71. MERISKO-LIVERSIDGE E, LIVERSIDGE GG, COOPER ER: Nanosizing: a formulation approach for poorly-water-soluble compounds. *Eur. J. Pharm. Sci.* (2003) **18**:113-120.
• **A review describing the use of wet milling technology to formulate poorly water-soluble compounds as nanocrystalline particles.**
72. FAHR A, HOLZ M, FRICKER G: Liposomal formulations of cyclosporin A: influence of lipid type and dose on pharmacokinetics. *Pharm. Res.* (1995) **12**(8):1189-1198.
73. KAYSER O, OLBRICH C, YARDLEY V, KIDERLEN AF, CROFT SL: Formulation of amphotericin B as nanosuspension for oral administration. *Int. J. Pharm.* (2003) **254**:73-75.
74. YANG S, LU L, CAI Y *et al.*: Body distribution in mice of intravenously injected camptothecin solid lipid nanoparticles and targeting effect on brain. *J. Control. Release* (1999) **59**:299-307.
• **A study showing that solid lipid nanoparticle are a promising sustained release and targeting system for lipophilic antitumor drugs.**
75. DEMIREL M, YAZAN Y, MÜLLER RH, KILIC F, BOZAN B: Formulation and *in vitro-in vivo* evaluation of piribedil solid lipid micro- and nanoparticles. *J. Microencapsul.* (2001) **18**:359-371.
76. YANG S, ZHU J, LU Y, LIANG B, YANG C: Body distribution of camptothecin solid lipid nanoparticles after oral administration. *Pharm. Res.* (1999) **16**:751-757.
77. MÜLLER RH, KECK CM: Challenges and solutions for the delivery of biotech drugs – a review of drug nanocrystal technology and lipid nanoparticles. *J. Biotechol.* (2004) **113**:151-170.
•• **An excellent review addressing the usage of solid lipid nanoparticles, nanostructured lipid carriers and lipid-drug conjugate nanoparticles in the delivery of biotech drugs.**
78. PORTER CJH, CHARMAN WN: *In vitro* assessment of oral lipid based formulations. *Adv. Drug Deliv. Rev.* (2001) **50**:S127-S147.
79. CHARMAN WN: Lipids, lipophilic drugs, and oral drug delivery – some emerging concepts. *J. Pharm. Sci.* (2000) **89**:967-978.
80. MEHNERT W, MÄDER K: Solid lipid nanoparticles. Production, characterization and applications. *Adv. Drug. Deliv. Rev.* (2001) **47**:165-196.
81. MÜLLER RH, MAAßEN S, WEYHERS H, MEHNERT W: Phagocytic uptake and cytotoxicity of solid lipid nanoparticles (SLN) sterically stabilized with Poloxamine 908 and Poloxamer 407. *J. Drug Target* (1996) **4**:161-170.
82. MÜLLER RH, MAAßEN S, WEYHERS H, SPECHT F, LUCKS JS: Cytotoxicity of magnetite loaded polylactide, polylactide/glycolide particles and solid lipid nanoparticles. *Int. J. Pharm.* (1996) **138**:85-94.
83. FREITAS C, MÜLLER RH: Effect of light and temperature on zeta potential and physical stability in solid lipid nanoparticle (SLN) dispersions. *Int. J. Pharm.* (1998) **168**:221-229.
84. FREITAS C, MÜLLER RH: Correlation between long-term stability of solid lipid

nanoparticles (SLN) and crystallinity of the lipid phase. *Eur. J. Pharm. Biopharm.* (1999) **47**:125-132.

85. DINGLER A, GOHLA S: Production of solid lipis nanoparticles (SLN): scaling up feasibilities. *J. Microencapsul.* (2002) **19**:11-16.
86. GOHLA SH, DINGLER A: Scaling up feasibility of the production of solid lipid nanoparticles (SLN). *Pharmazie* (2001) **56**:61-63.
87. UGAZIO E, CAVALLI R, GASCO MR: Incorporation of cyclosporin A in solid lipid nanoparticles (SLN). *Int. J. Pharm.* (2002) **241**:341-344.
88. MÜLLER RH, RUNGE S, RAVELLI V *et al.*: Oral bioavailability of cyclosporine: solid lipid nanoparticles (SLN®) versus drug nanocrystals. *Int. J. Pharm.* (2006) **317**:82-89.

•• **A study proving that SLN is a suitable oral delivery system to enhance the oral bioavailability of CsA.**

89. LUO Y, CHEN D, REN L, ZHAO X, QIN J: Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability *J. Control. Release* (2006) **114**:53-59.
90. GOUNDALKAR A, MEZEI M: Chemical modification of triamcinolone acetonide to improve liposomal encapsulation. *J. Pharm. Sci.* (1983) **73**:834-835.
91. FRESTA M, VILLARI A, PUGLISI G, CAVALLARO G: 5-Fluorouracil: various kinds of loaded liposomes: encapsulation efficiency, storage stability and fusogenic properties. *Int. J. Pharm.* (1993) **99**:145-156.
92. OLSON F, MAYHEW E, MASLOW D, RUSTUM Y, SZOKA F: Characterization, toxicity and therapeutic efficacy of adriamycin encapsulated in liposomes. *Eur. J. Cancer Clin. Oncol.* (1982) **18**:167-176.
93. GABIZON A, DAGAN A, GOREN D, BARENHOLZ Y, FUKS Z: Liposomes as *in vivo* carriers of adriamycin: reduced cardiac uptake and preserved antitumor activity in mice. *Cancer Res.* (1982) **42**:4734-4739.
94. MOHAMMED AR, WESTON N, COOMBES AGA, FITZGERALD M, PERRIE Y: Liposome formulation of poorly water soluble drugs: optimisation of drug loading and ESEM analysis of stability. *Int. J. Pharm.* (2004) **285**:23-34.
95. WATERHOUSE DN, MADDEN TD, CULLIS PR *et al.*: Preparation, characterization, and biological analysis of liposomal formulations of Vincristine. *Methods Enzymol.* (2005) **391**:40-57.
96. FAHR A, SEELIG J: Liposomal formulations of cyclosporin A: a biophysical approach to pharmacokinetics and pharmacodynamics. *Crit. Rev. Ther. Drug Carrier Sys.* (2001) **18**(2):141-172.
97. SCHOTE U, GANZ P, FAHR A, SEELIG J: Interactions of cyclosporines with lipid membranes as studied by solid-state nuclear magnetic resonance spectroscopy and high-sensitivity titration calorimetry. *J. Pharm. Sci.* (2002) **91**(3):856-867.
98. FAHR A, VAN HOOGEVEST P, MAY S, BERGSTRAND N, ML SL: Transfer of lipophilic drugs between liposomal membranes and biological interfaces: consequences for drug delivery. *Eur. J. Pharm. Sci.* (2005) **26**(3-4):251-265.
99. DUPONT B: Overview of the lipid formulations of amphotericin B. *J. Antimicrob. Chemother.* (2002) **49**(Suppl. S1):31-36.
100. WONG BERINGER A, JACOBS RA, GUGLIELMO J: Lipid formulations of amphotericin B: clinical efficacy and toxicities. *Clin. Infect. Dis.* (1998) **27**(3):603-618.
101. PODA GI, TETKO IV, ROHRER DC: Towards predictive ADME profiling of drug candidates: lipophilicity and solubility. *229th American Chemical Society National Meeting & Exposition; ACS.* San Diego, CA 2005.
102. TETKO IV, BRUNEAU P: Application of ALOGPS to predict 1-octanol/water distribution coefficients, logP, and logD, of AstraZeneca in-house database. *J. Pharm. Sci.* (2004) **93**:3103-3110.
103. ILLUM L, WASHINGTON C, LAWRENCE S, WATTS P: Lipid vehicle drug delivery composition containing Vitamin E. In. UK: Danbiosyst UK Limited (1997):1-44.
104. JENNING V, SCHÄFER-KORTING M, GOHLA S: Vitamin-A loaded solid lipid nanoparticles for topical use: drug release properties. *J. Control. Release* (2000) **66**:115-126.
105. JORES K, MEHNERT W, MÄDER K: Physicochemical investigations on solid lipid nanoparticles and on oil-loaded solid lipid nanoparticles: a nuclear magnetic resonance and electron spin resonance study. *Pharm. Res.* (2003) **20**:1274-1283.
106. ÜNER M, WISSING SA, YENER G, MÜLLER RH: Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) for application of ascorbyl palmitate. *Pharmazie* (2005) **60**:577-582.
107. LEUNER G, DRESSMAN J: Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* (2000) **50**:40-60.
108. SUCKER H: Hydrosole, eine alternative für die parenterale anwendung von schwer wasserlöslichen Wirkstoffen. In: *Pharmazeutische Technologie –Moderne Darreichungsformen*. Müller RH *et al.* (Eds), WVG, Stuttgart, Germany (1998):383-392.

Website

201. http://www.fda.gov/cder/OPS/BCS_guidance.htm
US Food and Drug Administration. Center for Drug Evaluation and Research. The Biopharmaceutics Classification System (BCS) Guidance.

Affiliation

Alfred Fahr[†1] PhD &
Xiangli Liu[2] PhD
[†]Author for correspondence
[1]Professor and Chair of Pharmaceutics
Friedrich-Schiller-Universität Jena,
Institute for Pharmacy, Lessingstrasse 8,
D-07743 Jena, Germany
Tel: +49 3641 949900;
E-mail: alfred.fahr@uni-jena.de
[2]Scientific Assistant
Friedrich-Schiller-Universität Jena,
Institute for Pharmacy, Lessingstrasse 8,
D-07743 Jena, Germany