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Drug delivery strategies for poorly water-soluble drugs: the industrial perspective

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Introduction: For poorly soluble compounds, a good bioavailability is typically needed to assess the therapeutic index and the suitability of the compound for technical development. In industry, the selection of the delivery technology is not only driven by technical targets, but also by constraints, such as production costs, time required for development and the intellectual property situation.
Areas covered: This review covers current developments in parenteral and oral delivery technologies and products for poorly water-soluble compounds, such as nano-suspensions, solid dispersions and liposomes. In addition, the use of biorelevant dissolution media to assess dissolution and solubility properties is described. Suggestions are also included to systematically address development hurdles typical of poorly water-soluble compounds intended for parenteral or oral administration.
Expert opinion: A holistic assessment is recommended to select the appropriate delivery technology by taking into account technical as well as intellectual property considerations. Therefore, first and foremost, a comprehensive physico-chemical characterization of poorly water-soluble compounds can provide the key for a successful selection and development outcome. In this context, the identified physical form of the compound in the formulation is used as a guide for a risk–benefit assessment of the selected oral delivery technology. The potential of nano-suspensions for intravenous administration is unclear. In the case of oral administration, nano-suspensions are mainly used to improve the oral absorption characteristics of micronized formulations. The development of an *in situ* instantaneous solubilization method, based on stable, standardized liposomes with low toxicity, opens new avenues to solubilize poorly water-soluble compounds.

Keywords: biorelevant solubilization, drug delivery, liposomes solubilization, nano-suspension, poorly water-soluble drug, poorly water-soluble drug dissolution, solubilization

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1. Introduction

Poorly water-soluble drugs continue to present challenges for oral and parenteral delivery. After oral administration, the degree of absorption may be highly variable and unreliable, thus, requiring suitable formulations to improve bioavailability. To allow parenteral (intravenous; i.v.) administration, the desired dose of the drug should be delivered in a solution type of formulation which prevents precipitation at the injection site and further dilution in the bloodstream. In sharp contrast to water-soluble drugs, where the formulations are used to facilitate processing and accurate dosing, formulations for many poorly water-soluble compounds should also increase bioavailability. For such insoluble compounds, a successful formulation is, therefore, absolutely essential to develop an efficacious drug product.

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Article highlights.

- The physical form of a poorly water-soluble compound can guide the selection of the formulation technology for the compound.
- Characterization of the poorly water-soluble compound should precede formulation screens.
- Drugs and formulations intended for oral administration are characterized by reliable solubility and dissolution testing in reproducible biorelevant dissolution media prepared from standardized powders.
- Liposomes can be considered as a solubilization technique for poorly water-soluble compounds due to the availability of standardized *in situ* solubilization methods.
- Nano-suspensions are well suited to develop line extensions and eliminating food effects. For early research work, dependent on the availability of nano-milling equipment and severity of and lack of oral absorption, the suitability of nano-suspensions may be explored in comparison with micronized formulations.
- Crystalline nano-suspensions are not generally suitable for intravenous administration given their slow release and dissolution properties. However, they can be considered as depot formulations for intramuscular or subcutaneous administrations.
- Amorphous nano-suspensions using albumin as a matrix-excipient are suitable for intravenous delivery as proven by the product Abraxane.
- The use of cyclodextrins suitable for intravenous administration and nano-suspension technologies may be protected by certain patents. The commercial terms associated with the intellectual property may influence the selection of the commercial formulation for poorly water-soluble compounds.
- Due to the increasing number of poorly water-soluble drug candidates, formulations may require the use of volatile organic solvents (solid dispersions, liposomes and amorphous nano-suspensions).
- Regulatory authorities are developing new guidance to deal with special delivery technologies related to nanotechnology. This guidance should be considered when compiling CMC documentation.

This box summarizes key points contained in the article.

Underestimating the importance of formulations for poorly water-soluble drugs may result in the selection of the wrong lead candidates, prolong development timelines and significantly increase cost of development. To enable a proper selection of compound and corresponding formulation, the compounds require special attention regarding physicochemical characterization. A close interaction between chemical development (responsible for the supply of the drug substance in a chemically and physically well-defined form) and pharmaceutical development (responsible for incorporating the drug in the dosage form to make the drug product) is crucial. It ensures that there is a good technological match between drug and dosage form early on in development.

Although poorly water-soluble compounds possess a reputation of being cumbersome development candidates, drug lipophilicity is often necessary for efficient interaction with the target receptor. Furthermore, lipophilicity is also a requirement to pass the lipidic domain of natural (bilayer-phospholipid) membranes. Also, seemingly highly water-soluble drugs which are delivered in salt form can pass the membrane in the uncharged lipophilic base or acid form which is in equilibrium with the salt form in the water phase. The lack of water solubility does not necessarily prevent poorly water-soluble compounds from distributing through the body after oral absorption or parenteral administration. Poorly water soluble, lipophilic compounds use a 'lipid highway' which involves reversible binding to circulating lipid carriers such as albumin and lipoproteins and possibly blood cells, thereby transporting the compound to the target receptor. The exchange/transfer of the compound between the various lipid domains, including the lipidic domain of the formulation, may occur through diffusion and/or collision mechanisms [1].

There are multiple delivery options for oral administration of poorly soluble drugs, whereas for parenteral administration there are a comparatively limited number of suitable approaches. In addition, related to the wide interest on nanotechnology, there are an increasing number of research ideas which may also be suitable. Simultaneously, regulatory authorities such as the FDA and EMA (European Medicine Agency) are becoming increasingly aware of the complications and quality requirements related with drug delivery technologies for poorly water-soluble compounds [2-7]. Also, the intellectual property (IP) situation and patentability of formulation play a paramount role for the industrially oriented scientist in selecting a particular delivery technology. This factor is often ignored by most if not all scientific papers and is all the more remarkable considering that patents are the source of scientific innovation. The industrial pharmaceutical technologist is often confronted with an increasingly complex jungle of options to select the 'best' formulation/delivery option. Both scientific and commercial perspectives have to be considered to satisfy increasingly challenging quality and development requirements.

From a financial perspective, unlike classical solid dosage form manufacturing processes, for example, granulation and tabletting, bioavailability enhancing formulation technologies for poorly soluble compounds are usually more expensive. They require significant additional capital expenditure and resource investments. This may be more acceptable for line extensions which is already generating revenues but can be risky for new chemical entities (NCEs) which are yet to be commercialized.

This review article is an update of a previously published review article [8]. It summarizes the latest advancements in formulation strategies for oral as well as parenteral administration of poorly water-soluble compounds and especially taking industrial aspects into consideration.

2. Physical forms of the formulated drugs

A detailed physico-chemical characterization of a potential therapeutic compound should start before formulation experiments or investing financially into its future. This seems obvious and is indeed common practice in big pharmaceutical companies. However, its importance is frequently underestimated in small pharmaceutical companies, which perhaps are unaware of the development challenges poor solubility can present or are financially constrained. The recommended minimal characterization of poorly water-soluble drug substance, relevant for oral formulation development, analogous to [9] is provided in **Table 1**.

If i.v. administration is the target, some characteristics do not need to be assessed for pharmaceutical development in as much detail, because the drug is in the solubilized form.

The results of the characterization serve as a basis to decide rationally whether the drug is suitable at all for further formulation development, estimate development efforts and which delivery approach(es) could be explored to maximize bioavailability. Undesirable properties are, for example, lack of stability in the solid state, multiple and unpredictable polymorphs, extreme hygroscopicity and light sensitivity, extremely low solubility and (if oral administration is envisaged) instability in (simulated) physiological media such as simulated gastric fluid (SGF), fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF).

Drug purity is also a key. As a cautionary note, to identify a development path for future formulation options, experiments performed with 95% or less pure drug substances should be considered with extreme caution. This is because the impurities may influence the therapeutic/toxicity profile and influence the physical form of the drug substance and related solubility characteristics. At this point, a complete false decision base may be created.

Based on the previously performed compound profiling, it is now of importance to select possible formulation strategies to be able to examine the *in vivo* efficacy and biopharmaceutical behavior (absorption, distribution, metabolism, elimination and toxicity; ADMET) of the compound. When the therapeutic index of a series of poorly water-soluble compounds has to be compared, in principle, optimal formulations for every compound are needed. In the literature various, somewhat complex, decision trees have been proposed (see for a typical example [10]). In order to enable a more systematic approach to assess which formulation strategy may be best for a drug, a correlation between the physical form of the drug substance in the formulation and possible parenteral and oral formulation technologies is proposed for consideration (**Figure 1**).

The drug may be in solubilized, crystalline or amorphous form in the formulation. In this context, 'solubilized' encompasses mono-molecular dispersion/solutions of the poorly water-soluble compounds in the formulation. The presence of mixtures of the drug in a different physical form may result in physical instability (e.g., crystalline suspension in presence of relatively high concentration of solubilized drug may give rise to Oswald ripening; presence of crystalline seeds in amorphous material may trigger crystallization of the amorphous fraction). The physical form of the drug can be used as a transparent guide to assess and understand the pros and cons of the various formulation options/technologies. It encourages an intuitive categorization of the technical risks associated with the physical form of the selected formulation approach.

2.1 Solubilized form

Technologies/formulations comprising the solubilized form of the drug substance may be suitable for oral drugs where oral absorption is not limited by the passage (permeability) through the intestinal epithelial membranes. For i.v. administration the solubilized form is clearly preferred. The solubilized form has the inherent advantage that the drugs are already in solution and no dissolution step is necessary to become bioavailable. Disadvantage of the solubilized form may be the lack of long-term (chemical) stability and the risk for drug precipitation on dilution in the biological milieu. The risk of precipitation is, however, dependent on how the drug is solubilized. In case of, for example, using water miscible solvents, surfactants or pH adjustment (or using the salt form of the drug) to dissolve drugs, the chance that dilution and restoring physiological pH will result in precipitation will be higher compared to solubilization technologies in which the drug is dissolved in water immiscible dispersed oil phases (e.g., oil-in-water emulsions and liposomes). The degree of dissolution in the formulation should be sufficiently high to enable the co-administration of low (non-toxic and physiologically acceptable) amounts of the excipients.

There are two main solubilization types, water miscible and water immiscible. Water miscibles are exemplified by organic solvent/water mixtures, aqueous pH adjustment, aqueous cyclodextrin, surfactant and mixed micellar solutions. Water immiscible solubilization types are exemplified by oily solutions, oil-in-water emulsion (macro emulsion, self-emulsifying systems) and liposomes. In the water miscible type, the solubilizing capacity for the poorly water-soluble compound in the aqueous medium decreases because of dilution of the solubilizing component (solvent or surfactant) and as a result the drug may precipitate in the excess of water phase (i.e., blood circulation or gastrointestinal liquid). With the water immiscible type, where the drug is associated and solubilized in the oily component of the formulation, the formulation does not lose its solubilizing potential on dilution with water as long as the oil/lipophilic component remains intact.

2.2 Amorphous form

The amorphous form in the formulation (e.g., solid dispersion) may be considered when the drug cannot be suitably solubilized. On hydration of a formulation containing the amorphous form, supersaturation may occur where concentrations are

Table 1. Physico-chemical characterization of poorly water-soluble drug before starting oral formulation screen.

Characteristic	Method
Basic information	
Purity	HPLC
Appearance and crystal habit and size*	Visual inspection and microscopy
UV-Vis spectrum	Spectrophotometry
Crystal form	XRD or Raman spectroscopy
Melting point	DSC
pK_a	Titrimetric methods
Log P or D	HPLC
Solubility	
Solvents (water miscible/immiscible)	HPLC or UV-Vis
Aqueous media pH 1 – 10	HPLC or UV-Vis
SGF, FaSSIF, FeSSIF	HPLC or UV-Vis
Accelerated stability	
pH (solvent water mixture)	HPLC
Light (solvent water mixture)	HPLC
Heat (solvent water mixture and solid)	HPLC
Mechanical stress*	XRD or Raman spectroscopy
Crystal form in dispersion*	XRD or Raman spectroscopy or microscopy
Hygroscopicity	Visual inspection/Karl Fischer/Raman spectroscopy

*Not needed in case of intended intravenous administration.
DSC: Differential scanning calorimetry; FaSSIF: Fasted state simulated intestinal fluid; FeSSIF: Fed state simulated intestinal fluid; SGF: Simulated gastric fluid; UV-Vis: UV-visible spectrometry; XRD: X-ray diffraction.

higher than achievable when formulations containing the crystalline drug are dissolved. The supersaturated solution may give rise to an increased oral absorption. The use of the amorphous form is clearly a double edged sword: on one hand, the possibility to increase oral absorption and on the other, a possible lack of chemical and physical stability and risk of crystallization. The development of such dosage forms, therefore, requires extensive real time stability testing accompanied by intensive quality control (QC) to monitor possible onset of crystallization of the drug. In addition, the production of such dosage forms either require the use of melt extrusion or hot melt technologies or spray drying from solvents (examples of solid dispersion products are given below). Melt technologies may be limited when the drug is very heat sensitive. Spray drying can be cumbersome due to the use of solvents and further development into a solid dosage form. An oral dosage form comprising the amorphous form of the drug may be very useful for oral toxicity testing because supersaturated solutions may give a higher oral absorption to maximize exposure of the animal to the drug. However, also in this case robust stability data are needed to guarantee that the drug during the testing period will stay in the preferred amorphous state. Immobilization of the poorly water-soluble compound in highly porous inorganic carriers has an interesting delivery potential which may combine the amorphous form of the drug and increase of surface area to further increase the dissolution rate [11,12].

The amorphous form of the poorly water-soluble drug paclitaxel in the product Abraxane® is used for i.v. administration [13]. This is the only commercially available example of i.v. administration of a solid (amorphous) form of a poorly water-soluble drug.

2.3 Crystalline form

The most robust form of the drug substance, from a chemical stability perspective, which can be used to develop a dosage form for a poorly water-soluble drug is the crystalline form. To be orally bioavailable the solid crystalline form first has to dissolve. The dissolution rate of the drug substance (for pH insensitive compounds) depends on: i) the crystal form being used and ii) the particle size. The selection of the crystal form is of paramount importance. Omitting polymorph screens entirely at an early development stage on the drug substances may cause serious development problems during later development stages. To increase the dissolution rate after oral administration, the smallest possible particle sizes of dispersed drug, in the form of nano-suspensions, have been considered for at least 20 years. These efforts indeed resulted in a few products (see below). So far, only one crystalline nano-suspensions for subcutaneous and intramuscular (i.m.) has been successfully commercialized but i.v. formulations using this approach have yet to be commercialized.

3. Formulations for compound selection

3.1 Parenteral

For an initial comparison of the *in vivo* profile of several drug candidates against each other in a family of compounds or an individual candidate, the parenteral (i.v.) route is preferred. This route eliminates uncertainties regarding assessment of degree of efficacy, related to an (unknown) fraction of absorbed oral dose. However, in practice, the selection of an adequate i.v. formulation is sometimes an impassable hurdle. Formulations containing the solubilized form of the compound (**Figure 1**) which on dilution in aqueous medium (simulating blood) do not show precipitation are preferred. Uncontrolled precipitation of drugs may give rise to a significant reduction of the absolute bioavailability and consequently an overestimation of the degree of oral bioavailability. Clearly, comparison of the efficacy and pharmacokinetics (PK) of several drug candidates with different precipitation tendencies may give rise to a completely false selection procedure.

In general, for any of the formulation options, excipients which are well established and accepted by regulatory authorities should be preferred. Preclinical research with cocktails of exotic excipients may initially result in seemingly adequate formulations, but sooner or later the formulation has to be reformulated to make it more acceptable for clinical research. Delay in switching to more reliable formulations can be more

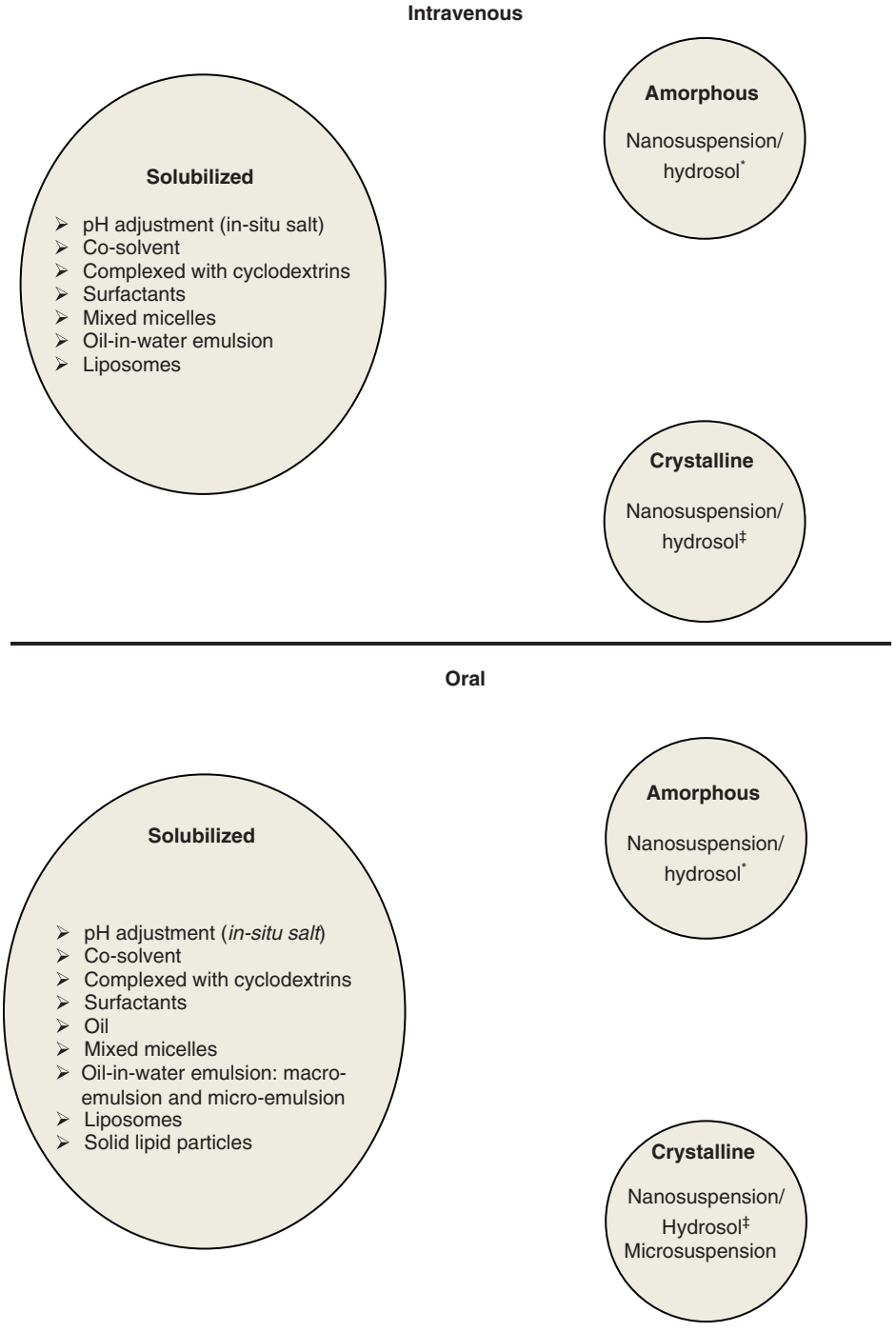

Figure 1. Categorization of formulation options for intravenous and oral poorly water-soluble drugs based on the physical form of the drug in the formulation.

*Prepared using a solvent dilution method.

‡Prepared using milling of crystalline drug.

costly in coping with the consequences (e.g., repeating tox testing, stability testing and even clinical trials). The choice of excipients in preclinical research is also technologically (e.g., compatibility) and biologically influenced (e.g., the target animal and disease model and the non-observed adverse effect level). If further development of the formulation/product is envisioned, commercial factors such as cost-of-goods, manufacturing costs and availability, guarantee of world-wide supply, the patent status and associated commercial terms and conditions need to be considered as well.

The pros and cons of the i.v. formulation options (**Figure 1**) are now critically reviewed. Formulation development costs to administer intravenously poorly water-soluble compounds may be reduced in preclinical development by using the same DMSO solution of the drug as used for drug discovery in *in vitro* screens. This approach is, however, not recommended, because DMSO is rather toxic and the dilution of the DMSO may result in uncontrollable drug precipitation in the blood circulation. PEG solutions, although less toxic, also do not prevent precipitation. Attempts to make the use of PEG solutions acceptable by injecting the PEG solution very slowly (to reduce the risk of precipitation) may look problem solving but carry the risk that the resulting PK data may depend on the injection rate and concomitant precipitation tendency. Also, the use of N,N dimethylacetamide or N-methylpyrrolidone, justified by the existence of two FDA approved products which contain these rather exotic solvents at low concentrations (Busulfex® and Eligard®), is not recommended. Ethanol and propylene glycol may be considered but can only be used at 10 – 20% in aqueous vehicles. However, with high water content, the ability to keep very poorly soluble compounds in solution may be limited.

If compounds only dissolve at non-physiological pH by adjustment to acidic or alkaline pH, there will be a risk that the compounds may precipitate after mixing with blood at the injection site and/or in the circulation. Extreme pH can cause phlebitis and *in vivo* precipitation may cause embolisms. This approach looks simple but may ignore risks that at a later phase clinical testing, such as unacceptable pain and tolerability at the injection site experienced by patients, may put a brake for further development.

Solubilization with surfactants, for example, Tween 20 or 80 (polysorbate 20 and 80), Cremophor® EL, polyoxyl 35 castor Oil (USP/NF) and Solutol HS 15 (PEG 660-hydroxy stearate), are also an option but they possess anaphylactic properties [14-23]. On dilution in aqueous media (infusion solutions or blood), the surfactant concentration may decrease below levels at which the drug dose can be solubilized. In addition, the general use of Solutol HS 15 in development may be hampered by the fact that there is no registered product with Solutol HS 15 on the market in the US. The FDA, therefore, considers Solutol HS 15 as a novel excipient.

The use of complexing agents such as cyclodextrins can also be considered. Only two cyclodextrins are at present acceptable for parenteral use, hydroxypropyl-β-cyclodextrin and sulfobutyl-β-cyclodextrin sodium salt. Both excipients are protected by some IP rights as elaborated below. It is very rare that research NCEs can be complexed with lower than 10 molecules of cyclodextrin excess to drug. For these reasons, at especially high-dose testing during toxicity investigations, cyclodextrins may cause prohibitive side effects.

Oil-in-water emulsions may be another option but this requires a very high solubility of the poorly water-soluble compounds in the oil phase to achieve adequate concentrations in 10 – 20% oil emulsions. In addition, the oil emulsions may be destabilized by the drug load. In practice, most poorly water-soluble compounds also possess a rather low oil solubility. As a result, this formulation technology is useful only in exceptional cases.

Mixed micelles comprising bile salts and lecithin are being used to solubilize lipophilic vitamins for i.v. administration (Konakion® MM pediatric (2.2%), Konakion (1.9%) and Cernevit®, multivitamins for infusion). In spite of low toxicity [24,] they are not abundantly being used and hardly mentioned in key reviews [25]. It should be noted that on dilution (in infusion bags or on i.v. administration), these formulations could undergo conversion from micelles to liposomes.

Liposomes also have the potential to solubilize drugs. In contrast to micelles (e.g., polysorbate) and mixed micelles, they do not (immediately) convert into other physical structures on dilution in aqueous media. The release of poorly water-soluble compounds occurs through diffusional or collisional transfer to other lipid components, such as lipoproteins, in the 'lipid highway' of blood [1,26]. In several review papers on the preclinical use of vehicles for poorly water-soluble compounds, liposomes are only considered as last option [25,27-32] despite the low toxicity of the used phospholipid excipients. This is probably because of the efforts to make tailored drug loaded liposomes at the preclinical level. Because of the availability of ready-for-use liposomes with defined particle size and instantaneous loading procedures with poorly water-soluble drugs [33], liposomes are certainly useful options to increase the solubility of poorly water-soluble compounds [34].

Hydrosols/nano-suspensions (note: from a physicochemical classification point of view, crystalline and amorphous nano-suspensions belong to the group of hydrosols [8]) may also be considered for i.v. administration. However, as exemplified in the Abraxane product, the preparation of amorphous precipitates of palcitaxel and albumin as a matrix excipient will be very challenging at a small scale for NCEs at the preclinical research stage (see description of the Abraxane product below for more details).

It is claimed that nano-suspensions with small particle size allowing i.v. administration are suitable to assess the absolute bioavailability [35]. This is an optimistic interpretation of the value of a nano-suspension injection because a prerequisite for determining absolute bioavailability is that the compound on i.v. injection is in the same molecular dispersed state in the blood as obtained after oral administration. It is, however, not clear to what extent the particles indeed do dissolve in the blood circulation, especially when it is claimed that the nanoparticles may have extended release properties on ingestion by macrophages [35]. The production of sterile, non-agglomerating nano-suspensions with well characterized crystal form and particle size distribution on a small scale may also be challenging. Oscillating beads milling equipment may be used for small scale milling [36]. The extrapolation of results obtained from oscillating bead milling equipment using only two exemplary compounds to poorly soluble compounds presented in this study may not be appropriate.

A possible occurrence of amorphization or conversion to a metastable polymorph of the milled poorly water-soluble compounds has not been considered [36]. Also, the chemical stability of the compound during milling and sterility needs to be addressed. Finally, if there is a clear intention to use the identified preclinical research formulation for further development, it may be necessary to assess the IP freedom before embarking on preclinical testing with this technology.

An example of a decision tree for selecting an i.v. formulation derived from [25] is provided in **Figure 2**.

The formulation options are listed in decreasing degree of attractivity. The sequence of formulation options does not focus on the fact that every option has its pros and cons and that an adequate characterization of the drug substance before starting formulation screen should be a sound basis for the formulation screen. The characterization of the drug substance which, for example, encompasses pH-solubility and -stability profile and solubility profile in organic solvents would eliminate the first options of the formulation screen right away. For these reasons, **Figure 3** summarizes a more objective approach, starting from a detailed drug substance characterization followed by in parallel assessment of the technologies, without taking preference for supposed simple approaches, but taking pros and cons of every option into consideration.

Because the type of formulation may influence the i.v. PK (and in some cases even the body distribution) of the poorly water-soluble compound [37], it is important that toxicological assessments following the preclinical efficacy assessment will be performed with the same formulation (type) as intended for the clinic. In situations where there is a switch between the i.v. formulations of **Figure 1**, regulatory authorities may request, for example, bridging tox studies and repeating stability studies and QC development. For this reason, adequate attention should be paid during preclinical development to select the best i.v. formulation approach.

3.2 Oral

During early development stages, it is not possible to classify drugs intended for oral administration according to the biopharmaceutics classification system (BCS) [38] or to the recently proposed development classification system (DCS) [39] because initially the therapeutic dose is unknown. The DCS and BCS classify oral drug substances for solubility in water and permeation properties. For oral absorption of poorly water-soluble drugs according to the BCS, the membrane permeability kinetics could be either rapid or slow (BCS class II or IV, respectively). Although *in vitro* methods (Caco-2 and parallel artificial membrane permeation assay) can be used to assess these permeation kinetics, it is sometimes not possible due to lack of solubility in donor compartments for conclusive results.

Lipophilic drugs may be very poorly soluble in water and in simple buffers, but in the gastrointestinal fluids they can often be solubilized by the bile to a significant extent. Increases in solubility of one to two orders of magnitude are possible for compounds with log P in octanol/water (log P_{oct}) values higher than four. In some cases, this would lead to a quite different interpretation of the possibilities for absorption *in vivo*.

For promising compounds that are both ionizable and lipophilic, solubility experiments in biorelevant media will help characterize the likely solubility profile *in vivo* [40]. Several publications address the composition and applications of these media [41-45]. The solubility testing in biorelevant media, which have quite complex compositions and physicochemical properties, should be performed in media prepared in a reproducible way using standardized products [46].

The obtained *in vitro* results have to be cross-checked against *in vivo* results. In terms of the proposed categorization based on the physical form of the drug in the formulation (**Figure 1**), it is recommended to compare the *in vivo* performance (oral fraction absorbed) of formulations against the drug in solubilized, amorphous or crystalline form. Additionally, the formulations have to be characterized (besides chemical content and purity) in terms of particle size (crystalline form) or physical form (crystalline and amorphous forms) along with dilution and solubilization behavior (solubilized form). Regarding the use of the crystalline form, it has to be considered at the research stage whether the coarse quality of the drug or micronization or nano-milling of the drug is adequate for oral testing.

In a recent review on nano-suspensions [47], no examples are given to compare the bioavailability of micronized versus nano-sized drug. Interestingly, an oral dosage form of fenofibrate wherein the drug is available as coarse, micronized or nanosized particles allow the bioavailability to be compared [48]. Doses of 145, 160 and 200 mg, respectively, are bioequivalent in humans. Thus, the nano-sized formulation has only a 10% higher bioavailability compared to the micronized formulation. The improvement in bioavailability may not be sufficiently ground breaking and may not persuade the preclinical scientist to seriously consider nano-suspensions as first choice to see if the drug is orally active. Suspending micronized material in an aqueous solution containing a polymer or surfactant (as a wetting agent) can reduce problems such as aggregation, amorphization (melting during processing), polymorph conversion and Ostwald ripening [49]. However, when nano-milling equipment is available and there is a severe lack of oral absorption/systemic exposure, nano-suspensions may be a viable option to be explored in comparison with micronization. The interesting finding that food effect (increase of bioavailability caused by uptake of food) could be eliminated by nano-suspensions [48] is clearly more important for line extensions.

The performance of the various formulation types can be compared to confirm *in vitro* results and to ascertain how the physical form in the formulation influences oral absorption in selecting both the best formulation and the best physical form. In case of high permeability compounds, a decreasing ranking order from amorphous > solubilized > crystalline may be observed with respect to the degree and kinetics of oral absorption. However, for compounds with

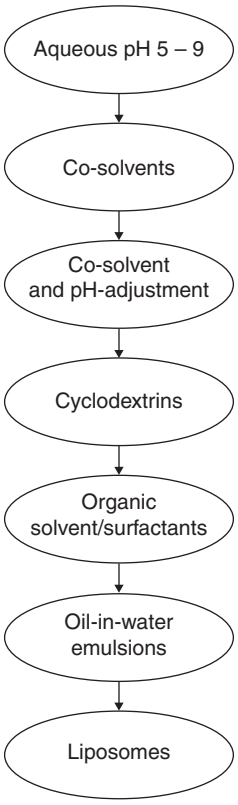

Figure 2. Sequential decision tree for selecting intravenous vehicles for poorly water-soluble compounds (partly according to Strickley [25]).

low permeability, amorphous and solubilized and even crystalline formulations (in case of fast dissolution) may behave similarly because regardless of degree and kinetics of solubilization low permeability will be rate limiting.

Even when it is suspected that a compound may belong to Class IV in BCS which is the least attractive, the compound cannot be automatically eliminated from the development pipeline because the absorbed dose may still be adequate to achieve therapeutic blood levels. Finally, the additional development efforts required to develop BCS/DCS II and IV compound may still be highly acceptable if the therapeutic profile of the compound is unique. This statement is supported by the existence of BCS Class IV products aprepitant [50], chlorotiazide, itraconazole, furosemide and cyclosporine A [40]. Pharmaceutical technologists are, therefore, well advised not to reject development candidates summarily drawing on low solubility and low permeability data too early, but should consider examining the formulation options outlined in this review.

4. Hidden poorly water-soluble compounds: the salt issue

Any review on poorly water-soluble compounds is complicated by the fact that there is a class of compounds which have seemingly high water solubility but convert into low soluble compounds especially after oral administration. This is true for ionizable compounds. For example, sodium salts of an acid may be very water soluble and seemingly a simple method to improve water solubility. However, after oral administration and dilution in gastric fluid (pH 1 – 2), the acid drug may precipitate [51]. The precipitate may be an amorphous (or even oily) or crystal form with unpredictable particle size. Further passage into the duodenum may bring about re-dissolution because of the higher pH values in this region (ca. pH 6 – 7.5). The re-dissolution (and absorption through the epithelium) may be highly irreproducible because of lack of control on the physical form and particle size of the precipitated acid drug. In the case of basic salts (uncontrolled) precipitation of the base may occur in the duodenum [52,53]. Poor reproducibility caused by precipitation may be diminished by means of, for example, crystallization-retarding agents, acids or bases (to influence local pH) as additional excipients and gastric acid resistant coated dosage forms.

These possible complications for pseudo water-soluble compounds can have consequences for the selection of the best chemical and pharmaceutical development pathway. To maximize development success, salt and non-salt forms should be evaluated in parallel. In case of the salt form, issues like which counter ion to use, crystallinity, (pseudo)polymorphism, stability and hygroscopicity of the selected salt need to be addressed [54]. Also, formation of co-crystals may be considered as an alternative to salt formation [55]. In case of parallel exploration of the non-salt form, aside from basic chemical development requirements, formulation principles based on the physical form categorization suggested in **Figure 1** and comparing oral bioavailability with the salt form have to be performed.

An example of taking the base or salt form into development is neatly illustrated by the development history of the blockbuster Gleevec® (imatinib) by Novartis. The 1993 patent was for synthesizing the molecule of imatinib [56]. In this patent salt forms are also mentioned. *In vitro* testing showed no difference in efficacy between the base and the mesylic acid salt of the base [57]. In preclinical research it was found that the base was not adequately bioavailable. However, by using the mesylate salt, imatinib was found to be highly bioavailable in humans [58]. This sequence of events shows the complexity of compound development where it is, for example, not clear if in preclinical development the salt or the base should be used for clinical development.

In general, when all formulation options and salt or co-crystal options so far described fail, a pro-drug approach may be explored. An example of such a pro-drug approach is the highly complex reformulation of the oral product Aprepitant for i.v. injection (Emend® for injection; fosaprepitant dimeglumine) by formulating the dimeglumine phosphate pro-drug with polysorbate followed by lyophilization [59].

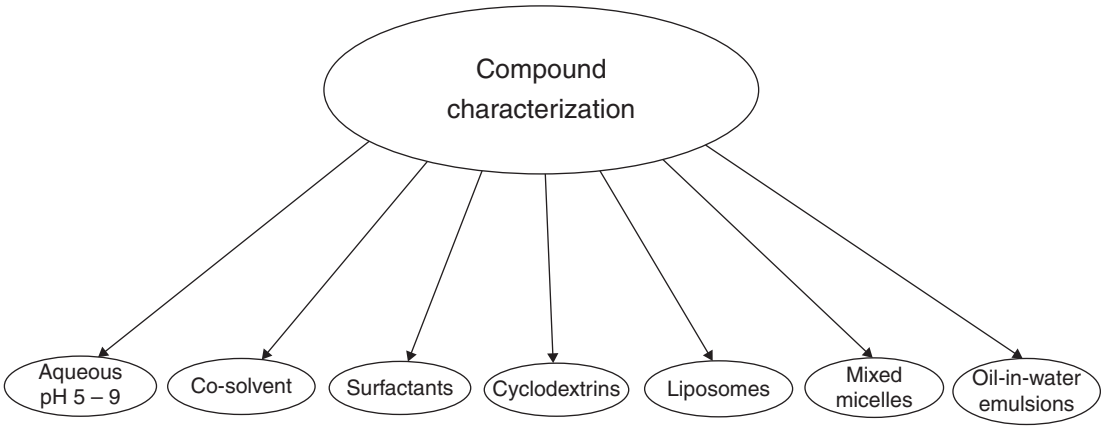

Figure 3. Parallel decision tree for selecting intravenous vehicles for poorly water-soluble compounds.

5. Intellectual property

Review papers on assessment of delivery technologies tend to be silent on the IP situation of the technologies and the associated commercial terms. In addition, technological inventions in the patent literature are rarely being considered. This is probably because the experiments have not been peer reviewed and are not described in much detail. Only in specific journals dedicated to IP assessment of technologies, more (but not complete) information on relevant patents can be found. These journals tend to list the patents without much critical assessment on the value of the inventions [60-62].

The commercial associated with the IP situation of certain formulation technologies is, however, of extreme importance for industrial scientists. Therefore, the decision basis for selecting formulations for oral/parenteral administration is not only centered on technical and biological assessment but has also commercial aspects.

A striking example is the interest in (crystalline) nano-suspensions. Although the technology is > 20 years old [63,64], it is recently becoming more popular as seen from the number of recent review papers describing this technology. Also major companies, such as Novartis, recently started to publish the use of this technology [65].

This sudden increase of attention to this technology may give the impression that this technology is superior from a technological perspective (e.g., [66]). Most likely, however, this increased interest is caused by the fact that a key patent [63] has expired in January 2011 in the US and industry has now easier access to the technology. However, the use of certain organic milling media is still covered in general [64]. Also, further selection patents covering, for example, other milling methods, use of surfactants and stabilizers and mini-mills, which still have a long patent life should be taken into consideration (see www.uspto.gov; search for Elan Corp. plc as assignee for more information and inspiration).

Another example is the use of cyclodextrins (hydroxypropyl-β-cyclodextrin and the sulfobutyl-β-cyclodextrin) for parenteral use. Despite being on the market for 20 years, the number of i.v. products using cyclodextrins as solubilizers is somewhat limited (Alprostradil, itraconazole, mitomycin, voriconazole, Tc-99m teoboroxime [67], Amiodarone [68]). This could possibly be explained by the fact that many NCEs cannot be adequately solubilized by the cyclodextrins. It may also be partially explained by the IP situation (relevant for parenteral use) of the hydroxypropyl-β-cyclodextrin and the sulfobutyl-β-cyclodextrin. Indeed, hydroxypropyl-β-cyclodextrin is protected by US Patent Specification 6,407,079 [69] till June 2019 in the US, whereas in other countries no patent protection exists for hydroxypropyl-β-cyclodextrin. US Patent Specification 5,134,127 [70] related to sulfobutyl-β-cyclodextrin sodium salt expired on 23.01.2010 in the US. More recent US Patent Specifications 7,629,331 [71] and 7,635,773 [72] cover special purer grades of sulfobutyl-β-cyclodextrin sodium salt. They expire in 2025 and 2029, respectively. The status of the corresponding patent applications in Europe is unclear.

Because the majority of pharmaceutical products are intended for oral administration and in these products the crystalline form of the drug is mostly used, it is also important to consider the patentability of the crystal form. As discussed above, the crystal form of a poorly water-soluble compound is from a chemical stability perspective the most robust one. To select the most stable crystal form a polymorph screen has to be performed. The identified crystal forms may be patentable. In this respect, it should be appreciated that polymorph patents can be granted in the US even on drugs/compounds which are known for many years (e.g., the carotenoid astaxanthin [73]), whereas in Europe, the European Patent Office (EPO) may grant only polymorph patents for compounds which were never in the public domain [74]. The importance of the IP on the crystal or amorphous form of a drug substance in a formulation and related technology is illustrated by the recent dispute on Abraxane between Abraxis and Elan [13].

Formulations and delivery technologies may also be considered to improve the performance of products and

extend the patent life of products (by formulation patents) and/or to create higher technological hurdles for generic industries to copy the original product. Examples of such a strategy are the oral products of fenofibrate which was first on the market with a formulation containing the coarse form of the fenofibrate (Lipanthyl®) having a high inter-individual variability in oral absorption and pronounced food effect. Then, an improved formulation containing spray coated micronized fenofibrate entered the market (Lipidil-Ter®) with a higher degree of oral absorption, less variability and food effect. Recently, a product with nanosized fenofibrate (Tricor®, Lipidil 145 ONE®) with no food effect and further increased oral absorption became available [48].

As a consequence of the royalty bearing commercial terms around IP, potential users cautiously hesitate to use excipients and related technology for their R&D compounds, despite the fact they could technologically be very useful. Depending on the business terms of the company owning the IP, the existence of IP rights may require a license agreement with the owner of the excipient/technology patent to access the rights to use the excipient/technology. Such an agreement may influence further commercial deals with the product using, for example, a specific cyclodextrin.

In return for milestone payments and royalties, some companies grant IP access that guarantees a certain degree of exclusivity in a therapeutic field which needs to be negotiated. The commercial conditions under which access to IP can be obtained may vary considerably. A selection of such and related excipients should be supported by a close cooperation among (patent) lawyers, development scientists and management of the company and the company owning the IP. Also, the type of protection being sought, for example, composition-, use-, method of preparation-, medical treatment claims and the countries in which the patent is valid needs to be considered.

The interested reader is referred to the web pages of the United States Patent and Trademark Office (www.uspto.gov) and the EPO (www.epo.org) for more information.

6. Status of delivery technologies for poorly water-soluble compounds

In the following section, some of the latest developments in selected oral and parenteral drug delivery technologies for poorly water-soluble compounds which are more in focus are provided and critically reviewed. Only technologies which are used in products are being considered. Solubilizing excipients and corresponding products have been previously reviewed [25,75]. Self emulsifying drug delivery systems (SEDDS) [76-78] and cyclodextrins [79,80] have been recently reviewed.

6.1 Solid dispersions

Solid dispersions are solid compositions wherein a poorly water-soluble compound is embedded in a polymer matrix in a monomolecular, amorphous or microcrystalline form [8,81-83].

Properties of solid dispersions as well as their advantages/disadvantages and characterization have been reviewed before [8,84]. Marketed products based on solid dispersion type of formulations (**Table 2**) show that this technology is used for NCEs as well as to make improved formulations (line extensions).

Sporanox® is an antifungal drug available in two different oral dosage forms in the market in the US [85]. Sporanox capsules comprise a solid dispersion with 100 mg of itraconazole coated on sugar spheres. Key inactive ingredients forming the polymer matrix wherein the drug is embedded are hypromellose and, PEG 20,000. Sporanox (itraconazole) oral solution contains 10 mg of itraconazole per milliliter, solubilized by hydroxypropyl-β-cyclodextrin (400 mg/ml) as a molecular inclusion complex. Sporanox oral solution and Sporanox capsules should not be used interchangeably. Patients should be instructed to take Sporanox oral solution without food, if possible. In contrast, Sporanox (itraconazole) capsules should be taken with a full meal to ensure maximal absorption. In spite of using a solid dispersion formulation in the capsules, optimal absorption enhancing properties are still dependent on the uptake of food. This formulation can, therefore, not be considered as an ideal oral formulation which shows, independent on the food uptake, a comparable degree of absorption.

Intelence® is an antiviral product containing the NCE etravirine (TMC 125). Each 100 mg tablet contains 100 mg of etravirine and hypromellose as a polymer matrix forming excipient and other excipients for tabletting purposes (microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and lactose monohydrate) [86].

Prograf® is an immunosuppressant containing the NCE tacrolimus available for oral administration as capsules (tacrolimus capsules). The capsules contain the equivalent of 0.5, 1 or 5 mg of anhydrous tacrolimus and hydroxypropyl methylcellulose as a polymer matrix forming excipient and other excipients for powder granulation purposes (lactose, croscarmellose sodium and magnesium stearate) [87].

Crestor® containing the NCE rosuvastatin calcium is used to treat high cholesterol and related conditions and to prevent cardiovascular disease. Each tablet contains: hypromellose NF as a polymer matrix forming excipient, triacetin NF as a plasticizer and other excipients (microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, titanium dioxide USP, yellow ferric oxide and red ferric oxide NF) for tabletting purposes [88].

Gris-PEG contains ultra-microsized crystals of the antibiotic griseofulvin. In spite of the presence of ultra-microsized crystals, this product still belongs to the class of 'solid dispersions' [81,82]. Each Gris-PEG tablet contains: griseofulvin ultramicrosize 125 mg, PEG 400 and 8000 and polyvinylpyrrolidone, as polymer matrix forming excipients and other excipients (colloidal silicon dioxide, lactose,

Table 2. Marketed products based on solid dispersion formulations of poorly water-soluble drugs.

Trade name	Drug	Company
Sporanox®	Itraconazole	J&J
Intelence®	Etravirine	Tibotec
Prograf®	Tacrolimus	Fujisawa
Crestor®	Rosuvastatin	AstraZeneca
Gris-PEG	Griseofulvin	Pedinol Pharmacal, Inc.
Cesamet®	Nabilone	Valeant Pharmaceuticals International
Kaletra®	Lopinavir and ritonavir	Abbott

magnesiumstearate, methylcellulose, methylparaben and titaniumdioxide) for tabletting purposes [89]. This product can be considered as a line extension of Grifulvin V which comprises microsized griseofulvin. When administered to fasting subjects, the microsized product showed higher serum levels and peak serum levels than the ultramicrosized formulation but the extent of the bioavailability was nearly the same. A standard breakfast enhanced the rate of absorption of the drug from both the products, especially from the formulation containing the ultramicrosized drug. Both products were equivalent in the rate and extent of bioavailability after food ingestion. The peak serum level of ultramicrosized product in nonfasting was about twice higher than that in fasting subjects [90].

Kaletra® is a co-formulation of the NCEs, lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 protease. As co-formulated in Kaletra, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. Kaletra film-coated tablets are available for oral administration in two strengths. The yellow tablets with 200 mg of lopinavir and 50 mg of ritonavir contain the following inactive ingredients: Copovidone as a polymer matrix excipient, sorbitan monolaurate as a plasticizer and other excipients (colloidal silicon dioxide and sodium stearyl fumarate) for tabletting purposes. The solid dispersion which is produced by melt extrusion (Meltrex® technology of Soliqs) is a line extension with improved properties compared to the gelatin capsules which contained oleic acid, propylene glycol, polyoxyl 35 castor oil as solubilizers and purified water and has to be stored at 2 – 8°C. The Kaletra tablets can be stored at 20 – 25°C and taken with or without food, whereas the Kaletra capsule or oral solution has to be taken with food [91].

The marketed solid dispersions presented above may be line extensions to improve their performance (e.g., elimination of food effect) or may be used for NCEs to obtain an adequate oral bioavailability.

6.2 Nano-suspensions

Nano-suspension technology is used for a relatively few number of oral products (**Table 3**).

Rapamune® is an immunosuppressant available for administration as an oral solution and in its nano-suspension (with mean drug particle size of < 200 nm [47]) form converted to a tablet. The inactive ingredients in Rapamune oral solution are (in brackets the possible functionality of the excipients in the formulation is mentioned) Phosal 50 PG® (phosphatidylcholine (emulsifier), propylene glycol, mono- and di-glycerides (oil phase), ethanol, soy fatty acids (co-emulsifier) and ascorbyl palmitate (antioxidant)) and polysorbate 80 (emulsifier/solubilizer). Rapamune oral solution contains 1.5 – 2.5% ethanol and requires refrigerated storage. The inactive ingredients in Rapamune tablets (storable at room temperature) include sucrose, lactose, PEG 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, PEG 20,000, glyceryl monooleate, carnauba wax, dl-α tocopherol and other ingredients. The functionality of the individual excipients is hard to assess because the relative amounts are not published. A dose of 2 mg of Rapamune oral solution has been demonstrated to be clinically equivalent to 2 mg Rapamune tablets; hence, it is interchangeable on a milligram-to-milligram basis. Solution as well as tablet can be taken with or without food [92]. The tablets are a line extension of the oral solution formulation.

Emend (aprepitant) is an oral product for prevention of acute and delayed chemotherapy-induced nausea and vomiting. Each capsule contains 40, 80 or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The functionality of the individual excipient mixture is hard to assess because the relative amounts are not published. Probably, the sodium lauryl sulfate acts as a wetting agent to prevent aggregation of the drug after dissolution of the tablet; the other excipients serve probably tabletting purposes [93]. During the development of aprepitant, it was found that a nano-milled formulation was able to overcome nonlinear PK in the fasted state and reduced the positive food effect observed with the micronized formulation (containing drug particles with probably < 150 nm in diameter) within the clinical dose range [94].

Tricor (fenofibrate tablets) is a lipid regulating agent available as tablets for oral administration. Tricor was reformulated in 2005 and is available in tablets of 48 and 145 mg. The particle size of the drug (d50) is < 500 nm [48]. This line extension of, for example, Lipidil-Ter with drug particle size of 5 – 15 µm is controversial, as it is seen as an attempt to stifle competition from generic equivalents of the drug and is the subject of antitrust litigation by generic drug manufacturer Teva. As described above, the nano-suspension formulation showed no food effect and further increased oral absorption compared to the micronized formulation.

Triglide®, SkyePharma/Shionogi Pharma's tablet formulation of fenofibrate, uses insoluble drug delivery IDD-P technology (IDD means insoluble drug delivery, whereas P refers to microparticle; see www.skyepharma.com for

Table 3. Marketed oral products based on nano-suspension formulations of poorly water-soluble drugs.

Trade name	Drug	Company
Rapamune®	Sirolimus rapamycin	Wyeth/Pfizer
Emend®	Aprepitant	Merck & Co.
Tricor®	Fenofibrate	Abbott
Triglide®	Fenofibrate	SkyePharma/Shionogi Pharma
Megace® ES	Megestrol acetate	Par pharmaceutical companies; Bristol Myers

more details), which has comparable absorption under both fed and fasting conditions. The IDD-P technology comprises instead of ball milling, high shear homogenization of an aqueous dispersion of the drug.

Megace® ES (megestrol acetate, United Stated Pharmacopeia) is indicated for the treatment of appetite loss, severe malnutrition or unexplained, significant weight loss in AIDS patients. The drug is in the market in the form of an oral suspension and nano-suspension in tablet form [95,96]. The oral suspension contains 40 mg of micronized megestrol acetate per milliliter and the following inactive ingredients (in brackets the possible functionality of the excipients in the formulation is mentioned): alcohol (max. 0.06% v/v from flavor), citric acid (taste and pH buffer), lemon-lime flavor (taste), PEG, polysorbate 80 (wetting agent), purified water, sodium benzoate (anti-microbial preservative), sodium citrate (pH buffer), sucrose and xanthan gum (viscosity increase). The tablets contain megestrol acetate 160 mg and the excipients for tabletting purposes: colloidal anhydrous silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycollate. In fasting subjects, the C_{max} was 30% less than the fed C_{max} value. For the oral suspension, fasting C_{max} was 86% less than fed C_{max}. In fasting subjects, the AUC was 12.1 ng.h/ml for Megace ES and 8,9 ng.h/ml for oral suspension. This means that the oral bioavailability in fasted subjects is 35% better for the micronized suspension. In fed subjects, the absorption of the two formulations was comparable [97].

The above discussed nano-suspension products are in most of the cases improvements (line extensions) wherein the particle size of the micronized drug in the original product is reduced.

There are two parenteral products on the market which can be classified as nano-suspensions (**Table 4**).

Abraxane is a new injectable formulation of paclitaxel based on the nanoparticle albumin-bound ('nab') technology of Abraxis [98]. Compared to the Cremophor/ethanol formulation of the comparator product paclitaxel, Abraxane shows a superior clinical profile in breast cancer [62]. The proposed mechanism of delivery of this nab-driven chemotherapy is thought to be by targeting a previously unrecognized tumor-activated, albumin-specific biologic pathway with a nanoshell of the human blood protein albumin. This nano-shuttle system is believed to activate an albumin-specific (Gp60) receptor-mediated transcytosis path through the cell wall of proliferating tumor cells, using caveolin-1 activated caveolar transport. Once in the stromal microenvironment, the albumin-bound drug may be preferentially localized by a second albumin-specific binding protein, SPARC, a protein secreted into the stroma by tumor cells. The resulting collapse of stroma surrounding the tumor cell may thus enhance the delivery of the nab-chemotherapeutic to the intracellular core of the tumor cell itself.

Abraxane does not contain Cremophor EL and the anaphylactoidal side effects related to this surfactant (which would demand a premedication with corticosteroids/antihistamines) are avoided [99]. Also, a possible increase of concentration of extractables originating from infusion bags may be suppressed. The product comprises a nano-suspension with particles of about 130 nm diameter in which the amorphous paclitaxel is embedded in human albumin [100]. The amorphous form of the drug substance in the formulation may be necessary to enable a relatively fast dissolution of the drug in the blood circulation.

As derived from the patent literature [62], the nano-suspension is prepared by first dissolving the drug in a water immiscible organic solvent (e.g., dichloromethane). The organic phase is emulsified and high-pressure homogenized in presence of albumin. The solvent may evaporate during the high-pressure homogenization (because of the temperature increase) or evaporated by warming the emulsion above the boiling point of the solvent.

The Abraxane production technology, however, cannot be considered as a simple technology easily accessible for, as an example, preclinical development scientist (note as well: the technology is patented too) for the following technological reason: the technology is dependent on the use of human albumin. Although albumin is subjected to heat treatment to eliminate, for example, hepatitis viruses and is used on its own as injectable product [101], it still may be contaminated with viruses or prions which are not killed by the applied heating procedure. The large scale availability as excipient may be limited (like any blood derived product). The emulsification and possibly high shear homogenization procedure may influence the antigenicity of the albumin. The paclitaxel (or another poorly water-soluble compound) may precipitate in a partially amorphous/crystalline form [13] and this may pose risks for conversion of the amorphous to the crystalline form during long-term storage which may influence the dissolution rate of paclitaxel from the albumin particles. The handling of solvents does require recycling precautions and guarantee of removal below acceptable solvent residue levels. Last but not least, the handling of a cytostatic is problematic under production conditions. In spite of these issues, it should be realized that the FDA approved the product and these potential issues were, therefore, addressed by Abraxis satisfactorily.

Table 4. Marketed parenteral products based on nano-suspension formulations.

Trade name	Drug	Company
Abraxane®	Paclitaxel	Abraxis
Invega® sustenna®	Paliperidone palmitate	J&J

Invega® sustenna® is indicated for the acute and maintenance treatment of schizophrenia in adults and is available as a white to off-white sterile aqueous extended-release nano-suspension [47] for i.m. injection containing paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone. The inactive ingredients are (in brackets the possible functionality of the excipients in the formulation is mentioned) polysorbate 20 (wetting agent), PEG 4000 (wetting agent), citric acid monohydrate (buffer), disodium hydrogen phosphate anhydrous (buffer), sodium dihydrogen phosphate monohydrate (buffer), sodium hydroxide (buffer) and water for injection [102]. This is in cases the nano-suspension is used for controlled release of the drug via parenteral delivery, which is in sharp contrast to its applications in oral delivery where rapid dissolution of nano-suspension is the key driver for its usage. Such aqueous nano-suspensions intended for (i.m.) injection may be challenging regarding, for example, particle growth and particle aggregation during storage, sterility and milling impurities.

6.3 Liposomes

At present, five i.v. products comprising poorly water-soluble compounds using liposomes as solubilizers (AmBisome® (amphotericin B), Mepact® (Mifamurtide), EndoTAG®-1 (palcitaxel), Visudyne® (Verteporfin for injection; benzoporphyrin), Definity® (octafluoropropane)) are in the market (note; there are in total at least 10 injectable liposomal products in the market). Abelcet is not a liposome formulation but a complex of phospholipids with amphotericin B. The compositions and characteristics of the products are described in **Table 5**.

AmBisome is registered [103] for treatment of presumed fungal infection in febrile, neutropenic patients, cryptococcal meningitis in HIV infected patients, infections with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate (Fungizone), and visceral leishmaniasis is basically a line extension of the Fungizone product wherein a bile salt was used to solubilize the antifungal amphotericin B [104]. The amphotericin B liposomes are small unilamellar vesicles smaller than 100 nm in diameter and comprise hydrogenated soy PC, 1,2 distearoylphosphatidylglycerol, cholesterol, α-tocopherol in a 1:7 drug:lipid weight ratio. Compared to the original product, the liposomal formulation is not hemolytic; in addition, the therapeutic index of the antifungal is improved [104].

EndoTAG®-1 is a liposomal product of paclitaxel of Medigene, using positively charged liposomes, which possesses the orphan drug status at the EMA and FDA for treatment of pancreas cancer (http://www.medigene.de/endotag1).

Mepact (Mifamurtide) is an orphan drug which is registered in the EU for treatment of osteosarcoma [105] and originally developed by Ciba-Geigy Ltd [106] and now marketed by Takeda Pharmaceutical Co. The product comprises multilamellar vesicles (MLV) containing the NCE, MTP-PE (muramyltripeptide-phoshatidylethanolamine) and the phospholipids 1-pamitoyl, 2-oleoylphosphatidylcholine and 1,2 di-oleoylphosphatidylserine in a 1:250 w/w drug:lipid ratio. Large liposomes containing phosphatidylserine (PS) were selected to target after i.v. administration to macrophages. The idea to use PS was derived from the observation that sickle cell erythrocytes and aged erythrocytes expose PS on their surface (in normal erythrocytes PS is in the inner leaflet of the bilayer of phospholipids [107]) and that sickle cells and aged erythrocytes are much faster eliminated from the blood circulation by phagocytosis of macrophages compared to normal blood cells. On uptake, the macrophages are activated by the muramylpeptide, which also occurs in the cell membrane of bacteria, to become selectively tumoricidal. In addition, the encapsulation of MTP-PE in liposomes resulted in a better therapeutic index compared to the MTP-PE itself [108,109]. The liposomal dosage form is prepared by lyophilization of the tert-butanolic solution of the liposome components. The resulting dry cake is hydrated before use to form reproducibly a MLV suspension suitable for i.v. administration [106].

Visudyne (Verteporfin for injection with the poorly water-soluble NCE benzoporphyrin as drug substance) therapy is indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis. Visudyne therapy is a two-stage process requiring administration of both Verteporfin for injection and irradiation with non-thermal red light. Verteporfin (benzoporphyrin) is solubilized in liposomes which comprise large unilamellar vesicles with a diameter of 150 – 300 nm and containing phosphatidylglycerol from egg, 1,2 dimyristoylphosphatidylcholine, ascorbyl palmitate and butylatedhydroxytoluene [110,111] in a 1:7.5 – 15 drug:lipid weight ratio. On i.v. administration, the drug transfers to lipoproteins which carry the drug to the site of action [111-113]. The manufacturing process involves mixing and evaporating the ingredients from dichloromethane to form an intermediate product ('presomes'). Lactose is added in a hydration and size reduction process, followed by aseptic filtration, filling and lyophilization [114]. The relatively small size of the liposome and fast transferring properties of benzoporphyrin from the liposome to lipoproteins make the liposomes an excellent solubilizer for this drug [1].

Activated Definity (Perflutren lipid microsphere) injectable suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial

Table 5. Marketed parenteral liposomal products containing poorly water-soluble compounds.

Trade name	Drug	Company
Ambisome®	Amphotericin B	Astellas Pharma US
EndoTAG®-1	Paclitaxel	Medigene
Mepact®	MTP-PE	Takeda
Visudyne®	Benzoporphyrin	Novartis
Definity®	Octafluoropropane	Lantheus Medical Imaging

border [115]. Prior to Vialmix® activation, the Definity vial contains 6.52 mg/ml octafluoropropane in the headspace. Each milliliter of the clear liquid contains 0.75 mg lipid blend (consisting of 0.045 mg 1,2 dipalmitoylphosphatidicacid, 0.401 mg 1,2 dipalmitoylphosphatidylcholine and 0.304 mg MPEG5000 1,2 dipalmitoylphosphatidylethanolamine), 103.5 mg propylene glycol, 126.2 mg glycerin, 2.34 mg sodium phosphate monobasic monohydrate, 2.16 mg sodium phosphate dibasic heptahydrate and 4.87 mg sodium chloride in water for injection. The pH is 6.2 – 6.8.

7. Regulatory aspects

Regulatory authorities show an increasing interest to guide, especially parenteral delivery systems. Possible reasons may be that certain formulations based on surfactants are not covered by IP anymore and that generic companies are copying these formulations. It has to be assured that the copied products are as safe as the originator product and that both products possess the same characteristic properties.

Examples are doxorubicin liposomes [7] and paclitaxel surfactant formulations [116] in which especially the colloidal properties and dilution characteristics are challenged. As discussed in the relevant document of the EMA on surfactant-based parenteral formulation, the author expresses fundamental concerns on the reproducibility of dissolution of the poorly water-soluble drug from the surfactant micelles into the blood circulation. Also, the risk for drug precipitation at highly diluted condition is high, when the surfactant is below the critical micelle concentration. The determination of 'free' drug versus micellar drug is also discussed [116].

In addition, there is some considerable interest in nanotechnology and also products based on these new technologies need to be regulated [117,118]. Nano-suspensions discussed in this publication are covered by this. Liposomes enjoy special attention from regulatory authorities as the use of liposome to enhance therapeutic index of drugs is known and regulated for many years. The FDA issued in 2002 a draft guidance on liposomes [6]. Due to their small size, liposomes are also considered to be a part of nanotechnology related regulations [118]. The complexity of the QC may be influenced by the actual purpose of the liposomes. Formulations with targeting properties may present significantly higher hurdles and supporting data in comparison to liposomes used for solubilization.

Companies interested in the development of commercial products which are related to nanotechnology (maybe even including surfactant-based formulations) must consider these latest thoughts on proposed characterization and QC as issued by regulatory authorities (**Table 6**) [119].

Also, cyclodextrin-based formulations may be scrutinized by regulatory authorities in future. In recent publications, it was studied in detail that poorly water-soluble compounds may form high molecular mass aggregates with cyclodextrins [120,121]. It was claimed that these aggregates do not influence PK and efficacy of the poorly water-soluble compounds. However, no such data were supplied. In addition, NCEs which may require a large excess of cyclodextrin to get solubilized may even form larger aggregates. The weak binding between guest and cyclodextrin molecules in such aggregates may not prevent precipitation of the poorly water-soluble drug due to dissociation of the complex resulting from diluting the formulation as part of a preparation of a diluted infusion or on injection in the blood circulation.

8. Expert opinion

The selection and development of oral as well as parenteral dosage forms for a poorly water-soluble drug is far more complicated compared to water-soluble drugs. As a matter of fact, without having an adequate formulation, such drugs cannot be administered and developed. This implies that sufficient attention (and budgets) must be reserved for exploration of the most suitable combination of poorly water-soluble drugs and the corresponding formulations.

Driven by the enormous pressure to develop products as quickly as possible, it often happens that the first selected formulation for preclinical research is also dragged into clinical research. In the case of poorly water-soluble compounds, the need for obtaining excessive exposure levels of the drug in animals to assess the toxicity profile of the compound often requires oral dosage forms especially designed to achieve these levels, for example, by using a solid dispersion with amorphous form of the drug to make supersaturated solutions. Because the dose level used in clinical research will be lower, it is not necessary to take the same dosage form as used for toxicity testing into the clinic. In case companies prefer to use for further clinical research up to, for example, Phase II a solid dispersion, the solid dispersion must be produced at a larger scale and large scale production issues using, for example, melt extrusion or spray drying need then to be addressed. In addition, extensive stability testing to prove that the amorphous drug in the solid dispersion does not convert to its crystalline form need to be performed.

At the R&D stage for selecting a formulation, quite complex decision matrices exist. A holistic assessment, early on, combining chemical development aspects (e.g., polymorphism, salt form, purity, stability), pharmaceutical development, biological/pharmacological aspects and commercial aspects such as assessment of the IP situation is also mandatory. The selection

Table 6. Common techniques used to characterize nanomaterials.

Characteristic*	Method‡
Morphology	
Size (primary particle)	TEM, SEM, AFM, XRD
Size (primary/aggregate/ agglomerate)§	TEM, SEM, AFM, DLS, FFF, AUC, CHDF, XDC, HPLC, DMA(1)
Size distribution	TEM, SEM, AFM, DLS, AUC, FFF, HPLC, SMA
Molecular mass	SLS, AUC, GPC
Structure/shape	TEM, SEM, AFM, NMR
Stability (3D structure)	DLS, AUC, FFF, SEM, TEM
Surface	
Surface area	BET surface charge SPM, GE, titration methods
ζ Potential	LDE, EAS, PALS
Surface coating composition	SPM, XPS, MS, RS, FTIR, NMR
Surface coating coverage	AFM, AUC, TGA
Surface reactivity	Varies with nanomaterial
Surface–core interaction	SPM, RS, ITC, AUC, GE
Topology	SEM, SPM, MS
Chemical aspects	
Chemical composition (core, surface)	XPS, MS, AAS, ICP-MS, RS, FTIR, NMR
Purity	ICP-MS, AAS, AUC, HPLC, DSC
Stability (chemical)	MS, HPLC, RS, FTIR
Solubility (chemical)	Varies with nanomaterial
Structure (chemical)	NMR, XRD
NMR, XRD	
Crystallinity XRD, DSC	XRD, DSC
Catalytic activity	Varies with nanomaterial
Other methods	
Drug loading	MS, HPLC, UV-Vis, varies with nanomaterial
Drug potency/functionality	Varies with nanomaterial
In vitro release (detection)	UV-Vis, MS, HPLC, varies with nanomaterial
Deformability	AFM, DMA(2)

*The list of characteristics is not definitive. Other characteristics may be reported.

‡Only common techniques are listed. Other techniques may be valid. The choice of techniques should be justified.

§These techniques will measure the average particle size, but cannot necessarily distinguish among primary particles, aggregates and agglomerates.

AAS: Atomic absorption spectroscopy; AFM: Atomic force microscopy; AUC: Analytical ultracentrifugation; BET: Brunauer, Emmett and Teller method; CHDF: Capillary hydrodynamic fractionation; DLS: Dynamic light scattering; DMA(1): Differential mobility analyzer; DMA(2): Dynamic mechanical analyzer; DSC: Differential scanning calorimetry; EAS: Electroacoustic spectroscopy; FFF: Field flow fractionation; FTIR: Fourier transform infrared spectroscopy; GE: Gel electrophoresis; GPC: Gel permeation chromatography; ICP-MS: Inductively coupled plasma mass spectrometry; ITC: Isothermal titration calorimetry; LDE: Laser Doppler electrophoresis; MS: Mass spectrometry (GCMS, TOFMS, SIMS, etc.); PALS: Phase analysis light scattering; RS: Raman spectroscopy; SEM: Scanning electron microscopy; SLS: Static light scattering; SMA: Scanning mobility particle sizer; SPM: Surface probe microscopy (AFM, STM, NSOM, etc.); TEM: Transmission electron microscopy; TGA: Thermal gravimetric analysis; UV-Vis: UV-visible spectrometry; XDC: X-ray disk centrifuge; XPS: X-ray photoelectron spectroscopy; XRD: X-ray diffraction.

or avoidance of a delivery technology protected by patents may also have far-reaching consequences for the ensuing formulation and product development.

To facilitate systematic preclinical screening for an oral vehicle, it is proposed to take the physical form of the drug as a guide for selecting the formulation principle based on crystalline, amorphous or the solubilized forms of the drug. In a following step, a more finely-tuned selection of, for example, which solubilization technology is best for the compound should be performed. In any event, we strongly recommend preceding the formulation screen with a detailed physicochemical characterization of the compound (irrespective of the administration route).

For the oral route, the dissolution and solubility testing in simulated bio-relevant media such as FaSSIF, FeSSIF and SGF will be the key to assess oral absorption of the compound and examine the possible enhancement of solubility and/or dissolution by the formulation. Because simulated biorelevant intestinal fluid media comprising lecithin and taurocholate are relatively unstable and require reproducible components to enable comparison of dissolution studies, it is recommended to prepare these liquid media from standardized powders [46].

The i.v. route provides information on the absolute bioavailability and basic ADMET data of the poorly water-soluble drugs as such. Further, the efficacy and toxicity profiles can be evaluated without the additional task to provide orally absorbable forms. However, to enable i.v. administration of poorly water-soluble compounds there are also not that many satisfactory formulation options. All have technology and toxicology pros and cons. Some have also serious IP implications, which must be weighed in terms of possible superior technology or potential royalty stacking and dependence on exclusive technology provider.

In general, there will at any R&D stage be a continuous dilemma between selecting a feasible formulation enabling parenteral administration and/or oral administration but with suboptimal, for example, bioavailability/tolerability characteristics and a more ideal formulation with a more optimal bioavailability/tolerability profile. The suboptimal formulation may develop fast at a minor scale and be sufficient to study the characteristics of the poorly water-soluble compound as part of a proof of concept clinical trial. Further development of such formulations and related manufacturing may, however, not be suitable at all for larger scale production and later clinical trial testing, unless major investments are being made. This is for instance the case when spray drying or nano-milling is used for production of early clinical trial material for poorly water-soluble compounds. Also, switching between different formulation principles (e.g., based on the physical form of the API) for different clinical research stages may require at least bridging clinical trials to cope with a possible change of pharmacokinetic profile of the various formulations. For these reasons, especially for poorly water-soluble compounds, these issues need to be addressed

as part of a formulation and manufacturing strategy, throughout preclinical research to Phase III–IV studies.

From a technology stand point, liposomes can now be used as solubilizers for i.v. poorly water-soluble compounds. First, five marketed products use liposome as solubilizers. Second, the development of an *in situ* instantaneous solubilization method based on stable, standardized liposomes with low toxicity opens new avenues to solubilize poorly water-soluble compounds [33,34] in the preclinical as well as clinical setting. Compared with other solubilization technologies, liposomes do not present pH, solvent and detergent/surfactant related toxicity. The used liposomes are stable and the particles do not (immediately) change/dissociate on i.v. administration which may cause the drug to precipitate. The potential to use crystalline nano-suspensions for i.v. use is hampered by the fact that the particles must dissolve reproducibly in the blood circulation. Nano-suspensions are more useful for slow release after i.m. administration (see discussion about Invega sustenna above and [122]).

Nano-suspensions comprising mainly amorphous drug can indeed be successfully developed as proven by Abraxane. The nab technology used is, however, not very simple and hardly useful for preclinical scientists in routine use.

The selection of a suitable oral or i.v. formulation is based on a risk–benefit assessment of the formulation technology. Such assessments are quite different for NCEs compared to line extensions of existing drugs. For NCE, there is the risk that the drug does not work at all and/or is too toxic. Emphasis is placed on the development on how to get into the clinic as quickly as possible using tried formulation technology which is as simple as possible. There will be low enthusiasm to use formulation technologies for NCEs, which are not well established in terms of toxicity and/or stability, complexity and freedom to operate because this would increase the risk of failure. However, in some cases simple formulations may not work at all and other options, mainly to enhance oral bioavailability, should then be considered. This trend is clearly seen for drugs in solid dispersions, whereas for oral (micronized) suspensions there is a clear preference to use nanotechnology for making line extensions, mainly to eliminate food effects. Liposomes as solubilizers may be considered for NCEs (e.g., benzoporphyrin and MTP-PE) as well as line extensions (e.g., amphotericin B and palcitaxel). The availability of a standardized liposome solubilizer [33] may further increase the attraction of liposomes to increase the solubility for i.v. formulations of NCEs.

Production of dosage forms for poorly water-soluble compounds may be performed without (volatile) process solvents. Examples are micronized or nano-suspensions, oil based formulations and cyclodextrin formulations. The production of dispersed dosage forms (solid dispersion) for poorly water-soluble compounds may require the use of volatile organic process solvents [123]. Although, no details are disclosed on the production methods for solid dispersions, it can be assumed, with the exception of Kaletra tablets (produced by melt extrusion), that the main product components are prepared by spray drying from organic solvent. Also the injectable products Visudyne, Mepact and Abraxane are produced with the help of solvents. Consequently, when pharmaceutical companies would like to explore new drug delivery technologies, production units are required to handle solvents (explosion proof, recycling capabilities, drying to remove residue to acceptable low levels according to ICH guidelines). Large pharmaceutical companies can cope with this situation. However, small pharmaceutical companies not in the possession of a production unit must depend on contract manufacturing services for research compounds. Unfortunately, manufacturing facilities also able to handle process solvents and research compounds (which may be considered as potentially dangerous because of lack of toxicity data) are not widely available. As a result, the most suitable formulation options may not be considered by small pharmaceutical companies. It is predicted that there will be a trend to improved solvent handling at contract manufacturing organizations.

In spite of this, it is remarkable to note that about 50% of the products discussed in this paper were originally developed by small pharmaceutical companies, whereas line extensions are clearly the area of large pharmaceutical companies.

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