When Poor Solubility Becomes an Issue: From Early Stage to Proof of Concept

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**Abstract**

Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. The issue arose especially when drug discovery and medicinal chemistry moved from wet chemistry to combinatorial chemistry and high throughput screening in the mid-1990s. Taking into account the drug product development times of 8–12 years, the apparent R&D productivity gap as determined by the number of products in late stage clinical development today, is the result of the drug discovery and formulation development in the late 1990s, which were the early and enthusiastic times of the combinatorial chemistry and high throughput screening. In parallel to implementation of these new technologies, tremendous knowledge has been accumulated on biological factors like transporters, metabolizing enzymes and efflux systems as well as on the physicochemical characteristics of the drug substances like crystal structures and salt formation impacting oral bioavailability. Research tools and technologies have been, are and will be developed to assess the impact of these factors on drug absorption for the new chemical entities.

The conference focused specifically on the impact of compounds with poor solubility on analytical evaluation, prediction of oral absorption, substance selection, material and formulation strategies and development. The existing tools and technologies, their potential utilization throughout the drug development process and the directions for further research to overcome existing gaps and influence these drug characteristics were discussed in detail.

**Keywords**

Drug solubility, Bioenhancement, Formulation, Poor water solubility.
1. Introduction

With the introduction of combinatorial chemistry and high throughput screening, the properties of new chemical entities shifted towards higher molecular weight and increasing lipophilicity that results in decreasing aqueous solubility (Lipinski et al., 1997; Lipinski, 2000).

Solubility in different solvents is an intrinsic material characteristic for a defined molecule. To achieve a pharmacological activity, the molecules must in general exhibit certain solubility in physiological intestinal fluids to be present in the dissolved state at the site of absorption. The aqueous solubility is a major indicator for the solubility in the intestinal fluids and its potential contribution to bioavailability issues.

During drug substance development the molecules are screened in nanomolar receptor assays. The molecules with the best receptor binding are selected for further pre-clinical studies, for which more drug substance is synthesized. Already at this stage, solubility is of critical importance, because solubility estimates for the poorly defined drug substance serve its pharmacological and toxicological profiling.

When going first into humans, sufficient and well characterized solubility becomes even more critical. From now on the solubility or dissolution of the dose ranges in the various biophysiological media to which the drug substance or formulated drug substance will be exposed is expected to be reproducible and remain unchanged for the final development and eventually marketing.

It is well accepted today throughout the scientific community that drug substance solubility and especially aqueous drug substance solubility is an issue for the drug discovery as well as the early and late stage pharmaceutical development process and therefore needs to be addressed very early on, during compound design and optimization.

The solubility or dissolution of the drug substance can be mainly altered on two levels, through material engineering of the drug substance or through formulation approaches. Whatever route is taken to enhance or modify the solubility and/or dissolution of a lead substance, it needs to be scalable to a commercially viable process later on in the development.

Besides the aqueous solubility of a drug substance, its permeability is a second critical aspect for oral bioavailability. The Biopharmaceutical Classification System (BCS) was introduced in the mid-1990s to classify the drug substances with respect to their aqueous solubility and membrane permeability (Amidon et al., 1995). Drug substances, for which solubility enhancement can improve the oral bioavailability, are substances that are classified in class 2 (poor soluble/permeable) and class 4 (poor soluble/poor permeable). Especially for class 2 substances, solubility enhancement is part of the strategies to improve the oral bioavailability.

The BCS classification takes into account the required dose since low dosed drugs will sufficiently dissolve in the intestinal fluids of the GI tract to be absorbed, while higher doses of drugs with similar aqueous solubility will not. To generally describe “solubility” the Pharmacopoeia (USP) uses seven different solubility expressions as shown in Table 1. The European Pharmacopoeia uses similar solubility definitions except the ‘practically insoluble’ characteristic, which is not specified (European Pharmacopoeia 5.0).

Table 1. Solubility definition in the USP.

<table>
<thead>
<tr>
<th>Description forms (solubility definition)</th>
<th>Parts of solvent required for one part of solute</th>
<th>Solubility range (mg/ml)</th>
<th>Solubility assigned (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble (VS)</td>
<td>&lt;1</td>
<td>&gt;1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>Freely soluble (FS)</td>
<td>From 1 to 10</td>
<td>100–1,000</td>
<td>100</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 10 to 30</td>
<td>33–100</td>
<td>33</td>
</tr>
<tr>
<td>Sparingly soluble (SPS)</td>
<td>From 30 to 100</td>
<td>10–33</td>
<td>10</td>
</tr>
<tr>
<td>Slightly soluble (SS)</td>
<td>From 100 to 1,000</td>
<td>1–10</td>
<td>1</td>
</tr>
<tr>
<td>Very slightly soluble (VSS)</td>
<td>From 1,000 to 10,000</td>
<td>0.1–1</td>
<td>0.1</td>
</tr>
<tr>
<td>Practically insoluble (PI)</td>
<td>&gt;10,000</td>
<td>&lt;0.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>
When looking at the product launches between 1995 and 2002, out of 100 substances 14 were considered class I, 12 were classified as class II, 28 were class III and 46 were class IV substances (Mehta, 2002). If a drug substance exhibits a poor aqueous solubility, the product development will have to focus on the investigation of various other drug substance characteristics like its physicochemical, biopharmaceutical properties and the targeted dose to identify the potential impact of the solubility on the further product development. Today, about 35–40% of the lead substances are known to have an aqueous solubility of less than 10 µM or 5mg/ml at pH 7 and it is not expected that this figure will change in the future.

2. Physical/chemical properties of the drug substance

Solubility is an intrinsic material property that can only be influenced by chemical modification of the molecule as such, like salt complex or prodrug formation. In contrast to this, dissolution is an extrinsic material property that can be influenced by various chemical, physical or crystallographic means like complexation, particle size, surface properties, solid state modification or solubilization enhancing formulation strategies.

Solubility is one of the key physicochemical parameters of a new molecule that needs to be assessed and understood very early on in drug discovery and drug candidate selection process. Starting with the first amount of the substance synthesized, commonly a few milligrams, the first series of analytical tests include that of the equilibrium solubility of the substance in a given solvent, as well as the apparent or dynamic solubility, which reflects the concentration of the substance in solution under certain conditions. The value of equilibrium solubility is often limited by the test duration, which is normally between 4 and 24 h. The solubility and apparent solubility of the substance in an aqueous system are dependent on several factors (Table 2).

Rather than single point determinations, a solubility profile of the substance is required to identify potential issues for drug precipitation in vivo. Especially the pH profiling for weakly basic salts is of critical importance as their solubility will vary in the intestinal pH (typically pH 1–8) and precipitation may occur. The pH profiling should be performed in different bio-relevant buffer systems to mimic the high concentrations of the most common counter ions of pharmaceutical salts in GI fluids. This screen allows detection of a potential counter ion exchange and formation of more stable/less soluble salts of a molecule that will lead to precipitation in vivo. The pH profile additionally provides the basic guidance to choose among potential solubilization strategies.

Conversion of the molecule to other salts or hydrates needs to be taken into account and evaluated in the solubility profiling. Different salts of the substance can be formed dependent on the buffer systems as well as their ionic strength. It is generally accepted that there should be a minimum difference of three units between the pKa value of the ionizable group and of the possible counter ion (Bowker, 2002). Ampholytes display a more complex solubilization process (two step reaction) including micelle formation at high ionic strength. Buffer salts as well as hydrates might have different solubility characteristics.

Therefore different analytical methods have been developed to assess the substance in solution or solid state (precipitates) (Giron and Grant, 2002). Analytical methods for the substance in pH-controlled solutions are LC coupled with UV and MS. For the solid state analysis, powder X-ray diffraction, energy dispersive X-ray (EDX), Raman spectroscopy, IR, microscopy (polarized light microscopy (PLM), environmental scanning electron microscopy (ESEM)) and thermal analysis are used.

The solubility profiling should include any other biorelevant dissolution media like simulated gastric fluid (SGF) with and without enzymes, fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) at pH 5.0 and 6.5 or human gastric or intestinal fluids (HIF’s).

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Table 2.
Factors influencing solubility.

<table>
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<tr>
<th>Composition of the aqueous media</th>
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<tr>
<td>Temperature</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>Solid state (amorphous, crystalline)</td>
</tr>
<tr>
<td>Polymorph type</td>
</tr>
<tr>
<td>Counter ions (salt formation)</td>
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<tr>
<td>Ionic strength</td>
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In parallel to the analytical characterization of the initial material of the drug substance, substantial efforts are invested into understanding and optimization of the crystalline structure and to identify a potential pseudo-thermodynamic stable form of the substance. These investigations are looking into the polymorphs, solvates and salts formed by the substance under various conditions to identify the most suitable material for dosage form development, scaling up and later manufacturing.

Polymorphs appear in a number of different structures as non-mixed polymorphs (free base or acid) or as mixed polymorphs like salts, co-crystals (Vishweshwar et al., 2006), guest substances, hydrates or solvates (Bernstein, 2002; Brittain, 1999).

While the polymorph screening focused more on the number of different polymorphs by crystallization in different solvents in the past, it now has shifted towards qualitative data on polymorph formation under thermodynamically controlled conditions to get more accurate data on the potential risk for polymorphic changes in the final dosage form under the expected storage conditions. These constant and controlled conditions include pressure, temperature, solvent and time.

Once a polymorph is found and characterized, additional polymorph evaluation experiments should be performed to provide information on its kinetic stability.

The evaluation starts with determining, e.g., if the substance forms only one anhydrate or several anhydrates. Once different polymorphs have been identified it is important to characterize whether they are monotypically or enantiotropically related. In case of an enantiotropic phase transition, the transition temperature as well as the temperature stability range must be very well characterized. Long-term stability is tested in slurry experiments for at least 2 months in different non-solvate forming solvents and/or at temperatures in the stability range of the anhydrates. From this series of polymorph experiments the most thermodynamically stable form is selected and will be further evaluated in competitive slurry experiments at room temperature with any other known anhydrates and solvates. Reversibility between the different forms will be included in the evaluation in long-term slurry experiments and summarized using binary and ternary phase diagrams. As an example, formoterol fumarate has been found to form seven modifications in the polymorph screen. Running the polymorph experiments, the dihydrate form has been determined as the most stable solid form due to its favorable capacity of forming efficient hydrogen bonds between the formoterol and the fumarate leading to a well-packed crystal structure (Jarring et al., 2006).

To improve physicochemical properties of the drug substance with regard to manufacturing, isolation and long-term storage, as well as to improve solubility and/or dissolution properties of the drug substance, salt formation is traditionally preferred by medicinal chemists for weak bases or weak acids. Since only 20–30% of the new molecules form salts easily, the 70–80% remain challenging (Serajuddin and Pudipeddi, 2002).

Salt formation is a two-step process in which proton transfer in solution has to take place followed by a crystallization step. Identification of a suitable solvent to achieve sufficient attractive forces of the substance salt as well as to overcome ion and molecule solvation is required. To achieve a thermodynamically stable salt with sufficient aqueous solubility, it is important to understand the salt structure formed by a specific counter ion. Counter ions act as a template that interacts through non-covalent bonds with the molecule by their conformation and bonding capabilities, which directly influence the three-dimensional structure. Data bases on the possible salt structures of functional groups can provide some valuable predictions on the number of possible solvates and hydrates and their coordination number defined as the number of non-covalent bonds formed by the ion (e.g., Cambridge Crystallographic Data Center). Selected salts of a molecule will be assessed in a salt screening following the same principle as polymorph screening to investigate the long-term stability as well as its conversion to other, more stable salts and its precipitation in different aqueous and bio-relevant media.

With the increasing knowledge about the implications of polymorphs and salts in drug discovery, automated tools are being developed to standardize and implement these experiments as a routine process in drug discovery and lead substance selection (York, 1999; Rohl, 2003).

To overcome poor aqueous solubility or erratic bioavailability, chemical modification leading to a prodrug has successfully been used for several substances. The most common used prodrug approach is the incorporation of a polar or ionizable moiety into the molecule. The incorporation of N-acyloxyalkyl moieties of different chain
length leads to a reduced crystal lattice interaction and decreasing melting point with increasing number of methylene groups (Stella et al., 1998). In vivo studies in dogs with the N-acyloxyalkyl derivatives of phenytoin confirmed a higher bioavailability in the fed state that did not correlate with decreasing water solubility (Stella et al., 1999). Prodrugs also might reduce the pre-systemic metabolism of the substance in the GI tract or the release of the drug substance itself by enzymatic cleavage of the prodrug moiety close to the site of drug absorption. Fosphenytoin is a phosphate prodrug of phenytoin that is metabolized by phosphatases to release its active moiety phenytoin. In vivo studies in dogs and humans have demonstrated a better bioavailability after oral, intramuscular and intravenous administration. Additionally fosphenytoin has shown a better safety profile compared to its original form phenytoin sodium (Stella, 1996). Examples for successful phosphate prodrugs are fosphenytoin (Cerebyx™) and amprenavir phosphates (VX-175/GW 908). Another successful prodrug development is bortezomib, a boronic acid pro-drug (Velcade™) (Sanchez-Serrano, 2006). Current research is focusing on the development of new prodrug moieties like N-glycines, sulfenamides and cysteamines to improve bioavailability by better solubility or metabolic stability.

Once the most favorable thermodynamically stable form of a lead substance is determined and its solubility profile is characterized, investigations into its biopharmaceutical characteristics using in vitro, in silico or in vivo trials in animals will provide the necessary information on the substances predicted in vivo performance and for the design of a drug delivery system.

3. Biopharmaceutical evaluation of the drug substance

The biopharmaceutical evaluation and prediction is another crucial part of the lead drug candidate selection process. It is well established today that drug substances that do not meet at least certain biopharmaceutical criteria are returned to the medicinal chemist for lead optimization (Clark and Grootenhuis, 2003).

One of the most critical aspects of in vitro screening assays is the determination of the true concentration of the free drug in the assay. The concentration of free drug in the assay is normally calculated rather than measured.

### Table 3.

<table>
<thead>
<tr>
<th>In vitro systems to identify permeability and absorption.</th>
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<tr>
<td>CaCo-2 cell lines</td>
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<tr>
<td>Madin-Darby canine kidney (MDCK) cell lines</td>
</tr>
<tr>
<td>Parallel artificial membrane permeability assay (PAMPA)</td>
</tr>
<tr>
<td>Immobilized artificial membrane chromatography (IAM)</td>
</tr>
<tr>
<td>Advanced compartmental absorption and transit (ACAT)</td>
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<tr>
<td>Lipophilicity (log D and log P)</td>
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Unexpected low solubility and precipitation of the drug in the media due to the dilution sequence (e.g. dilution from an aqueous buffer solution or from DMSO solution) has been reported. When the calculated drug concentration in the assay is not reached, wrong conclusions are most likely to be drawn regarding efficacy, toxicity or permeability (Di and Kerns, 2004).

The main in vitro tools used for the assessment of drug absorption and permeability are listed in Table 3.

The CaCo-2 cell monolayers are well-established in vitro systems that are used in various stages of the drug development process to assess drug absorption and the underlying processes (Shah et al., 2006). CaCo-2 cell lines provide valuable information about the permeability and absorption potential of a drug substance. They can further be used in later development to provide information about the potential impact of metabolic or efflux systems on the drug substance and to classify the drug according to the BCS.

When using CaCo-2 cell monolayers to measure permeability of poorly soluble substances attention must be drawn to possible drug accumulation within the cells, binding to proteins or adhesion to plastic surfaces. To avoid variability beyond ±10% in the permeability data obtained with CaCo-2 cell tests, standardization and calibration are critical.

The parallel artificial membrane permeability assay (PAMPA) is an artificial, intrinsic permeability measurement that is used for drug lead substance selection and for pre-clinical studies in a high throughput manner. The PAMPA system is based on synthetic phospholipids and fatty acids that mimic physiological conditions. PAMPA is used as a low cost alternative to cell based systems for early ADME screening (Avdeef, 2005). High confidence in the predictions using PAMPA has been reported for drugs with good...
effective permeability (>10^{-6} cm/s) and the poor effective permeability (<2.5^{-6} cm/s), while the results for drugs in between are difficult to interpret.

For efficient and rapid investigation into mechanisms of drug absorption, CaCo-2 cell monolayers are combined with the PAMPA assay (Kerns et al., 2004). Drugs that correlate in the comparison are mainly absorbed through passive diffusion. Substances, which show higher permeability in PAMPA than in a CaCo-2 model, are substrates for efflux or for reduced passive diffusion of acids under CaCo-2 pH gradient setup. Substances with a higher CaCo-2 cell permeability when compared to the PAMPA system have underlying absorptive mechanisms like paracellular, active transport or increased passive diffusion in a CaCo-2 cell pH gradient.

Immobilized artificial membranes (IAM) are solid phase models of liposome membranes for partitioning studies of drugs into membranes. IAM chromatography is a simple experimental tool that allows for large number screening tests in the drug discovery phase to identify the potential of a drug substance of being absorbed, independently from other factors involved in poor bioavailability like pre-systemic metabolism, efflux systems or transporters (Pidgeon et al., 1995).

Poor prediction still persists for the drug absorption in the colon. Due to the reduced paracellular or carrier-mediated absorption, efflux mechanisms, the reduced surface area, the colonic solubility environment (pH 6–7), the reduced volume and mixing and the unknown chemical metabolism of the substance along the GI tract, the contribution to drug absorption still remains unclear. However, poorly soluble substances and drugs from extended release formulations reach the colon at a considerable concentration and stay there for a long time. Even if absorbed slowly, this may contribute substantially to absolute bioavailability.

For the predictions of human drug absorption today the specific absorption rate (SAR) or human absorbable dose (Dabs) model is frequently used. The SAR plots the absorption number versus the dose number (Collins and Rose, 2004). The Dabs model is based on the permeability of a substance, its solubility in simulated intestinal fluids, the surface area of the human GI tract defined as 800 cm^2 and a GI transit time of 3.3 h (Yu, 1999). Plotting the D_{abs} versus the expected therapeutic dose already gives some hint whether drug absorption will be the rate-limiting step for a conventional dosage form. For example, pioglitazone, a weak base with a good solubility at low pH will not require an enabling formulation due to its solubilization in the stomach; neither would tadalafil, a non-ionizable substance over the physiological pH range and a low solubility in all relevant media, because of its low dose (20 mg).

Another model proposed is using the maximum absorbable dose (MAD) concept taking into account a small intestinal transit time of 4.5 h, a small intestinal fluid volume of 250 ml, the substance solubility and an absorption constant for the drug substance (Johnson and Swindell, 1996). The MAD values provide good predictions if the projected human dose can be absorbed. Evaluating a series of substances it can serve as a guiding tool for rank ordering of the potential lead drug candidates in a specific series of substances (Curatolo, 1998).

Using the MAD model as a starting point, computational systems have been developed to simulate drug absorption in vivo (Johnson, 2003). Additional input parameters like water absorption from the GI tract and changing gastrointestinal permeability have been introduced to improve the simulations.

Another computational system for the simulation of drug absorption is based on the advanced compartmental absorption and transit (ACAT) model (Agoram et al., 2001). The ACAT model is an extended version of the compartmental absorption and transit (CAT) model that uses seven small intestinal compartments for prediction. The ACAT takes into account the colon as another compartment for drug absorption, which cannot be neglected for poorly soluble and poorly permeable substances as well as for sustained release formulations. The selection of the dissolution media for
each compartment is an important factor that affects the accuracy of the prediction in the ACAT model. Using FaSSIF media for example, provides better correlations than simple buffer systems at pH 6.5 for soluble substances, however, for poorly soluble substances under-predictions are more likely for pH 6.5 buffer, while over-predictions are the case for the FaSSIF media. The output of the ACAT model has been improved by including other parameters on the drug substance like particle size/radius, density, diffusion coefficient, log D, pKa and molecular weight.

The simulations for both systems are relatively good, but tend to be less accurate for the poorly soluble substances due to the difficulty in modeling the colonic drug absorption.

The major limitations seen today in the in silico models concern the potential drug precipitation in the GI tract (e.g. weak bases, salts of poorly soluble substances), the impact of colonic drug absorption, especially of poorly soluble substances when at high dose and the effect of the drug particle size on absorption. While further validation work is ongoing, the existing in silico tools already provide important information for lead candidate selection and/or optimization and can be developed further to improve the accuracy of the simulation (Kuentz et al., 2006).

Following the biopharmaceutical evaluation of the substance’s solubility/dissolution behavior in aqueous or biorelevant media, permeability, chemical and metabolic stability are assessed, in vitro. Thereafter, the absorption, food effect, first pass metabolism, PK profiles are finally quantified in different animal species (rats, dogs, monkeys) in a close-escalating manner. These studies are designed to establish first in vivo oral exposure rate and dose linearity. For these studies the drug is administered as a solid, suspension or solution. These studies should also provide information on any dependency of absorption on particle size as well as on the upper limit of exposure, the clearance and potential food effects of a standard formulation.

Later on, in particular when potential for extended release formulation development is considered, more in depth investigations into the mechanism of drug absorption can be performed using, for instance, a regional perfusion model that can be applied to animals (e.g. dogs) or humans (Lennernäs et al., 1992). The regional perfusion model is also used to establish a correlation between the human permeability and the CaCo-2 cell permeability (Lennernäs et al., 1997) and provides important information for the design of the drug delivery system. To facilitate and improve the investigation into regional drug absorption and its underlying mechanisms, special capsules have been developed that permit a time- and position-controlled release of the drug substance or formulation in defined areas of the GI tract (Wilding et al., 2000).

To get at least some data on a substance performance in humans before lead substance selection or entering into the clinical development, the European Medicines Agency (EMEA) recently accepted the concept of a single micro-dosing study in humans (EMEA, 2003). Micro-dosing studies allow one single dose of less than 1/100th of the calculated pharmacological dose and not more than 100 µg in total dose for small molecules. Even so there is only very limited experience of micro-dosing studies and their value in the drug development process so far. Micro-dosing is expected to become a useful tool in identifying substances with critical biopharmaceutical properties as well as improving significantly in silico predictions of drug absorption and deposition (Wilding and Bell, 2005).

While some tools provide highly valuable data for lead substance selection for one substance, they might not for others. Therefore the series of different in vitro, in vivo and predictive methods and tools provide a good base for putting together a meaningful evaluation program that needs to be designed for each individual substance based on the information gathered during drug discovery and substance characterization.

4. Drug candidate selection

Multidisciplinary teams are becoming an essential part of the lead candidate selection process in the pharmaceutical industry. Their objective is to address early on the various characteristics of the drug substances from the chemical as well as the pharmacological, toxicological and biopharmaceutical point of view. These multidisciplinary teams judge together the ability of the substance to pass the various criteria to become an effective and safe medicinal product (Bowker, 2002). While receptor affinity in a high throughput screening still represents the base line for selection, much more attention is paid to the characteristics themselves as they may determine potential issues during development (Table 4).
Lead substance selection processes can be part of the development process at various stages between drug discovery and clinical development. The tools discussed above can basically be used at all stages of the drug discovery and lead optimization process, their accuracy, precision and predictive nature will improve gradually with the accumulation of knowledge about the substance.

During the discovery phase, where a large number of substances are evaluated, some crude estimations based on MAD, molecular physical parameters, e.g. ‘rule-of-five’ (Lipinski et al., 1997) and permeability data of structural related substances could raise alerts and provide directions away from structural areas known to cause absorption issues. Once a series of substances is synthesized, a pharmacokinetic screening in animals and CaCo-2 cells should be performed. At least for some of the substances synthesized, this screen, together with solubility testing, can provide further guidance to the lead optimization program. When a few substances are selected as potential lead drug candidates, metabolism and pharmacokinetic studies in at least 2 animal species as well as further solubility studies should be performed. The data will give better output in the predictive tools like the MAD and in silico models taking into account the expected human dose (Curatolo, 1998).

The decision-making process for entering in a clinical program includes a critical review of the tests performed and the consistency of the data resulting from these experiments which could reveal issues caused by the solubility characteristics of the substance.

Substances lacking sufficient aqueous solubility, especially when expected to be administered in high dose may not display their toxicological profile as they do not achieve the calculated concentration in the toxicological assay.

If a substance forms stable and less soluble forms (e.g. salts) with physiological fluids or food components, the potential risk for drug precipitation in the GI tract needs to be considered. The physical properties must also be addressed from a processing point of view. During synthesis and manufacturing in a large commercial scale, the hygroscopcity, amorphicity, crystallinity and polymorphism of a substance need to be controllable and manageable in an industrial environment. For substances with dissolution- or solubility-limited absorption, variability in bioavailability is often observed and can be a critical selection criterion. The variability might be seen as a food effect, but might also come along only in specific patient populations (elderly, pediatric) or disease stages. In such cases, formulation strategies must be considered early on decreasing the intra-and inter-subject variability.

All qualified data on the pharmacological and biopharmaceutical properties of a drug substance have to be taken into account during lead identification and optimization process. The lead candidate selection is a complex decision process that involves all disciplines. The selection process does not necessarily lead to the selection of one lead substance; it can also provide clear directions and recommendations for further lead substance optimization.

While extensive data on the lead substances normally exist at the stage of the decision process, they do not necessarily exist for possible back-up substances or a potential optimized lead substance. Lacking these data makes it very difficult during the lead candidate selection process to take decisions for discontinuation of the lead substance or modification on the molecule, either introducing additional functional groups or ‘downsizing’ the molecule at this stage. The decision process will include an assessment as to whether the foreseen limitation of the lead substance can be easily solved by specific technologies or by drug delivery strategies that are commercially viable or can be successfully developed during the time-lines set for the development of the substance to a marketed product.

5. Formulation strategies for solubility and bioenhancement

The initial drug discovery screening is typically performed with the amorphous forms of substances in dimethyl sulphoxide (DMSO). These “formulations” of high-energy
forms of the substance are sufficient for the receptor and efficacy screen, but neglect any solubility characteristics of the substance at this stage and therefore cannot allow for a relevant biopharmaceutical (i.e. absorption) assessment.

For the continuation of the early drug discovery program, sufficient concentration of the amorphous or crystalline drug dissolved in aqueous test media is needed for appropriate in vitro and in vivo testing. When the solubility of substances in aqueous media is limited, formulation strategies are required early on in the drug discovery and they remain of critical importance for lead substance selection and commercial drug product development. The major drug solubilization strategies are summarized in Table 5.

To support the early drug discovery program, experimental formulations are developed and studied for dissolution and short term stability. When aqueous solubility or dissolution of the substance is identified as an issue for the in vitro and in vivo testing, simple and effective formulation strategies are applied to secure the expected drug deposition in the in vitro and in vivo trials.

Particle size reduction is one of the first strategies investigated. Wet milling is used for particle size reduction and a particle size of about 200 nm is achievable. Should this not lead to the expected concentration in the in vitro assay or in vivo exposure, formulations with solubilizing agents like cyclodextrins or micellar systems are evaluated. Other systems that are used are solvent-and surfactant-based formulations (e.g. microemulsions) or solid dispersions. These latter systems require substantial development times and might be limited due to potential excipient-related toxicity or unwanted effects on the test system.

The solubilizing efficiency of low molecular weight polyethylene glycols (PEG) is used frequently for solubilizing the drug substance for in vivo studies. Besides the solubilizing effect, low molecular weight PEGs, e.g. PEG 400 have been demonstrated to have a dose-dependent influence on drug absorption. Dependent on the amount of PEG 400 in the formulation, the absorption of ranitidine was increased (by 41% with 1 g PEG) or decreased (by 38% with 2.5 and 5.0 g PEG). While the gastric emptying remained the same, PEG increases the intestinal transit time (by 9, 20 and 23% for 1, 2.5 and 5.0 g). The increase in absorption with 1 g PEG 400 might also display an effect of the PEG 400 on the intestinal permeability (Schulze et al., 2003).

As described above, the solubility of a substance depends on its solid-state form. To obtain the most soluble form of a drug substance, a technology has recently been developed to make sufficiently stable amorphous nanosuspensions with a particle size in the 100 nm range. The drug is dissolved in an organic water-miscible solvent. The organic solution of the drug substance is then added into an aqueous solution containing a stabilizer and mixed using an ultrasonic batch. The amorphous form of the drug results from a homogeneous nucleation process and it precipitates into the aqueous phase, from which the organic solvent is removed. To avoid particle growth by Ostwald ripening, a poorly water-soluble stabilizer (mainly a non-ionic polymer like PVP or HPMC) is incorporated into the aqueous phase to which the organic drug solution is added. The stabilizer acts as an inhibitor of Ostwald ripening and prevents particle growth during storage. While for felodipine, nifedipine and bicalutamide, Miglyol in a drug/inhibitor ratio of 4:1 was sufficient to prevent Ostwald ripening, for other investigational drug substances an additional component is needed. Decanol in this case was added as an additional, essentially water-insoluble component in a 1:1 ratio with Miglyol and a drug/inhibitor combination ratio of 4:1 successfully inhibits particle growth. The inhibitor or inhibitor combinations prevent Ostwald ripening when forming a homogeneous mixture with the amorphous drug substance (Lindfors et al., 2006a).

The dissolution of the amorphous material can be determined in a nanosuspension using a light scattering technique. The basic principle of the light scattering technique is the determination of the appearance of
colloidal particles during concentration increase. It has been found that the amorphous nanosuspensions dissolve several times more than the corresponding crystalline form. The differences in the solubility of the amorphous versus the crystalline form can be calculated from the chemical potential differences using the solubility and thermodynamic data from the melting point of the crystals (Unfors et al., 2006b).

Amorphous nanosuspensions can be used routinely as experimental formulations in the early drug discovery phase.

Nanodispersions of amorphous drug material have been recently prepared using sugar glasses. Sugar glasses are physically stable amorphous systems (in the glassy state) with a high aqueous solubility. Preparations of nanodispersions have been described using trehalose, sucrose and two different inulins (inulin DP21 and inulin DP23 with a degree of polymerization of 21 and 23, respectively) as sugar glass carriers. Amorphous nanodispersions of diazepam were prepared by dissolving the sugars in water and the drug in tertiary butyl alcohol. The two phases were mixed in a ratio of 6:4 water:alcohol and then freeze-dried. Diazepam was incorporated in its amorphous form in concentrations up to 100% at 10 and 20% drug load in all sugars and up to 97% at drug loads of 40 and 63% in trehalose, inulin 21 and 23 while the amorphous form represented only 89% in sucrose. After 60 days at 25 °C and 45% RH, no increase in the crystallization clearly progressed in the other sugars. At drug loads of 40% crystallization was also observed in inulin DP21 and at 63% for inulin DP23. This difference is due to the high glass transition temperature of the inulins favoring physical stability of the nanodispersions (Van Drooge et al., 2004a). The dissolution behavior of the different amorphous sugar glasses is dependent on the dissolution of the sugar glass and the incorporated drug concentration. In the fast dissolving sugars (trehalose and sucrose) the initial release was fast but then counteracted by crystallization that occurred due to supersaturation in the boundary layer at the tablet surface. For the slower dissolving sugars (inulin DP21 and inulin DP23) this phenomenon was less pronounced. Crystallization was found to be dependent on the drug load in the sugars as well. The optimum dissolution is achieved, when the dissolution profile of the amorphous drug coincides with the dissolution profile of the carrier (Van Drooge et al., 2004b). To improve the solubility of poorly soluble substances from sugar glasses, further investigation are being conducted, which include the addition of surfactants and the controlled crystallization to achieve sugar glasses with nanocrystallized drug.

Cyclodextrins (CD) are cyclic oligomers typically composed of 6-8 glucose units. CDs represent a class of solubilizing agents that form non-covalent, dynamic complexes with lipophilic molecules by inclusion. The inclusion complex modifies temporarily the physical properties of the substance. Governed by the equilibrium constant between the free drug, free CDs and the drug-CD complex, the drug will be released constantly and rapidly on dilution. CDs have been demonstrated to improve the stability of substances like proteins or peptides (Davis and Brewster, 2004). The CDs that are approved for pharmaceutical products can be classified into three major types differing only in their molecular weight and respective central cavity diameter. Alpha-cyclodextrin (α-CD) has a molecular weight of 972 and a central cavity diameter of around 5Å, these increase to MW 1135 and 6.2Å for β-CD and MW 1297 and 8Å for γ-CD, respectively. Despite the fact that β-CD complexes are used in the majority of oral CD products on the market, β-CD exhibits some limitations caused by its poor aqueous solubility, the potential formation of crystalline complexes and nephrotoxicity when administered parenterally. To improve the characteristics of β-CD, chemical modifications have led to two new derivatives, 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobutylether-β-cyclodextrin (SBE-β-CD). HP-β-CD is an amorphous isomeric mixture with improved aqueous solubility while maintaining its complexation potential. The complexation behavior of HP-β-CD was investigated using itraconazole as a model substance. The complexation of itraconazole with the HP-β-CD was found to be dependent on the CD/drug ratio and the pH of the system (Peeters et al., 2002). HP-β-CD was thoroughly investigated for its safety profile and found to be well tolerated orally and parenterally, with limited toxicity. Following intravenous application HP-β-CD show a short elimination half life of less than 2 h with dose-proportional kinetics. After oral application less than 3% of the HP-β-CD is absorbed (Gould and Scott, 2005). HP-β-CD has received a monograph in the EP and both, HP-β-CD and SBE-β-CD, are listed in the FDA list of inactive ingredients.
Parenteral and oral formulations have been approved and launched in US and Europe.

Lipid-based drug delivery systems represent a wide variety of formulations composed of lipophilic, amphiphilic and hydrophilic excipients that are able to solubilize poorly water soluble and lipophilic drugs. The systems are designed for each drug substance to exhibit additional features like self-emulsification when exposed to aqueous media. Lipid-based drug delivery systems have been proven to increase oral bioavailability, reduce food effect and to deliver lipophilic drugs to the lymphatic system (Charman, 2000).

In the past years, a lot of understanding has been developed around the lipid-based formulations in order to better design and evaluate these systems for the drug delivery of poorly soluble substances. It has been recognized that lipid formulations when taken orally, undergo physiological digestion, modifying the systems characteristics substantially before reaching the side of absorption.

Lipid digestion starts with the secretion of lipases and co-lipases from the salivary gland, gastric mucosa and the pancreas, which hydrolyse the triglycerides into di- and mono-glycerides and the free fatty acids. Upon release of bile salts, vesicles and colloidal particles are formed and released from the surface of the lipid. Further solubilization into a range of emulsion droplets, vesicular structures and mixed micelles containing bile salts, phospholipids and cholesterol takes place during travel along the GI tract (Porter and Charman, 2001). Each of these micellar and vesicle structures represents a different solubilization capacity for the drug substance and can have a direct impact on drug deposition. In vitro digestion models have been developed to assess formulation digestion and its impact on drug solubilization (Kaukonen et al., 2004a,b).

The solubilizing capacity of the lipid formulation for a drug substance is potentially impacted by digestion with implications on the bioavailability. Lipid formulation of the poorly water soluble danazol have been created using a simple solution in long chain triglycerides and two self-emulsifying systems that were composed of long chain lipids (C 18) and medium chain lipids (C 8–C 10). Upon in vitro digestion, precipitation of danazol occurred in the medium chain derived self-emulsifying system, which led to a five-fold lower bioavailability (AUC) in dogs than the long chain self-emulsifying system. The study also demonstrated that two different formulations (a solution in long chain triglycerides and a long chain based self-emulsifying system) revealed a similar bioavailability, which can be explained by digestion leading to similar absorption phase in vivo (Porter et al., 2004).

Highly lipophilic substances (log P > 5) with low aqueous solubility may be suitable candidates for absorption using the lymphatic pathway. Upon digestion, short and medium chain triglycerides and fatty acids are absorbed directly into the portal vein while long chain triglycerides and long chain fatty acids lead to the formation of chylomicrons triggering the lymphatic absorption. For efficient drug delivery into the lymphatic system, the drug should have a minimum solubility of 50 mg/ml in long chain triglycerides to be sufficiently dissolved in the chylomicrons (Porter and Charman, 2001). The lymphatic absorption results in smaller animals (e.g. rats) have been found to underestimate the potential transport capacity in humans. To better predict the lymphatic absorption in human a triple-cannulated dog model collecting thoracic lymph, portal and systemic blood samples has been developed to assess lymphatic absorption of formulated drug in the pre- and postprandial state (Khoo et al., 2001).

Halofantrine free base is a highly lipophilic substance (calculated log P ~8.5; solubility ~50 mg/ml in triglycerides). Halofantrine is mainly absorbed through lymphatic transport with an increased absorption following food intake. When formulated as a microemulsion containing long chain lipids or medium chain lipids in the fasted state, it could be demonstrated that formulation approaches using even small lipid volume formulations can stimulate the endogenous release of triglycerides, the formation of lipoproteins and the drug transport through the lymphatic pathway (Khoo et al., 2003). A similar effect was observed when using the poor lipid soluble hydrochloride salt of halofantrine. The studies suggest that the intestinal solubilization of halofantrine-HCl in the fed state leads to conversion into the lipid soluble halofantrine free base and its incorporation into chylomicrons formed during the lipid digestion (Khoo et al., 2002; Taillardat-Bertschinger et al., 2003).

With lipid-based formulation systems, specific emphasis has been given to the self-emulsifying drug delivery systems (SE) (Constantinides, 1995). An SE typically consists of 3–5 excipients in a certain ratio forming a thermodynamically stable microemulsion upon exposure
to water. With particle sizes below 200 nm in water the systems appear translucent. An SE can be designed using a rational approach in excipient selection and combination. The starting point is the selection of the substance for an SE, which needs to fulfill certain criteria with regard to the dose, permeability and log P (Benamer, 2006). Solubility studies with the substance in different lipophilic, amphiphilic and hydrophilic excipients are performed. Phase diagrams with blends of excipients, which typically consist of a combination of a lipophilic solvent(s) (oil), the hydrophilic solvent (water) and surfactant(s) and the drug substance are drawn up. The combinations of excipients, which lead to microemulsions with the drug substance, are further evaluated for their phase behavior and thermodynamic stability (Kang et al., 2004).

The selected lead formulations will be characterized for their isotropy, rheological behavior, thermodynamic and physical stability as well as the droplet size in aqueous media. CaCo-2 cells can be used to compare pure drug permeability against the permeability of the formulated drug to select the lead SE formulation. Published (Gao et al., 2004; Kang et al., 2004) and unpublished data from several case studies confirmed that, for drug substances for which the solubility in aqueous media is limiting the bioavailability, the rational approach towards the design of SE systems can improve the in vivo absorption of the drug substance.

Recent findings have suggested that poorly soluble substances are mainly incorporated in the mantle close to the core rather than in the lipophilic core of the emulsion droplet, drawing more attention to the surfactants themselves. Their hydrophobic chains and hydrophilic head groups mainly determine the solubilization capacities of the existing non-ionic surfactants. To increase the solubilization capacity, new non-ionic surfactants were designed by altering the hydrophobic chain and the hydrophilic head groups. N,N-Dimethylalkylamine-N-oxide (DDNO) has demonstrated an improved solubilization capacity for most of the poorly soluble substances (betamethasone, cortisone acetate, testosterone, phenylbutazone, griseofulvin) compared to the existing non-ionic surfactants (polyoxyethylene ether derivatives). Due to the toxicity profile of DDNO, which is mainly attributed to its metabolic stability, a biodegradable version of DDNO was synthesized by introducing a biodegradable carbonyl linker. The N,N-dimethyl-N-(3-dodecylcarbonyloxypropyl)amine oxide (DDCPNO) was then investigated for its solubilizing capacity. DDCPNO exhibited a greater solubilization capacity than the polyoxyethylene ether surfactants, but less than DDNO (Tolle et al., 2000). In further studies using another derivative of the amine-N-oxide surfactants, N,N-dimethyldecylamine-N-oxide (DDAO), it was found that the chain length of the lipids in the oil phase and their ratios with DDAO have an impact on the droplet radius and the aggregation number (Warisnoicharoen et al., 2000). Therefore, the solubilization in microemulsions depends on the nature of oil and its incorporation into the microemulsion system while in micellar structures the head groups are most important.

Carotenes represent a variety of lipophilic substances with a critical bioavailability. Lycopene, a poorly soluble carotene derivative exhibiting poor bioavailability from its natural sources (e.g. fresh tomato) has been investigated with regard to bioavailability enhancement by the food industry. While particle size reduction of the lycopene crystals slightly enhances the bioavailability, processing (e.g. tomato paste) led to a three- to fourfold bioavailability enhancement. Investigations into the oral bioavailability revealed a potential impact of the stereochemistry of the lycopene molecule. In natural sources the all-trans isomer is the dominant form (95%), which is in contrast to the in vivo stereochemical form of the lycopenes. In the skin and prostate, the cis-isomer represents 70% and 85%, respectively. As demonstrated by in vitro tests with micelles, chylomicrons and CaCo-2 cells, 30% of the all-trans lycopene is isomerized into its cis-isomeric forms. In a subsequent investigation it was demonstrated that processing had an effect on the formation of the cis-isomers, which would explain the high bioavailability with the processed natural source (tomato paste). The findings suggested that the stereochemistry may play a critical role on the absorption of lycopene and that the 5-cis-lycopene is the most favorable form for absorption.

To improve the bioavailability of lycopene through formulation, a complex of lycopene was formed with whey proteins (lacto-lycopene) and spray-dried to powder form. The lacto-lycopene complex was bioequivalent to the processed natural source (tomato paste) and exhibited the same distribution to buccal mucosa cells (Richelle et al., 2002).

The absorption of β-carotene is reduced when administered together with free or esterified phytosterols. While the sterol esters had a specific effect on the...
β-carotene absorption, these findings demonstrate clearly the importance of food components in drug absorption (Richelle et al., 2004).

6. Biopharmaceutical evaluation of drug delivery systems

When solubility is identified as a critical parameter for the bioavailability and/or lead candidate selection, the formulation strategies need to be evaluated and compared for their in vivo performance in humans. The main tools for comparative biopharmaceutical evaluation of different formulations or drug delivery systems with a substance are listed in Table 6.

<table>
<thead>
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<td>Simulated GI tract (e.g. TIM 1 and 2)</td>
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The starting point for formulation strategies is still the dissolution test. The dissolution test method might fulfill different objectives, like lead formulation selection, quality assessment for formulation reproducibility, establishing in vitro/in vivo correlation (IVIVC) and regulatory purposes.

For substances with a poor aqueous solubility and for which solubility is the major limitation of drug absorption (class 2 according BCS), in vitro dissolution media reflecting the in vivo conditions are crucial for the rapid screening and assessment of formulations. Several dissolution media have been proposed and evaluated like FeSSIF, FaSSIF, SIF and others but their prediction accuracy is still insufficient. One of the main reasons is the complexity of the physiology of the GI tract and the digestion process, which is not yet understood well.

To investigate the luminal composition of the upper gastrointestinal tract in the fasted and fed state, healthy volunteers received either 250 ml of water (fasted) or 500 ml Ensure Plus® (fed) and samples were aspirated from the gastric antrum and the duodenum at different time points. The Ensure Plus® was chosen as it reflects the standard FDA meal for bioavailability/bioequivalence studies. The results clearly demonstrate the differences in buffer capacity, surface tension, osmolality, pepsin levels and food components in addition to the known variations in pH and bile salt levels under fasted and fed conditions (Kalantzi et al., 2006a). These differences are not yet reflected well in the dissolution media, especially for the fed state. The solubility of ketoconazole and dipyridamole, for example, was observed to be much higher in the intestine at the same pH levels of standard dissolution media (Kalantzi et al., 2006b). This was also confirmed by a previous study, which characterized the human intestinal fluid (HIF) in fasted and fed (FDA standard breakfast) subjects using the Loc-I-Gut perfusion tube. The dissolution of several poorly soluble substances (clanazol, felodipine, cyclosporine and griseofulvin) confirmed a 3.5–30-fold higher solubilization in fed HIF compared to fasted HIF or FeSSIF. This increase is mainly caused by a 4-times higher concentration of bile salts and a 14-times higher concentration of phospholipids in the HIF under fed conditions (Persson et al., 2005).

In another study, the influence of the gastric hydrodynamics on the bioavailability in dogs was investigated using felodipine as a solution, a micronized (median particle size 8 µm) and coarse suspension (median particle size 125 µm). The micronized suspension had a 22-fold higher t\text{max} and 14-fold higher AUC compared to the coarse suspension and was not influenced by food intake, unlike the coarse suspension for which the AUC doubled in the fed state. For the poorly aqueous soluble felodipine, the motility pattern will have very little or no influence on the bioavailability when sufficient solubility is achieved through micronization (Scholz et al., 2002).

Recently a multicompartmental, dynamic, computer-controlled system used by the nutritional industry to assess and predict the absorption and metabolism of functional food components has been adapted for drug absorption and dosage form evaluation. The system mimics the GI tract through 6 small intestinal (TIM 1) and 2 large intestinal compartments (TIM 2). Each compartment is designed to represent the physiological conditions including body temperature, peristaltic movements, gastrointestinal pH profile, gastrointestinal mixing and transit times, the secretion of gastric acid and enzymes, bile salts, pancreatic juice and the absorption of digested materials. The system allows for the evaluation of drug absorption and bioequivalence under various conditions, including fasting, fed, and postprandial states. The results obtained from this system can be used to predict the in vivo bioavailability and bioequivalence of drug formulations, thereby facilitating the development of more effective and efficient drug delivery systems.

Table 6.

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In vitro and in vivo tools for formulation evaluations.
products through an artificial membrane. The artificial membrane consists of a Cuprophan dialysis membrane, which allows for a gradient driven absorption process and simulation of sink conditions. The dialysis membrane reflects absorption by passive diffusion only and does not allow for active transport mechanisms. The system is designed to estimate the in vivo performance of drug substances or drug delivery systems under fed and fasted conditions. The system provides important information on potential risks of food effects, drug precipitation and even drug-drug interactions. Overall a good reproducibility and correlations with in vivo human studies have been demonstrated using acetaminophen as a model drug (Blanquet et al., 2004). The major disadvantages are the limited output (only one study per day), the lack of automation and the variable recovery for, and limited absorption of, poorly soluble substances. Even though this prevents the system from being used widely today as a screening tool in development, it is expected that the system will be developed further to improve its performance for formulation screening before the first in human study.

Magnetic marker monitoring (MMM) also referred to as Magnetic Moment Imaging or Gastrointestinal Magnetomarkergraphy, has been introduced as a very interesting tool to continuously monitor the fate of the dosage forms by noninvasive means through the GI tract (Weitschies et al., 2001). A tablet of felodipine with extended release by erosion was developed and its gastrointestinal location and erosion monitored under fasted and fed conditions. The results confirmed that the location of the tablet, as well as the plasma concentrations, varied significantly from subject to subject under fed conditions. However, the plasma concentrations were mainly influenced by the location of the tablet in the gastrointestinal tract. Dose dumping, as observed in the fed state were directly correlated with the residence time of the dosage form in the proximal stomach. Under fasted conditions, the early gastric emptying was determined as the reason for the plasma concentration correlating with the tablet release profile (Weitschies et al., 2005).

Predictions of the plasma profile of lipophilic drugs with a known absolute bioavailability are achievable with biorelevant media (Nicolaiades et al., 2001) and will become an integral part of lead candidate and lead formulation selection as well as replacing a number of in vivo studies. Based on this understanding, drug delivery technologies can be optimized.

The complexity of the GI physiology and the drug absorption process is increasingly considered when selecting the lead candidates or developing a suitable drug delivery system. Drug delivery strategies are often developed based on an integrated approach of the underlying physiological processes, like the lipid binding and transport through the enterocytes via intestinal fatty acid binding proteins (FABP) (Velkov et al., 2005) and the lymph lipid precursor pool (LLPP) for the lymphatic absorption (Trevaskis et al., 2005, 2006a,b).

7. Future Outlook

Increasing understanding of the solid-state properties of drug molecules, and their evaluation and modification towards more stable and better dissolution characteristics, have created a series of new technologies during the past years. Their further development and routine application have and will continuously improve the drug candidate selection process.

The understanding of the physiological fluids under fasted and fed conditions will stimulate the development and qualification of biorelevant dissolution media. The concomitant application of plasma levels and the MMM will provide further insight into the performance of a drug delivery system.

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It has been recognized that colonic absorption may contribute substantially to the absorption of poorly soluble substances and from extended release formulations. Further knowledge of the role and involvement of the colon in drug absorption will lead to better predictions and new drug delivery strategies for poorly soluble substances.

Beside this, more interdisciplinary work is being conducted to improve drug discovery, drug lead candidate selection and pharmaceutical product development. Neither medicinal chemistry nor pharmaceutical sciences alone will solve the challenges for developing safe and efficient therapies for the unmet needs.

8. Summary

Understanding the different root causes for poor or highly variable oral bioavailability of a drug substance is already a key asset for finding a solution. Limited drug substance solubility in the physiological conditions of the GI tract is well known to be one of the main root causes. New tools and technologies have been developed and introduced into medicinal product development that substantially address the solubility factor early on as part of the lead candidate selection process. The continuous scientific evolution also makes us aware of the complexity of identifying and developing innovative therapies for unmet medical needs. An interdisciplinary approach of medicinal chemistry and pharmaceutical sciences from academia and industry is extensively practiced. This led and will further lead to tremendous progress in bringing new and innovative products to the market, but its perception by the community will lag behind due to the poor image of today’s industrial clinical product pipelines.

Material sciences groups are very closely looking into drug substances and their most suitable forms for development, in terms of stability and solubility. Early assessment of and eventually experimental formulation work is conducted to secure the solubilized drug concentration in the pre-clinical assays. The development work is supported by various computational tools allowing rough predictions on the possible crystal forms of a drug as well as on its in vivo performance. Formulation strategies for the clinical and commercial phase are investigated early on, when bioavailability issues are identified. Solubility enhancing formulation approaches have been developed and continue to evolve. More sophisticated work is on the way to better understand the physiological conditions of the GI tract and the underlying processes of drug absorption, which will lead to both, better in vitro evaluation and prediction tools, as well as to more targeted drug delivery systems.

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