Expert Opinion

Recent advances in intravenous delivery of poorly water-soluble compounds

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In recent years, with the widespread application of high-throughput screening technologies in drug discovery, an increasing number of new chemical entities with extremely poor aqueous solubility have been generated. Their poor solubility represents a major challenge for formulation of these compounds for both oral and parenteral administration. Formulations for intravenous (i.v.) application are of significant importance because they are frequently used in several key therapeutic areas, such as oncology and anesthesia. Furthermore, i.v. formulations of new compounds are often needed to determine basic biopharmaceutical parameters and to obtain proof of concept results in the early phase of product development. This review provides an overview of the recent advances in formulation approaches and drug delivery technologies for poorly water-soluble compounds applicable to i.v. administration. The advantages and disadvantages of different strategies are highlighted and an expert opinion on each technical field is presented.

Keywords: cochleate, complexing agent, cyclodextrin, dendrimer, i.v. formulation, liposome, liquid crystalline nanoparticle, nanoparticle, polymeric micellar system, prodrug

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1. Introduction

Intravenous (i.v.) delivery is a key mode of parenteral drug administration, allowing drugs to bypass all absorption barriers and gain direct entry into the general circulation. During preclinical development, an i.v. formulation of a new drug is always required for toxicological evaluation, particularly when the final product of the drug is intended for i.v. administration. In some cases, acute i.v. toxicity of a drug is also assessed, even if the drug is administered by means of non-i.v. parenteral routes. This is performed to assess the potential toxicity when the drug is accidentally injected intravenously. In pharmacokinetic evaluation, an i.v. study is conducted to determine the absolute bioavailability of the drug given by other routes.

If a drug is used for clinical conditions requiring immediate drug action, i.v. is the administration route of choice. Cardiac arrest, acute asthma attack and anaphylactic shock are examples of medical conditions where i.v. delivery of the therapeutic agent is indicated. In addition, i.v. delivery offers better control over the administration rate of a drug when dose adjustment is required to attain the optimal therapeutic effect. For example, the i.v. administration of a hypnotic drug for induction of general anesthesia allows individualized dose adjustment. Delivery by i.v. has much less restriction on the volume of fluid that can be given as compared with other parenteral routes of administration, such as subcutaneous (s.c.) and intramuscular (i.m.) injection. Therefore, continuous i.v. delivery (infusion) is the preferred way to administer a drug at a high dose that can only be accomplished with a large injection volume. Continuous infusion is also an effective mode of delivery for maintaining a constant level of a drug with a very short biological half-life. Drugs such as antineoplastic agents

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with serious irritating properties cause severe pain and tissue damage when given i.m. or s.c.; hence, these drugs must be given intravenously. The i.v. delivery of multiple therapeutic agents to a patient through a central i.v. infusion line has been a common practice in hospitals. The use of a common venous access is a convenient and safe way to administer multiple medications to a patient. Therefore, it is clinically desirable to develop a critical care injectable product that can be admixed with an i.v. fluid for infusion. With the advances in drug discovery techniques, more compounds with poor aqueous solubility have entered into the development pipeline [1].

Conventional formulation approaches for developing an i.v. formulation of a poorly water-soluble drug include salt formation by pH adjustment, cosolvent solubilization, surfactant micellization, complex formation, and lipid systems such as submicrometer emulsions and liposomes [2]. When these approaches fail to yield the desirable i.v. formulation, new i.v. drug delivery systems should be considered. These delivery systems are either prepared with new solubilizers/carriers or fabricated by new manufacturing processes.

Although oral and parental delivery systems for poorly water-soluble drugs share common development needs and challenges, the formulation methods are quite different, particularly for i.v. delivery. Specific requirements for an i.v. formulation should be considered when developing or selecting a new i.v. drug delivery system [3]. There are very stringent safety limits on the size and amount of particulate matter in an i.v. product [4]; dispersions acceptable for i.v. administration must be in the submicrometer size range as particles larger than ~ 7 μm cause pulmonary embolism [5]. A physiological pH (~ pH 7.4) should be the target and extreme pH values (< pH 3 or > pH 10.5) as well as high buffer capacity should be avoided [5]. Isotonicity is another key requirement, particularly for a product intended for large volume infusion, as hypotonic solutions cause hemolysis. Hypertonic solutions may be tolerated if administered slowly in small volumes [5]. The product must be sterile and pyrogen-free as well; these two important microbiological attributes of the product can be very challenging to achieve when a complex manufacturing process is involved. New excipients or carriers used for i.v. delivery should also be scrutinized for their safety profiles with respect to allergic reactions and systemic toxicity. In this review, recent progress in the development of new i.v. delivery systems for poorly water-soluble drugs is discussed.

2. Molecular complexes

Many poorly water-soluble drugs are capable of forming an association at the molecular level with various water-soluble materials by means of a wide variety of intermolecular forces [6]. This molecular association (also called complexation) can occur by electrostatic binding, hydrogen bonding and hydrophobic interactions. Complexes formed by hydrophobic interactions are the most exploited solubilization systems for poorly water-soluble drugs. Hydrophobic interactions promote complexation as a consequence of the increase in entropy in surrounding water molecules that occurs when non-polar regions of the drug and ligand (complexing agent) interact with each other rather than with water. This entropically driven complexation mechanism is responsible for the enhancement of the aqueous solubility of poorly water-soluble compounds, particularly if the complexing agent itself has extensive hydrophilic regions in addition to the hydrophobic binding site.

There are two types of complex formed via hydrophobic interaction: complexes formed by inclusion and those formed by stacking of aromatic rings. Inclusion complexes can be formed by fitting the drug molecule (guest) into a rigid cavity in the host molecule, as illustrated by the lock-and-key complex formation with cyclodextrins. Inclusion complexes can also be formed by enveloping the drug within a shape-conforming overcoat formed by flexible portions of the ligand, as demonstrated by induced-fit complexation with polymeric dendrimers. Inclusion complexes have been exploited to a great extent as drug delivery systems; complexation with cyclodextrins has been studied most extensively [7-9], whereas complexation by polymeric dendrimers is an evolving area of study, which has not yet resulted in commercial products. Stacking complexation has not been exploited commercially.

2.1 Cyclodextrins

Cyclodextrins have been the complexing agents most widely studied since the new millennium began. Typically, 1:1 complexes are formed between the drug and cyclodextrin, but higher order complexes have been noted [10-13]. The use of cyclodextrins as complexing agents for parenteral drug delivery is limited by their toxicity, which is related both to the total dose and to the structure of the cyclodextrin. Cyclodextrins tend to precipitate in the glomerular filtrate of the kidneys, causing severe renal problems. Thus, more water-soluble cyclodextrins have been generated, such as hydroxypropyl-β-cyclodextrin and Captisol® (Cydex Pharmaceuticals, Inc., Lenexa, KS), a sulfobutyl ether derivative of β-cyclodextrin with an average of seven sulfobutyl ether groups per cyclodextrin molecule (**Figure 1**). Owing to the very low pK_a of the sulfonic acid groups, Captisol carries multiple negative charges at physiological pH values; therefore, it can remain in solution during the formation of urine in the kidneys. The added alcohol functionalities introduced as the hydroxypropyl group in hydroxypropyl-β-cyclodextrin serve a similar purpose.

In general, very high concentrations of derivatized cyclodextrin are usually required to achieve effective solubilization of drugs. To reduce the total amount of cyclodextrin required, the use of co-solubilization techniques has been studied extensively. These techniques include pH modification, salt formation with counter-ions that can be incorporated into the cyclodextrin complexes, addition of surfactants, and use of cosolvents/co-complexing agents, particularly hydrophilic polymers. Some examples of adjuvants that have been studied and that are potentially useful in parenteral formulations are shown in **Table 1**; not all have actually been evaluated *in vivo*.

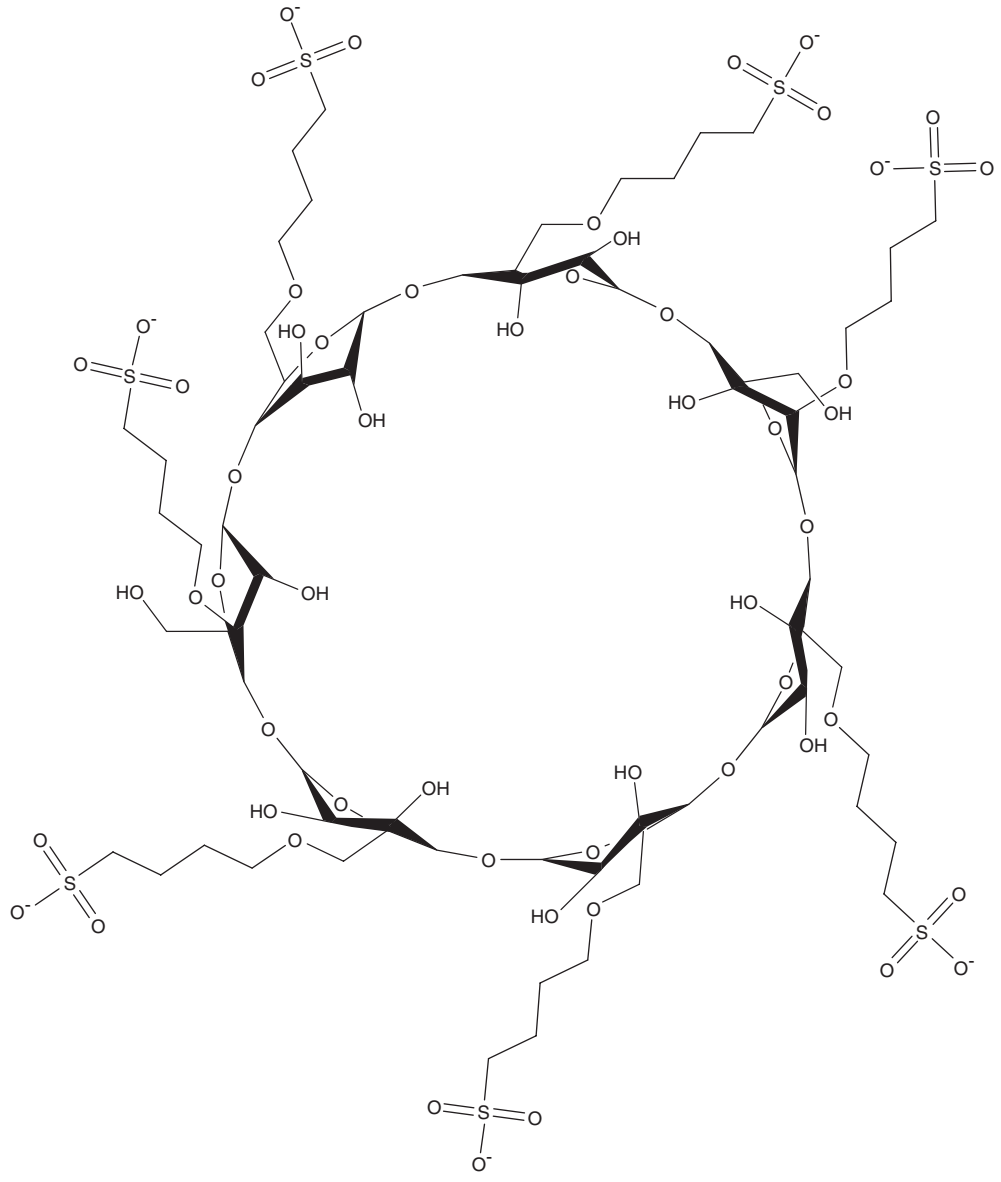

Figure 1. One of many isomeric forms of β-cyclodextrin heptasulfobutyl ether.

Marketed parenteral products formulated with cyclodextrins as the solubilizing agent are shown in **Table 2**.

Captisol remains a viable and preferred formulation excipient for vastly improving the solubility of poorly water-soluble drug candidates that contain the requisite structural moieties. Minimally, a mono-substituted phenyl ring or other non-polar group of similar size and shape should be strategically located only a few intervening atoms away from an easily protonated basic group for maximum binding. Negatively charged functional groups are expected to reduce the effectiveness of complexation unless located in a position structurally far removed from the phenyl moiety. Other groups roughly similar in size to a phenyl ring (cyclohexyl, adamantyl, *t*-butyl, neopentyl) may be acceptable. Hydroxypropyl-β-cyclodextrin is more likely to be suitable for formulating drug candidates that are negatively charged at physiologically acceptable pH values, but otherwise it is limited to the same structural candidates as Captisol. Cyclodextrins used within the dosage limitations and concentration ranges that have been established so far probably will not pose any safety concerns.

2.2 Dendrimers

Numerous investigators have explored the construction of custom-tailored complexing agents with defined structures (so-called dendrimers). Building on the cyclodextrin motif, one group added different glycosides to the periphery of β-cyclodextrin to enhance lectin-binding affinity [14]. Engineered polymers with defined branching have been

Table 1. Adjuvants for cyclodextrin solubilization of poorly water-soluble drugs.

Drug(s)	Cyclodextrin(s)	Adjuvant(s)	Ref.
NSC-639829	7SBECD	Surfactant (sodium lauryl sulfate)	[132]
Naringenin (a phenolic weak acid)	βCD, HPβCD, mβCD	pH adjustment, surfactant (polysorbates)	[133]
Sulfisoxazole (an amphoteric drug)	HPβCD	pH adjustment, salt formation (triethanolamine)	[134]
DRF-4367 (a weak acid)	HPβCD	pH adjustment, salt formation (meglumine)	[135]
Naproxen (as sodium salt)	βCD	Hydrophilic polymer and cosolvent (polyvinyl-pyrrolidone K-25)	[136]
Naproxen (a weak acid)	βCD	pH adjustment, hydrophilic polymer and cosolvent (polyvinyl-pyrrolidone)	[137]
Isoxazolyl-napthoquinone analogue (a very weak base)	HPβCD	pH adjustment, hydrophilic polymer and cosolvent (polyvinyl-pyrrolidone)	[138]
Vinpocetine (a weak base)	βCD	Salt formation (tartaric acid), hydrophilic polymer and cosolvents	[139]

βCD: β-cyclodextrin; dmCD: Dimethyl-β-cyclodextrin; HPβCD: 2-hydroxypropyl-β-cyclodextrin; 7SBECD: Heptasulfobutyl ether β-cyclodextrin (Captisol); mCD: Methyl-β-cyclodextrin.

Table 2. Marketed i.v. formulations using cyclodextrin complexing agents.

Alprostadil	α-Cyclodextrin	CAVERJECT® RigiDur® Prostavasin® Edex®	Pfizer (US) Ferring (Denmark) Ono (Japan) Schwarz Pharma (Germany)
Itraconazole	Hydroxypropyl-β-cyclodextrin	Sporanox® Injection	Janssen (Denmark) Ortho Biotech Products (US)
Mitomycin	Hydroxypropyl-β-cyclodextrin	Mitozytrex™ MitoExtra™	Novartis (Switerland) SuperGen (US)
Tc-99 Teboroxime	Hydroxypropyl-γ-cyclodextrin	CardioTec	Bracco (US)
Voriconazole	Heptasulfobutyl ether-β-cyclodextrin	VFEND®	Pfizer (US)
Ziprasidone	Heptasulfobutyl ether-β-cyclodextrin	Geodon®, ZELDOX®	Pfizer (US)

evaluated extensively [15,16]. Of particular interest has been the development of dendrimers to facilitate cellular uptake or to target certain cells [17-19]. Dendrimeric complexing agents can be constructed from an almost infinite number of monomeric building blocks to incorporate, for example, hydrogen bond receptor groups or charged moieties separated by defined distances [20,21]. This technology is still in its infancy, and will probably be the focus of intensive research efforts over the next few years.

An example of a dendritic polymer is illustrated in **Figure 2**. The molecule shown contains the two typical elements of a dendritic polymer: a core group and scaffold units. The core group has at least two (but typically three or four) reactive moieties that can be used to form covalent bonds with the scaffold units. Each scaffold unit possesses at least one 'inner' conjugating moiety capable of covalently bonding to the core group (or another scaffold unit in multigenerational dendrimers) and at least two more 'outer' conjugating moieties capable of reacting with either extra scaffold units to form an extra ring or to surface groups used to terminate the polymeric chain. A drug-dendrimer complex can be viewed as a three-dimensional structure with the drug substance entangled within the branching scaffold units. The chemical properties of the core and scaffold units are selected so as to have high affinity non-covalent interactions with the drug substance. In this example, ethylenediaminetetraacetic acid (EDTA) is used as the core group. It is covalently linked by amide bonds to four identical scaffold units, which are comprised of glutamic acid molecules connected to the core group by means of amide bonds to make a so-called generation one dendrimer. The carboxylate groups of glutamic acid function as the 'outer' reactive group of the first scaffold ring and are each covalently bonded to diethanolamine surface modification groups by means of amide bonds. This first generation dendrimer thus contains one EDTA unit, four glutamic acid units and eight diethanolamine units.

Under controlled synthetic conditions, instead of terminating the addition of scaffold units after completion of the first ring, more scaffold units could have been added to make a second ring, so that the second generation dendrimer would be comprised of 1 EDTA unit, 4 glutamic acid units in the

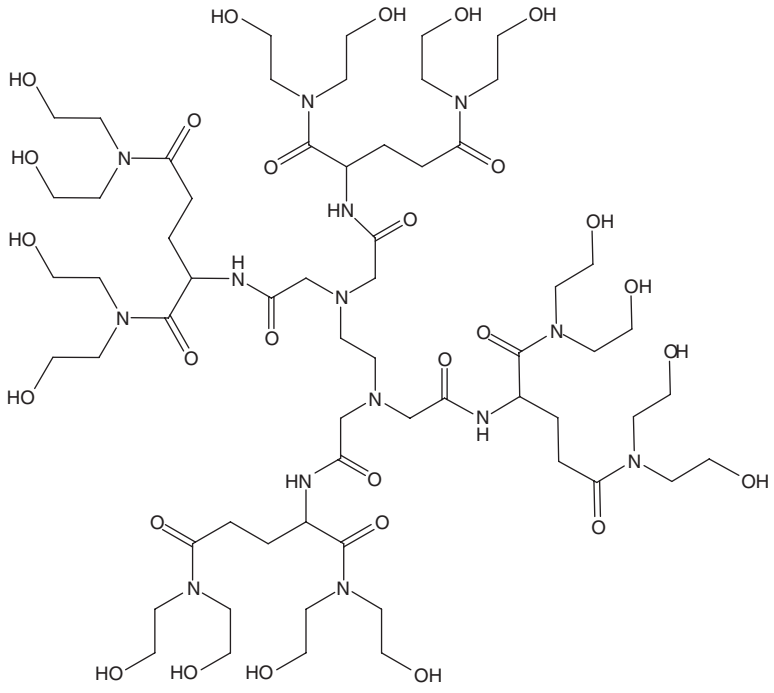

Figure 2. Example of a first generation dendritic polymer.

first ring, 8 glutamic acid units in the second ring and 16 diethanolamine surface modification units at the outer edge. A third generation dendrimer made from these same components would again have 1 EDTA unit as the core, 4 glutamic acid units in the first ring, 8 glutamic acid units in the second ring, 16 glutamic acid units in the third ring, and be capped off with 32 diethanolamine surface modification units. This synthetic scheme can theoretically be carried out *ad infinitum*, but typical dendrimers under investigation as drug carriers may have three to less than a dozen generations of scaffolding. The core unit can be modified to have different properties; in this example, it would be protonated at physiological pH and this would serve as a potential complexation site for anionic drugs. The multidentate scaffold units can also be modified to be more or less hydrophobic through choice of appropriate linking chemistries, and of course the outermost surface modification groups can be tailored to impart properties such as hydrophilicity, affinity for receptors, or other desired functionality. Unlike other polymeric complexing agents, which may vary in the number of monomer units present in the final polymer, dendrimers have a uniquely defined structure and composition.

A major challenge facing the evolving dendrimer technology is that to realize its potential, unique dendrimer complexing agents must be developed for each new drug candidate. In this respect, dendrimer technology faces the same hurdles as prodrug technology: the decision to use a dendrimer complexing agent must be made before any major investment in preclinical safety and biological efficacy studies has begun. Thus, dendrimer complexing agents are best viewed not as solubility-enhancing excipients, but as solubility-enhancing non-covalently linked prodrug moieties. Implementation of this technology will require close collaboration between drug discovery scientists and dendrimer technologists. No products using this technology have yet reached clinical trials.

Several new technologies similar in concept to dendrimers have emerged. By using long chain specially constructed ribbon-shaped polymers, drug complexation and solubilization could be realized. The drug molecule is trapped within a helical structure formed by a twisted ribbon of polymer fibers, the interior side of which forms high affinity non-covalent interactions with the surface of the drug substance. The polymeric fibers must be constructed of subunits that spontaneously form such helical structures using the drug substance as a template. The outer surface of the resulting helical structure is designed to have hydrophilic properties. SoluBest Ltd. (Ness Ziona, Israel) is promoting this concept under the trade name of Solumer™, a proprietary nanotechnology process [22]. A non-drug-related version of this technology has recently been described: so-called 'suitanes' consisting of two identical flat units stitched together at both ends are used to form a 'molecular overcoat' that presents an interior surface to the drug molecule capable of non-covalent high affinity interactions while presenting a hydrophilic exterior surface to the environment [23]. 'Suitanes' must be individually designed and constructed to suit each particular drug candidate. Many more custom packaging motifs can be expected to appear; like dendrimer technology, these non-covalently linked 'suits' or polymeric coatings must each be designed for a particular target drug substance, and therefore face the same hurdles as any other prodrug technology.

2.3 Other complexing agents

Serum albumin has been used extensively in research as a complexing agent, especially for lipophilic acids. Many drugs are highly protein bound *in vivo*; in theory, this can be used to the advantage of designing an i.v. delivery system with the drug preloaded onto albumin. Although this technique was advocated in the past, no commercial product uses albumin as a complexing agent; however, it continues to be 'rediscovered' [24]. Albumin is highly antigenic, so cross-species toxicological evaluation using multiple doses of formulations containing human albumin cannot be performed. Analogous formulations using rat albumin in rats, mouse albumin in mice, canine albumin in dogs, and so on, can be performed in principle, but safety of the actual formulation intended for human use can only be inferred from these results, not confirmed. However, a human albumin-based prodrug has been evaluated recently in human trials that is not a complex but is instead a covalently linked drug-albumin conjugate [25].

3. Polymeric micellar systems

Micelles are aggregates formed by amphiphilic molecules at a specific concentration known as the critical micelle concentration (CMC), above which the molecules spontaneously self-assemble to form a core-shell structure. In an aqueous solution, the shell is hydrophilic and the core is hydrophobic, which can serve as a reservoir for poorly water-soluble compounds. Micellization, the process of micelle formation, has become an important approach for preparing i.v. formulations of poorly water-soluble drugs.

Low-molecular-mass non-ionic surfactants such as polysorbates (e.g., Tween™ 20 brand polysorbate 20 and Tween™ 80 brand polysorbate 80, Croda, Inc., Edison, NJ) and polyoxyl castor oil derivatives (Cremophor® EL and Cremophor® RH 40, BASF Corp., Florham Park, NJ) have been used for enhancing the solubility of poorly water-soluble drugs in FDA-approved parenteral products for i.v. administration, for example, calcitriol injection (Calcijex®, Abbott Laboratories, North Chicago, IL) and amiodarone hydrochloride (Cordarone® Intravenous, Pfizer Inc., New York, NY) [7]. Owing to the relatively high CMC (millimolar range), a solubilized drug may precipitate out in blood as the result of micelle dissociation on dilution with blood. Cremophor is known to be poorly tolerated because of hypersensitivity reactions in some patients [26]. Undesirable side effects such as acute hypersensitivity reaction and peripheral neuropathy have also been reported with the administration of Tween 80 in patients [27].

In recent years, polymeric micelles formed by amphiphilic block copolymers have generated great interest for i.v. delivery of poorly water-soluble drugs [28-32]. Compared with surfactant micelles, the chemical composition, molecular mass and block length ratios of polymeric micelles can be easily tailored to allow control of the size and morphology of the micelles [33]. Furthermore, polymeric micelles have enhanced loading capacity, higher thermodynamic and kinetic stability, and better control over the rate of drug release than surfactant micelles. The CMC of polymeric micelles is generally in the micromolar range, which is remarkably lower than the typical millimolar range associated with surfactant micelles [31].

Among the block copolymers being investigated, polyethylene glycol (PEG) is the most commonly used hydrophilic block [32]. The use of poly(*N*-vinyl-2-pyrrolidone) (PVP) as the hydrophilic block has also been reported [34,35]. Hydrophobic blocks include poly(esters), poly(amino acids) and poly (propylene oxide). Block copolymers can be di-block, tri-block, grafted or star-like in molecular structures. Depending on the properties of the block copolymers, polymeric micelles can be prepared by different methods [36]. Micelles of water-soluble block copolymers are prepared by directly dissolving the copolymer and the drug in an aqueous solution. Micelles of less water-soluble block copolymers can be prepared by dissolving the drug and polymer in an organic solvent, which is subsequently removed by either evaporation of volatile solvent or dialysis against water if the solvent is miscible with water. Alternatively, micelles can be prepared by emulsifying a volatile organic solvent drug solution in an aqueous solution of the polymer to form an oil-in-water (O/W) emulsion. Teagarden and Baker. [37] have reported a new lyophilization (freeze-drying) method that involves the dissolution of the drug and polymer in a mixture of water/*t*-butanol followed by the removal of the solvents by lyophilization. Recently, the utilization of polymeric micelles for i.v. delivery of poorly soluble drugs has passed beyond the preclinical stage and advanced to clinical trials.

3.1 Poloxamer block copolymers

Poloxamers are ABA-type tri-block ether-linked copolymers of ethylene glycol and propylene glycol monomers, in which a central poly(propylene glycol) PPG block is flanked by terminal poly(ethylene glycol) PEG blocks (PEG-PPG-PEG). Poloxamers with different ratios of the hydrophilic oxyethylene units to the hydrophobic oxypropylene units are commercially available (Pluronics®, BASF Corp., Florham Park, NJ). Poloxamers are the most extensively explored copolymer for drug delivery applications [38]. The selection of poloxamers for drug solubilization should be drug-specific because both CMC and drug loading in poloxamer micelles are affected by the molecular composition of the block copolymer, especially the size of the PEG block [39]. A mixture of two poloxamer copolymers has been reported to have synergistic solubilizing effects on poorly water-soluble drugs [40]. Danson *et al.* reported [41] that a doxorubicin formulation known as SP-1049C was prepared by using a combination of a hydrophobic Pluronic L61 with a more hydrophilic Pluronic F127 (1:8, w/w). In a Phase I clinical trial, the formulation was given to patients with cancer refractory to conventional treatments at an escalating dose of 5 – 90 mg/m^2. The formulation was

shown to be effective in eliciting partial responses with dose-limiting toxicity (DLT) of 90 mg/m^2. The use of poloxamer copolymers as new polymer therapeutics for drug delivery has been reviewed by Kabanov *et al.* [33].

3.2 PEG-poly(ester) block copolymers

Poly(esters) which are used as co-forming blocks include poly (glycolic acid), poly(DL-lactic acid) and poly(ε-caprolactone) [42]. Micelles based on PEG-*b*-poly(DL-lactic acid) copolymers have been shown to increase the water solubility of paclitaxel 5000- to 12,000-fold [31]. A formulation when given to mice bearing prostate tumors resulted in an average 91% decrease in tumor volume after 3 cycles of treatment. No significant side effects or mortality were observed. In comparison, all animals in the group receiving Cremophor EL died within 1 day after injection because of the lethal anaphylaxis caused by Cremophor EL [43]. A PEG-*b*-poly(DL-lactic acid)-based micelle formulation of paclitaxel known as Genexol-PM (Samyang Corp., Seoul, South Korea) is now in clinical development and results from the Phase I trial showed higher maximum tolerated dose, lower AUC in plasma, and shorter half-life [44]. The formulation is now in Phase II trials [45].

3.3 PEG-Poly(L-amino acid) block copolymers

One of the advantages of using poly(L-amino acid) as the hydrophobic block is the potential for attaching drug or other moieties to the hydrophobic inner core through a functional group (e.g., amine or carboxylic acid) of the amino acids comprising the block [31]. Two micellar formulations of doxorubicin formulated with PEG-*b*-poly(aspartic acid) copolymers are now being studied in various phases of clinical trials [46,47].

A doxorubicin formulation consisting of PEG-*b*-poly (aspartic acid) copolymer conjugated with doxorubicin (~ 40% doxorubicin substitution on P(Asp)) known as NK119 has been developed by Nakanishi *et al.* [48]. The conjugated doxorubicin increased the hydrophobicity of the inner core, but did not contribute to antitumor activity. A sufficient amount of free doxorubicin was entrapped in the hydrophobic inner core and gradually released within 8 – 24 h after administration. In a Phase I clinical trial [46], NK119 was administered to patients with solid tumors by i.v. infusion every 3 weeks with an escalating dose starting at 6 mg/m^2. The formulation was well tolerated but only showed moderate responses. Infusion-related reactions were not observed in any cases. The maximum tolerated dose with dose-limiting toxicity was determined to be 67 mg/m^2.

NK105 is another paclitaxel micellar formulation based on a di-block copolymer of PEG-*b*-poly(4-phenyl-1-butanol)-L-aspartamide. The 4-phenyl-1-butanol was incorporated as a chemical modifier for enhancing the hydrophilicity of the P(Asp) moiety [48].

An *in vivo* pharmacokinetic study showed that the plasma and tumor concentrations of paclitaxel after a single i.v. injection of the micellar formulation to Colon 26-bearing mice were 90-fold and 25-fold higher than those of the free paclitaxel. The micellar formulation also showed significantly higher antitumor activity in the HT-29 colon cancer-bearing mice model as compared with free paclitaxel because of enhanced accumulation of the drug in the tumor tissue. The Phase I clinical trial began in April 2004 [47].

Owing to their nanoscale particle size, polymeric micelles can evade being scavenged by the mononuclear phagocyte system, resulting in prolonged drug circulation time in blood. This can lead to accumulation in a solid tumor by an enhanced permeability and retention effect [49,50]. In addition to passive targeting, attaching specific ligands to the hydrophilic block is a very promising strategy for active targeting to the diseased site. Targeting to specific tissues or cells has been reported by using thermo- [51,52] or pH-sensitive [53,54] polymers, ligands with high affinity to the surface vector molecules on tumor cells [55,56] and folic acid [51,57,58].

4. Nanosuspensions

Nanosuspensions, in which the drug is presented in a solid nanoparticulate form and dispersed in aqueous media containing lipophilic or polymeric stabilizers, have emerged as a viable option for delivery of high doses of poorly water-soluble drugs [59-62]. As a nanosuspension consists of the drug in solid form, a very high drug loading (up to 40%) may be achievable [63]. Furthermore, drug degradation may be reduced because most of the drug is in the solid-state (usually crystalline), where it is less accessible and thus less susceptible to destabilizing factors such as light or oxygen [59,64]. Another major advantage of this formulation approach is that it can be applied to compounds that are insoluble in water as well as lipophilic excipients [59]. Therefore, nanosuspension technologies have augmented the spectra of parenteral formulation technologies and can be used to salvage some drug candidates that cannot be delivered by other systems such as cosolvent, complexation, or lipid delivery systems.

Nanosuspensions can be prepared by either disintegrating larger drug particles (top-down) or building up nanoparticles from the molecular state (bottom-up) [65,66]. Different nanosuspension preparation methods are discussed below.

4.1 Fragmentation technologies

The use of conventional fragmentation technologies can only yield suspensions in a particle size range well above 1 μm. Therefore, new technologies have been developed to generate particles in the submicrometer size range. **Table 3** lists the key fragmentation technologies for the manufacturing of pharmaceutical nanosuspensions. The most commonly used process for generating nanoparticles of an insoluble drug substance is the nanomilling technology provided by Elan (NanoCrystal® technology, Elan Drug Technologies, Dublin, Ireland) [63]. In this process, the drug substance is placed in a milling chamber containing water, stabilizers and the milling media (usually called 'milling pearls'). The milling media are composed of extremely hard and durable materials such as crosslinked

Table 3. Key fragmentation technologies for preparation of nanosuspensions/nanoparticles.

Technology (company)	Description	Development status	Ref.
NanoCrystal® (Elan)	Media milling of crystalline drugs in an aqueous solution with the presence of stabilizers	Itraconazole i.v. infusion formulation in Phase I clinical trial	[63]
NanoPure® (PharmaSol)	High-pressure homogenization in non-aqueous or partially aqueous media	Preclinical	[67]
Dissocubes® (SkyePharma)	High-pressure homogenization in aqueous media in the presence of polymer or lipid stabilizers	Preclinical	[78]
LiNTEC (ABsize)	Laser-induced nanolization by irradiating drug particles suspended in aqueous media with low energy laser pulses	Preclinical	[72]

polystyrene. The mixture is agitated vigorously in a special milling chamber, thus grinding the drug substance into nanoparticles by impaction and/or shear forces. When applied to fabrication of oral formulations, this approach has become a mature and frequently used technology with several approved products already on the market such as Rapamune® (Sirolimus, Pfizer Inc., New York, NY), TriCor® (fenofibrate, Abbott Laboratories, North Chicago, IL) and Emend® (aprepitant, Merck & Co., Inc., Whitehouse Station, NJ). However, its application to i.v. formulations is more challenging owing to the fact that milling can result in the contamination of the product by the milling media by means of abrasion. This has been a major safety concern for products being administrated via the i.v. route. The extent of abrasion depends on the milling time necessary to achieve the desired particle size. For a very hard drug substance, which is resistant to fragmentation via milling, a long milling duration may be needed. This may lead to contamination of the product with the abrasion products of the milling media. In addition, because of the high energy input, solid-state phase transition of the drug substance may occur during the milling process.

High-pressure homogenization has emerged as a key alternative fragmentation technology for producing nanosuspensions [67,68]. The most frequently used technology is the piston-gap homogenization process. In this technology, the micronized drug particles are forced through a small gap at a very high pressure (15,000 – 30,000 psi). Within the gap, the static pressure decreases and the dynamic pressure increases, leading to the formation of water vapor bubbles, which subsequently collapse when leaving the gap [69]. The collapse of the water vapor bubbles creates high cavitation forces, causing the fragmentation of the drug particles. In addition, the high shear forces existing within the gap may contribute to particle size reduction. High-pressure homogenization is used by SkyePharma (Dissocubes® technology, SkyePharma PLC, London, UK) as well as Baxter (NanoEdge® technology, Baxter Healthcare Corp., Deerfield, IL) as part of their proprietary nanosuspension platforms [70,71].

A similar fragmentation technology has been developed by PharmaSol, which involves the homogenization of a drug substance in a non-aqueous or partially aqueous medium (NanoPure® technology, PharmaSol Gmbh, Berlin, Germany) [67]. This process can be operated at a very low temperature (down to -20°C), making it more suitable for the processing of heat-sensitive drug substances. However, this technology may find great challenges for producing i.v. nanosuspensions because large quantities of non-aqueous solvents are toxic for i.v. administration and the removal of these organic solvents from the finished product can be inefficient and very costly.

A laser-induced nanolization technology has been developed recently by ABsize, Inc.(Osaka, Japan) [72]. The technology uses a low energy laser beam to produce nanoparticle suspensions (1 – 300 nm). When a pulsed laser beam (wavelength: 200 – 600 nm; pulse width: several tens of femtoseconds to several hundred nanoseconds) is applied to insoluble drug particles suspended in water, the region of drug particles irradiated by laser absorbs laser light rapidly and is heated locally, which results in a marked inner stress between the light-absorbing region and its periphery, causing the formation of cracks and resulting in the final fragmentation of the drug particles. Unlike the milling or the high-pressure homogenization process, the laser-induced nanolization process does not involve direct contact between the drug particles and the milling media, thus avoiding any potential contamination. This is especially advantageous for preparing i.v. formulations. However, this technology is still at a very early stage of development and a scalable process has yet to be demonstrated.

4.2 Bottom-up technologies

Several technologies (**Table 4**) have been developed to produce nanoparticles from the drug substance in solution state. The principal challenge for these technologies is the control of the relatively complex precipitation process. A drug substance dissolved in a solution tends to precipitate out as a particle in the micrometer size range. The competition between nucleation and particle growth must be influenced towards nucleation by the use of suitable process parameters and excipients [73], which represents a major task for formulation development and process optimization. Furthermore, depending on the properties of the drug

Table 4. Key bottom-up technologies for preparation of nanosuspensions/nanoparticles.

Technology (company)	Description	Development status	Ref.
Nab (Abraxis Bioscience)	Encapsulation of drug into albumin nanoparticles	Abraxane approved by FDA in 2005 Several clinical trials	[76]
NanoEdge® (Baxter)	Precipitation of drug from an organic solvent followed by high-pressure homogenization in the presence of lipid or polymer stabilizers	Used to have Phase I and II clinical trials	[71]
HDDS® (Acusphere)	Spray-drying to produce porous microparticles consisting of drug nanoparticles embedded in a water-soluble matrix	Phase I clinical trial	[140,141]
NanoMorph® (Soliqs-Abbott)	Generation of amorphous drug nanoparticles by precipitation in the presence of polymer or lipid stabilizers	Preclinical	[74]
SCF: precipitation with compressed antisolvent (CritiTech)	Formation of drug nanoparticles by spraying a drug dissolved in an organic solvent into SCO_2	Preclinical	[142]
SCF extraction from emulsion (Ferro Corp.)	Extraction of the organic solvent in an O/W emulsion of the drug using SCO_2	Preclinical	[79]
SCF (Thar Technologies)	Formation of drug nanoparticles by either SCF antisolvent or rapid expansion of SCF method	Preclinical	[143]
SCF: aerosol solvent extraction (Telesso Technologies; Former Eiffel Technologies)	Precipitation of drug nanoparticles by spraying a drug solution in SCO_2	Preclinical	[144]

O/W: Oil-in-water; SCF: Supercritical fluid.

substance, the generation of metastable polymorphic forms during precipitation can be problematic. The NanoEdge technology developed by Baxter represents an approach that combines the bottom-up and fragmentation technologies [71]. In this technology, a suspension containing imperfect or friable precipitates is first generated by precipitation followed by particle fragmentation using high-pressure homogenization.

The NanoMorph® technology developed by SOLIQS (Abbott Gmbh & Co., KG, Ludwigshaven, Germany) involves the dissolution of a poorly soluble drug substance in an organic solvent such as ethanol followed by controlled mixing with an aqueous solution containing a stabilizer [74]. The process is optimized to create a high level of supersaturation so that the solubility of the amorphous state is exceeded and nucleation is favored over particle growth. Processing parameters facilitating precipitation of the amorphous form include rapid mixing in the mixing chamber with the aqueous stabilizer solution. In addition, a suspension rather than a true solution of the drug substance in the organic solvent can be formed first and heat is applied to yield a saturated solution in the mixing chamber milliseconds before mixing with the cold stabilizer solution and the consequent rapid nucleation. The NanoMorph process is capable of producing spherical amorphous nanoparticles of the drug substance. Although 10- to 100-fold increases in solubility can be achieved by means of the formation of the amorphous form, it becomes extremely challenging to maintain the drug in the metastable amorphous state over the product shelf life. Crystal growth resulting from the transformation of the amorphous form into a more stable crystalline form is the main instability problem [75]. This stability issue can be addressed by the selection of effective excipients (stabilizers) and optimization of the processing parameters. Furthermore, the tendency of solid-state transition may be reduced through some downstream processing means such as lyophilization or spray-drying under aseptic condition. Although the NanoMorph process is an advanced technology for oral formulations, it is in the earlier phase of development for its application to i.v. formulations.

Abraxane® (Abraxis BioScience, LLC, Los Angeles, CA), a paclitaxel nanosuspension formulation, was the first nanosuspension product for i.v. administration to be approved by the FDA in January 2005 [76]. During manufacturing, paclitaxel is dissolved in methylene chloride and emulsified in an aqueous solution of albumin to form an O/W emulsion by high-pressure homogenization. When the organic solvent is subsequently removed at reduced pressure, albumin nanoparticles with the entrapped solid drug are generated [77]. The resultant paclitaxel nanosuspension is lyophilized further to form the final product, which is reconstituted with a saline solution for injection before i.v. administration. The product can be stored at room temperature; but the reconstituted

formulation should be refrigerated at 2 – 8°C and administered within 8 h [76]. This technology represents the first commercial success for the development of nanosuspensions for intravenous administration.

High gravity reactive precipitation (HGCP), developed by Nanomaterials Company, represents a new technology that is designed specifically for industrial-scale production of engineered nanoparticles with particle sizes in both the micrometer and nanometer ranges. This technology is based on reactive precipitation, a process in which the final solid product is produced as the result of a chemical reaction; for example, when an acid is added to a solution of a base in a non-polar solvent, the polar salt is precipitated from solution as it is formed. High gravity micro-mixing of reactants within a rotating packed bed is used to enhance mass transfer and heat transfer between the reactants by several magnitudes, thus inducing rapid nucleation of the final product while suppressing crystal growth. As the reactants enter the rotating packed bed, they are spread or split into nanodroplets under high shear created by the high gravity. Nanomaterials has been successfully utilizing the technology for the production of inorganic nanomaterials such as $CaCO_3$ (15 – 40 nm), $Al(OH)_3$ (1 – 10 nm) and $SrCO_3$ (40 nm) on a commercial scale [63]. This technology is well suited to solvent/antisolvent and reactive precipitations of pharmaceutical compounds in both aqueous and organic solvents. Solvent/antisolvent precipitation is effected by addition of a solvent in which the drug is poorly soluble (the antisolvent) to a solution of the drug in a solvent in which it is highly soluble. If the rate of addition is fast enough, rapid nucleation and precipitation can be achieved. Control of the desired crystal form of individual drugs is possible by altering the precipitation conditions. In one of their early preclinical programs, Nanomaterials Company demonstrated generation of cefuroxime axetil nanoparticles with mean particle size of 293 nm and narrow particle size distribution (200 – 450 nm).

Several companies have developed technologies with the use of supercritical fluids (SCFs), in most cases carbon dioxide, for the fabrication of pharmaceutical nanoparticles (**Table 4**). Supercritical carbon dioxide (SCO_2) is a poor solvent for most drug substances; therefore, the generation of nanoparticles by dissolving the drug substance in SCO_2 followed by gas expansion has limited application. The addition of cosolvents to SCO_2 can improve the solubility of some drugs; however, particle size after gas expansion is difficult to control during this process. As a great number of organic solvents are poorly soluble in SCO_2, the most commonly used SCO_2 method is the antisolvent process, in which the drug substance is dissolved in an organic solvent followed by mixing with SCO_2 acting as an antisolvent [78]. In this process, the critical step for generating nanoparticles of the drug substance is to ensure a very rapid mixing of the organic solution with SCO_2. Several companies have developed proprietary SCO_2 technologies, differing in how the rapid mixing is achieved (i.e., ultrasound, a mixing rotor or a coaxial nozzle). A key advantage of these approaches for preparing nanoparticles for oral application is the generation of drug nanoparticles in the dry state without the need for a downstream drying process. If the finished product is for i.v. administration, a reconstitution step is required to form a fluid nanosuspension for injection. Particle size distributions of particles produced by this process are highly dependent on the drug properties. Without appropriate process optimization, particles in the micrometer size range and/or acicular morphology may be generated [79].

Supercritical fluid extraction from emulsions is a new particle engineering process developed by Ferro, Inc. [79]. In this technology, an O/W emulsion is first formed with the drug substance dissolved in an organic solvent as the internal phase and the surfactants or stabilizers in the continuous aqueous phase. Subsequent to forming the emulsion, the organic solvent is extracted by using SCO_2, causing controlled precipitation of the drug as nanoparticles. The newly generated nanoparticles are stabilized further *in situ* by the surfactants or polymers in the continuous phase. This process can result in very small nanoparticles (down to 100 nm) with a narrow particle size distribution, which can reduce potential crystal growth of the nanosuspension and result in enhanced physical stability [75]. However, this process may not be applicable to all drug substances because the formation of a stable submicrometer emulsion can represent a challenge for certain drugs.

In general, supercritical fluid technologies have demonstrated the potential for producing uniform nanoparticles. In comparison with other fragmentation and bottom-up nanoparticle formulation methods, these technologies may offer better control over particle size distribution and minimize solid-state changes of the drug substance in the nanoparticles [80]. However, at the current stage of development, supercritical fluid technologies have not shown a clear advantage over most frequently used fragmentation technologies such as ball milling for commercial manufacturing because of the higher cost and equipment/process complexity with respect to scale-up.

4.3 Formulation and pharmacokinetic considerations

The choice of excipients suitable for intravenous application is rather limited. Polymers such as poloxamers and polyvinylpyrrolidones [81-83] can be adsorbed onto the particle surface and thereby prevent the close contact of particles via steric stabilization. Other commonly used stabilizers including phospholipids such as lecithin derivatives [84] or polysorbates can prevent particles from aggregating through electrostatic repulsion or steric stabilization. However, an excess amount of stabilizer in the formulation may not be advantageous because the resultant higher concentration of the solubilized drug will accelerate the ripening effect [85]. Ostwald observed that kinetically formed precipitates tend to convert into thermodynamically more stable solid forms and that smaller particles tend to grow larger as precipitates age.

On the other hand, insufficient stabilizer could result in particle aggregation via bridging flocculation/aggregation resulting from incomplete coverage of the particle surface. Merisko-Liversidge *et al.* have recommended a range of drug-to-stabilizer ratio of 2:1 – 20:1 (w/w) [63]. For different drug substances, it is critical to determine the optimal amount of stabilizers in a nanosuspension formulation.

Physical instability represents the most significant challenge in developing a nanosuspension product with an acceptable shelf life. Owing to the very large surface area, nanoparticles tend to aggregate or grow in size by means of Ostwald ripening [85]. Furthermore, nanosuspensions consisting of drug substance in the metastable amorphous form can undergo solid-state transformation, leading to crystal growth [86]. The presence of larger particles (in the micrometer range) is a safety concern because large particles can cause clogging of fine lung capillaries. To minimize crystal growth in the finished product during storage, a highly uniform particle size distribution, the use of stabilizers and downstream processing such as lyophilization (freeze-drying) or spray-drying should be considered.

Lyophilization may reduce physical stability issues of nanosuspension formulations; however, poorly designed formulations may cause reconstitution problems [82]. When developing a lyophilized nanosuspension product, the selection of both type and concentration of stabilizers is important. The optimization of the lyophilization parameters such as the rate and temperature of the freezing step is also critical [87]. The complex production processes of a nanosuspension product make it extremely challenging to produce a product meeting the sterility requirements. Terminal sterilization by heat (autoclaving) or radiation (γ irradiation) is not always applicable owing to physical or chemical stability issues. Aseptic processing such as sterile filtration remains the most commonly used manufacturing method for i.v. nanosuspensions.

The fate of i.v.-administered drug nanoparticles is affected by the solubility of the drug in the bloodstream [88]. Drug nanoparticles are exposed to an instantaneous sink condition following i.v. administration. Under these conditions, their extremely large surface area could lead to a rapid and complete dissolution of drug nanoparticles in the bloodstream. Mouton *et al.* [60] have reported that an itraconazole nanocrystal suspension formulation with a mean particle size of ~ 300 nm had a similar pharmacokinetic profile to the drug dosed as an HP-β-CD solution in healthy human subjects. If solid drug nanoparticles do not dissolve quickly in the bloodstream following i.v. administration, the pharmacokinetic profile could be altered [89]. The undissolved drug particles have been shown to be taken up by the reticuloendothelial system (RES) and have a sustained release pharmacokinetic profile [60,61,89]. Rabinow *et al.* [89] have reported a reduced C_{max} and prolonged plasma half-life of an itraconazole nanosuspension formulation with a mean particle size of ~ 580 nm relative to the drug dosed as HP-β-CD solution formulation in rats. The accumulation of drug nanoparticles in the RES system and slow release of drug particles in these systems can be beneficial for passive targeting drugs to lung, liver and spleen. This can yield a more favorable toxicological profile, leading to increased tolerability and permitting higher dosing. However, as the chronic effects of uptake of solid drug particles by the RES are not well understood, when using this mode of delivery attention should be paid to the potential toxicity of long-term exposure of a drug to these organs.

5. Lipid formulations

For poorly water-soluble drug substances with adequate solubility in vegetable oils that are acceptable for parenteral administration (such as safflower or soybean oil), submicrometer emulsions (O/W type) represent a viable formulation option [90]. Although i.v. emulsion products have been successfully developed, the broad application of this approach has been limited by the poor solubility of most water-insoluble drugs in vegetable oils. As the oil phase of an injectable emulsion usually does not exceed 30%, the drug loading in an emulsion may not meet the high dose requirements in spite of reasonable drug solubility in the oil phase.

In the past 30 years, extensive research has been carried out in the area of liposome technologies. Poorly water-soluble lipophilic drugs can be incorporated into the lipid bilayer and hydrophilic APIs can be encapsulated into the aqueous core. Several liposome or liposome-like products for i.v. administration have shown commercial success, such as the stealth liposome formulation of doxorubicin (Doxil®, Alza Corp., Mountain View, CA) and the three amphotericin B lipid complex or liposome products (Abelcet®, Enzon Pharmaceuticals Inc., Edgewater, NJ; AmBisome®, Gilead Sciences, Inc. Foster City, CA; AmphoTec®, Alza Corp., Mountain View, CA) [91-94]. Drug loading of liposomal formulations can be quite high in terms of lipid-to-drug ratios, but the final drug concentration in the product is usually fairly low. As the manufacturing and maintenance of product storage stability of liposomes are complex and challenging, this approach has not been broadly applied for the formulation of poorly soluble drugs and approval of new products has been very limited in recent years. Visudyne® (Novartis International AG, Basel, Switzerland) is the newly approved liposomal product of verteporfin for photodynamic therapy of age-related macular degeneration [95]. Other liposome formulations of water-insoluble drugs in Phase II or Phase III clinical trials are paclitaxel [96], vincristine [97] and annamycin [98]. Despite the introduction of these marketed products, research on liposomal formulation strategies for solubilization of poorly water-soluble compounds has not advanced significantly as a general technique. The emphasis in recent years has been on the design of liposomal formulations incorporating targeting technologies that are outside the scope of this review.

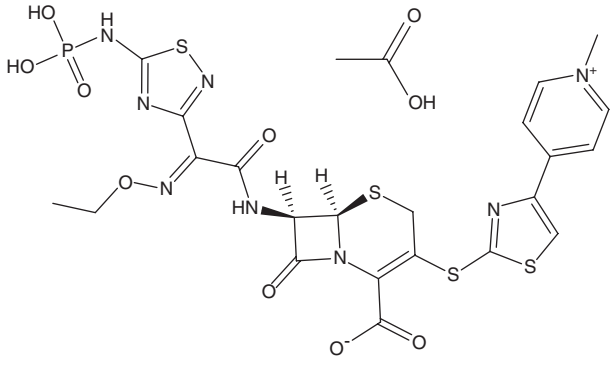

Figure 3. *N*-phosphono prodrug of a cephalosporin derivative.

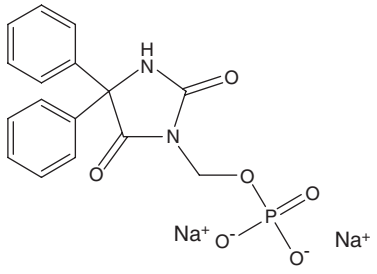

Figure 4. Fosphenytoin.

5.1 Cochleates

The name cochleate originates from the Latin word cochlea, which means snail shell. These structures were described by Papahadjopoulos *et al.* in 1975 [99]. Cochleates are cylindrical multilamellar structures formed by addition of calcium ions to negatively charged unilamellar phosphatidylserine vesicles in an aqueous medium. The addition of calcium ions causes the small vesicles to fuse into larger sheets of lipid bilayers, which subsequently roll up into cochleate structures. These structures can be used to incorporate ('encochleate') hydrophilic drugs into the aqueous domains, for example for a sustained release application. Alternatively, poorly water-soluble compounds may be incorporated into the lipid bilayer structures. A cochleate product of amphotericin B has been developed for oral administration and is now in clinical Phase I. Preclinical data for this product administrated intravenously to rats [100] have demonstrated the potential of cochelates for i.v. delivery of poorly soluble compounds.

5.2 Liquid crystalline nanoparticles

Recently, technologies capable of producing a new class of lipid nanoparticles called liquid crystalline nanoparticles (LCNP) have been reported [101]. These nanoparticles are formed with FDA-approved lipids and have different liquid crystalline lipid assemblies with a hydrophilic as well as a hydrophobic region. Poorly water-soluble drug substances can be incorporated into the hydrophobic regions of these liquid crystalline nanoparticles [102-105]. Depending on drug substance properties, high drug loadings (up to 50% by lipid weight) can be achieved combined with particle sizes < 100 nm and a narrow size distribution. Particle formation is achieved by simple low shear mixing of the drug substance and lipid in a solution containing a small amount of (polymeric) stabilizer. Production processes are scalable and sterilization of the final product may be achieved by autoclaving or sterile filtration. An LCNP propofol formulation has been developed and is now under clinical development [102]. In spite of increasing interest in this area of technology, it still has to be proven that this technology offers distinct advantages over other lipid delivery systems.

6. Prodrugs

A prodrug is a chemically modified drug molecule with significantly less pharmacological activity than its parent, which is designed to have different molecular properties so as to overcome various physicochemical, biopharmaceutical and/or pharmacokinetic limitations of the parent drug. A prodrug must undergo conversion to the parent drug within the body at a reasonable rate so that its therapeutic effect can be realized. As commonly understood, conversion of the prodrug to the active drug is usually thought to result from metabolic activity, such as cleavage of a promoiety (e.g., the deacetylation of heroin to morphine catalyzed by esterases) or addition of a new functional group (e.g., metabolic oxidation of primadone to phenobarbital by mixed-function oxidases). However, the term prodrug has been broadened by some scientists to include chemically unstable modifications of active drugs that spontaneously decompose to yield the parent drug when exposed to physiological fluids. Prodrug strategies are always limited by the requirement that the drug target must meet certain narrowly defined structural requirements, thus limiting the applicability of this approach. When the prodrug approach is applied to a poorly soluble drug for i.v. delivery, solubility enhancement becomes the key objective.

Ideally, a prodrug for i.v. administration should possess adequate solubility to be formulated into a solution, acceptable solution stability to provide an appropriate product shelf life, and the ability to be rapidly converted to the pharmacologically active parent drug, whether by chemical or by biochemical means. In addition, the promoiety (if one is used) must also be proven to be non-toxic. Water-soluble prodrugs of steroids such as sodium hemisuccinate esters and sodium phosphate esters represent successful examples for the use of prodrugs of poorly soluble drugs for i.v. administration [103]. Some recent developments in prodrug design strategies are reviewed below.

6.1 Phosphate prodrugs

The synthesis of phosphate esters is the most commonly used prodrug approach for enhancing the aqueous solubility of

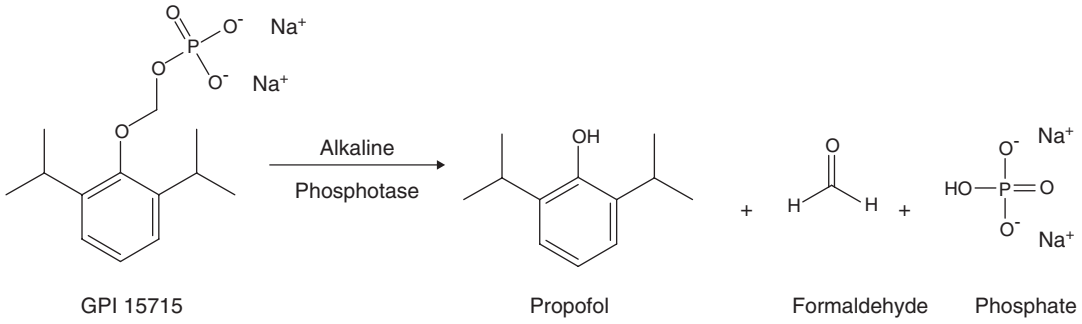

Figure 5. A phosphonooxymethyl ester prodrug of propofol.

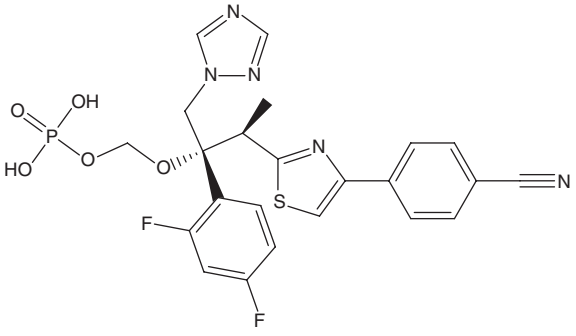

Figure 6. A phosphonooxymethyl prodrug of ravuconazole.

poorly soluble drugs. Phosphate esters are highly ionizable and have significantly higher aqueous solubility than the parent drug. Their stability in both solid-state and in aqueous solution allows development of stable injectable dosage forms. Furthermore, phosphate esters are rapidly cleaved *in vivo* by alkaline phosphatases to release parent drug and non-toxic inorganic phosphate. Whereas the preparation of phosphate prodrugs has mainly involved the formation of phosphate ester with drug alcohol groups, *N*-phosphono type prodrugs have also been synthesized for solubility enhancement. Such a prodrug was prepared with a poorly soluble new cephalosporin derivative (**Figure 3**) [106]. The prodrug was shown to convert rapidly to the parent drug following i.v. administration to rats and monkeys. *In vivo* activity was shown to be superior to that of vancomycin in systemic bacterial infection in mice [106].

6.2 Phosphonooxymethyl prodrugs

The development of phosphonooxymethyl (POM) prodrugs involves the attachment of the phosphate group to the parent drug through a methoxy spacer. Fosphenytoin (**Figure 4**), a disodium phosphate ester of 3-(hydroxymethyl)phenytoin, is a good example of the use of a POM prodrug as a water-soluble injectable form of phenytoin, commercially marketed as Cerebyx® (Sanofi-aventis, Paris, France) [107,108]. The phosphate group of fosphenytoin is first enzymatically cleaved to give 3-(hydroxymethyl)phenytoin, which is spontaneously hydrolyzed to form formaldehyde and phenytoin.

The POM prodrug approach was used recently to develop a water-soluble phosphonooxymethyl ester prodrug of propofol (**Figure 5**), an i.v. sedative-hypnotic agent widely used for anesthesia and sedation. Owing to its low aqueous solubility, propofol is now formulated as an injectable emulsion (Diprivan® brand of propofol, AstraZeneca, London, UK), which is not an ideal product because of poor physical stability, risk of bacterial contamination, potential for emulsion-induced embolism, and pain at site of injection. In the first human clinical trial [109], the phosphonooxymethyl ester prodrug (Aquavan™, Guilford Pharmaceutical, Inc., Baltimore, MD) was well tolerated with no signs of pain on injection. However, the pharmacokinetic parameters of the propofol produced from the prodrug were different from those reported for the lipid emulsion formulation; both the time to achieve peak concentration and the time for elimination were longer. On 12 December 2008, FDA approval was granted to this product (Lusedra™, Eisai Corporation of North America, Woodcliff Lake, NJ) for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.

The synthesis and biological evaluation of a POM prodrug of ravuconazole (**Figure 6**), a potent broad-spectrum antifungal agent, have been reported [110]. The prodrug was rapidly converted to the parent drug *in vivo* following i.v. administration to various animal models and showed efficacy comparable to that achieved by oral administration of the parent drug against fungal infection in mice. A POM prodrug of camptothecin was also prepared; the POM promoiety is attached to the alcohol group adjacent to the ketone of the lactone ring (**Figure 7**). Following i.v. injection to rats, bioconversion of the prodrug results predominantly in the generation of the open ring form of the parent drug; however, equilibrium between the lactone and carboxylate was found to be established rapidly (**Figure 7**) [111,112].

6.3 Amino acid prodrugs

Numerous examples can be found in the literature on the use of amino acids and amine-containing derivatives as water-soluble prodrugs for i.v. delivery [103]. Using this approach, the synthesis of water-soluble prodrugs of camptothecin and its

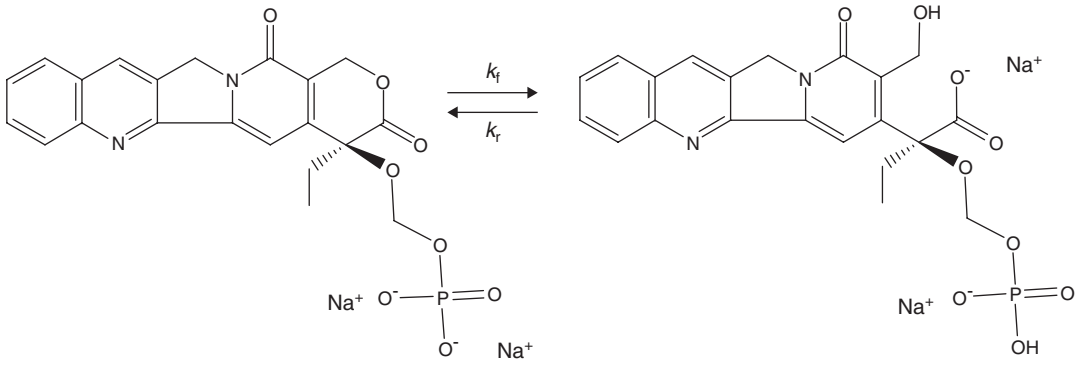

Figure 7. Equilibrium between lactone and carboxylate forms of phosphonooxymethyl prodrug of camptothecin.

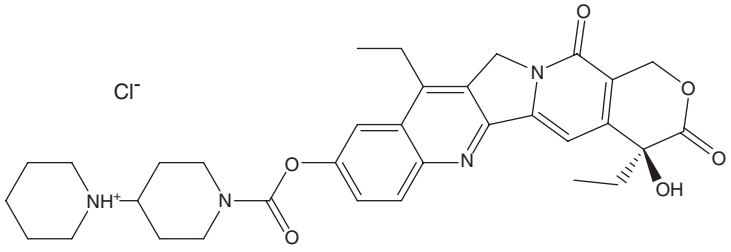

Figure 8. Irinotecan HCl.

derivative has been reported. The glycinate ester and longer chained amine-containing acid esters of camptothecin were incorporated in liposomal formulations [113]. Although these prodrugs could undergo rapid conversion to the parent drugs at physiological pH, new degradation products were generated by the glycine derivative and a slowdown in conversion rate was noted for derivatives with increased length of alkyl chain between amine and the ester group. Irinotecan is a water-soluble prodrug of a camptothecin derivative (SN-38), consisting of a cyclic tertiary amine as the solubilizing promoiety linked by a carbamate ester to the phenol group of the parent drug (**Figure 8**) [114]. Camptosar® (irinotecan HCl injection, Pfizer) has shown a broad spectrum of activity in solid tumor and has been approved for the treatment of advanced cancer of the large intestine and rectum.

d-γ-Tocopheryl *N,N*-dimethylglycinate hydrochloride was synthesized as a water-soluble prodrug of d-γ-tocopherol, which is one of the major forms of natural tocopherols (vitamin E) [115]. The hydrolysis of the prodrug was catalyzed mainly by esterases in liver microsomes. The liver availability of d-γ-tocopherol after the administration of the water-soluble prodrug was two times higher than that achieved by administration of the parent drug.

6.4 Polymer prodrugs

Water-soluble polymers have been investigated for their use in preparing prodrugs (conjugates) of poorly soluble anticancer drugs. Polymer bound prodrugs are not only water-soluble but also capable of tumor targeting by means of the enhanced permeability and retention effect [116]. *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer has been explored extensively for the formation of polymer drug conjugates [117]. HPMA-copolymer-doxorubicin (Dox) (**Figure 9**) was the first synthetic polymer conjugate to enter a Phase I clinical trial [118]. Doxorubicin is linked to the HPMA copolymer by means of a tetrapeptide chain (Gly-Phe-Leu-Gly); the doxorubicin content was 7 – 9% by weight. The peptidyl linkages are stable in plasma but will be cleaved by lysosomal thiol-dependent proteases following endocytic capture of the conjugate [119]. Since HPMA-Dox was reported, more HPMA copolymer conjugates of other anticancer drugs such as paclitaxel, camptothecin and carboplatin platinate have also progressed to clinical testing [119]. Results from the Phase I clinical trials of HPMA conjugates of paclitaxel and camptothecin have been disappointing as the conjugates displayed toxicity little or no better than the free drug. Toxicity was attributed to the rapid release of the free drug into the systemic circulation, possibly because of the weak ester linkage [120]. HPMA copolymer conjugates have also been synthesized to contain targeting ligands such as peptides, sugars and antibodies with the aim of further promoting increased tumor targeting by receptor-mediated delivery [121].

PEG-camptothecin prodrugs, which are formed with various spacer groups, have been studied extensively. A PEG-camptothecin prodrug called pegamotecan has been evaluated in clinical trials and showed good

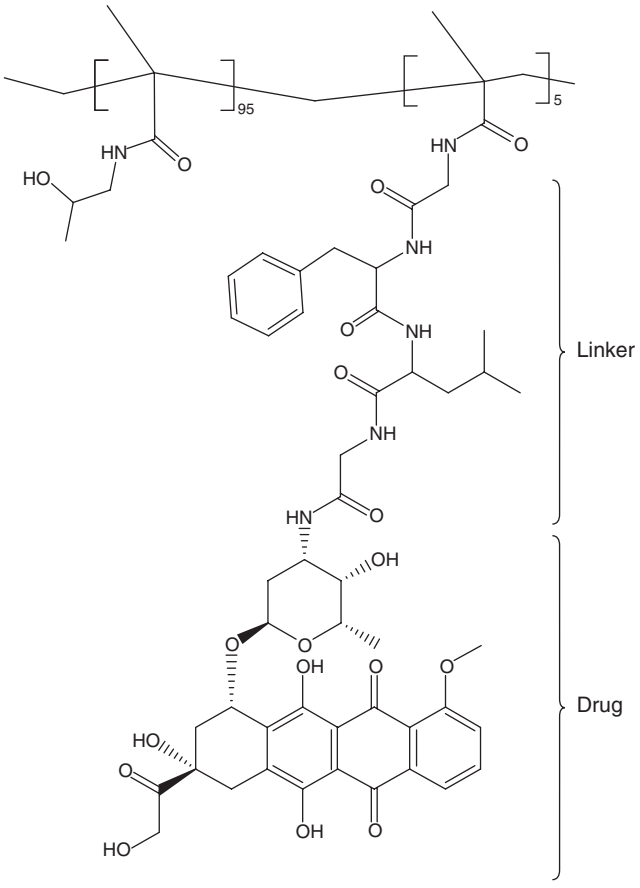

Figure 9. HPMA-copolymer-doxorubicin.

response from patients and low incidence of toxicity [122,123]. Poly(L-glutamic acid)-Gly-camptothecin is another water-soluble prodrug of camptothecin. Poly-(L-glutamic acid) is a biodegradable peptide homopolymer with carboxylic acid side chains carrying multiple anionic charges with the parent drug being bound to the polymer at multiple sites [124]. The percentage of parent drug in the polymer conjugate can be as high as 50% by weight [125]. Prolonged plasma residence time and enhanced antitumor activity in mice have been observed for prodrugs formed with poly(L-glutamic acid) with a higher molecular mass [124,126].

Poly(L-glutamic acid) paclitaxel conjugates have also been investigated for their use as prodrugs. Xyotax® (recently renamed Otaxio™, Cell Therapeutics, Inc., Seattle, WA) is a poly(L-glutamic acid) paclitaxel conjugate formed with the composition of one paclitaxel molecule per 10.4 glutamic acid monomers (**Figure 10**) [127]. This prodrug remains inactive while circulating in the bloodstream, which is also less toxic compared with the parent drug. Once in the tumor tissue, the prodrug is taken up by the tumor cell and the parent drug is released as the result of cleavage of the polymer backbone by lysosomal enzymes, principally cathepsin B inside the lysosomes [127]. Results from clinical trials with this prodrug have shown greater efficacy than paclitaxel in several human cancer models [127,128].

6.5 Prodrugs based on O→N acyl migration

Recently, a new approach to prodrug design has made use of the well-know O→N intramolecular acyl migration reaction in which an ester of an α-aminoalcohol is converted to an amide of an α-hydroxylamine by means of an intramolecular transfer of the acyl group [129]. Typically, such reactions occur rapidly at neutral pH, but are suppressed at mildly acidic pH by ionization of the amino moiety. Ionization of the amino moiety to form a salt also increases the aqueous solubility of the O-acyl analogue (**Figure 11**).

Isotaxel, the O-acyl analogue of paclitaxel, is 1.8×10^3 more soluble than paclitaxel itself. Isotaxel hydrochloride is stable as a solid, offering the possibility of creating a parenteral dosage form in which solid isotaxel hydrochloride, with suitable buffering agents added to modify pH, is reconstituted to form a mildly acidic solution stable for several hours that on injection rapidly converts to active paclitaxel. Thus, isotaxel is stable in solution for > 2.5 h at pH 2 in glycine hydrochloride buffer and is converted at neutral pH into the active paclitaxel with a half-life of a quarter of an hour [130].

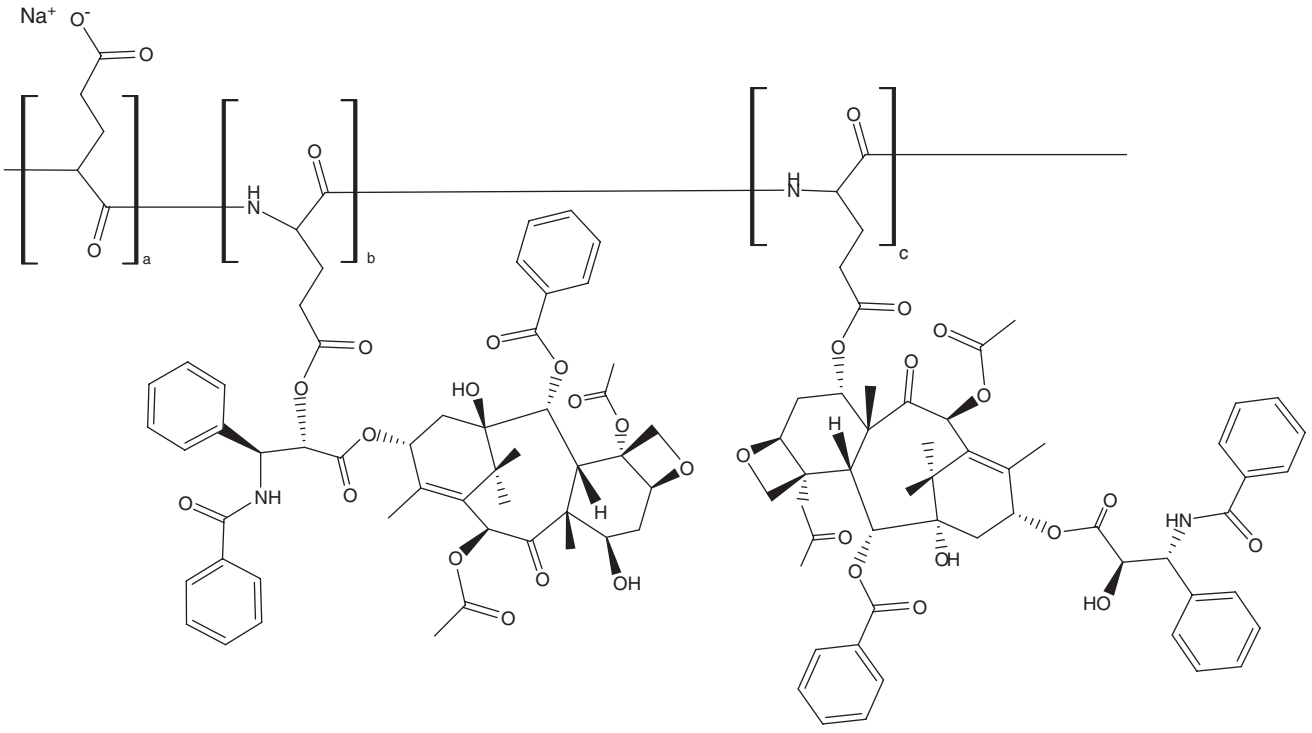

Figure 10. Poly(L-glutamic acid) paclitaxel conjugate.

7. Expert opinion

While searching for an appropriate technology for i.v. delivery of a poorly water-soluble drug, both drug-related variables and delivery system-specific factors should be considered. The chemical structure and physicochemical properties of a drug play an important role in determining the extent of molecular interaction between the drug and the delivery system involving the use of a carrier such as molecular complexes, polymeric micellar systems and lipids. The extent of this interaction will affect the final drug loading capability or the extent of solubilization of the delivery system. Uniquely tailored complexation agents, such as dendrimers, pose further challenges, as the safety of the complexation agent must be tested along with the drug – a problem also encountered with the prodrug approach. The feasibility of preparing a prodrug is also dependent on the availability of a derivatizable functional group in the parent compound and the types of functional group will influence the prodrug design with respect to the selection of promoieties. The solubility of the drug in the liquid medium of a nanosuspension can have a significant impact on the long-term physical stability of the finished product as a fluid product. The incorporation of a surfactant to a nanosuspension formulation may result in a higher drug solubility, which can potentially lead to undesirable crystal growth. The conversion of the fluid nanosuspension into a solid product by lyophilization can be a feasible way to overcome such a physical instability issue. The chemical stability of the drug in the delivery system is another key drug-related variable that may influence the selection of the manufacturing process, the final product physical form, and shelf life storage conditions.

A poorly water-soluble drug with a high therapeutic dose is always a challenge for i.v. delivery even though a relatively large volume of the product can be administrated intravenously as compared with other parenteral routes of administration. This is particularly true when a delivery system that uses a carrier is considered because the large quantity of carrier that is required to achieve the desirable drug dose may cause concerns about the toxicity of the carrier. In this case, the nanosuspension approach appears to be the technology of choice because a high drug loading can be attained in a nanosuspension formulation without the use of a carrier.

Owing to the stringent product microbiological quality requirements for i.v. products, the manufacturing processes must be capable of producing products that are pyrogen-free and sterile. If the finished product cannot be terminally sterilized by moist heat or radiation, the manufacturing of the product must be carried out under aseptic conditions, which can be challenging depending on the product sophistication and processing characteristics. However, with the recent advance in aseptic technologies such as barrier isolation technology [131], the technical hurdles in meeting the aseptic processing requirements can be overcome, but not without a significant increase in manufacturing cost. When an organic

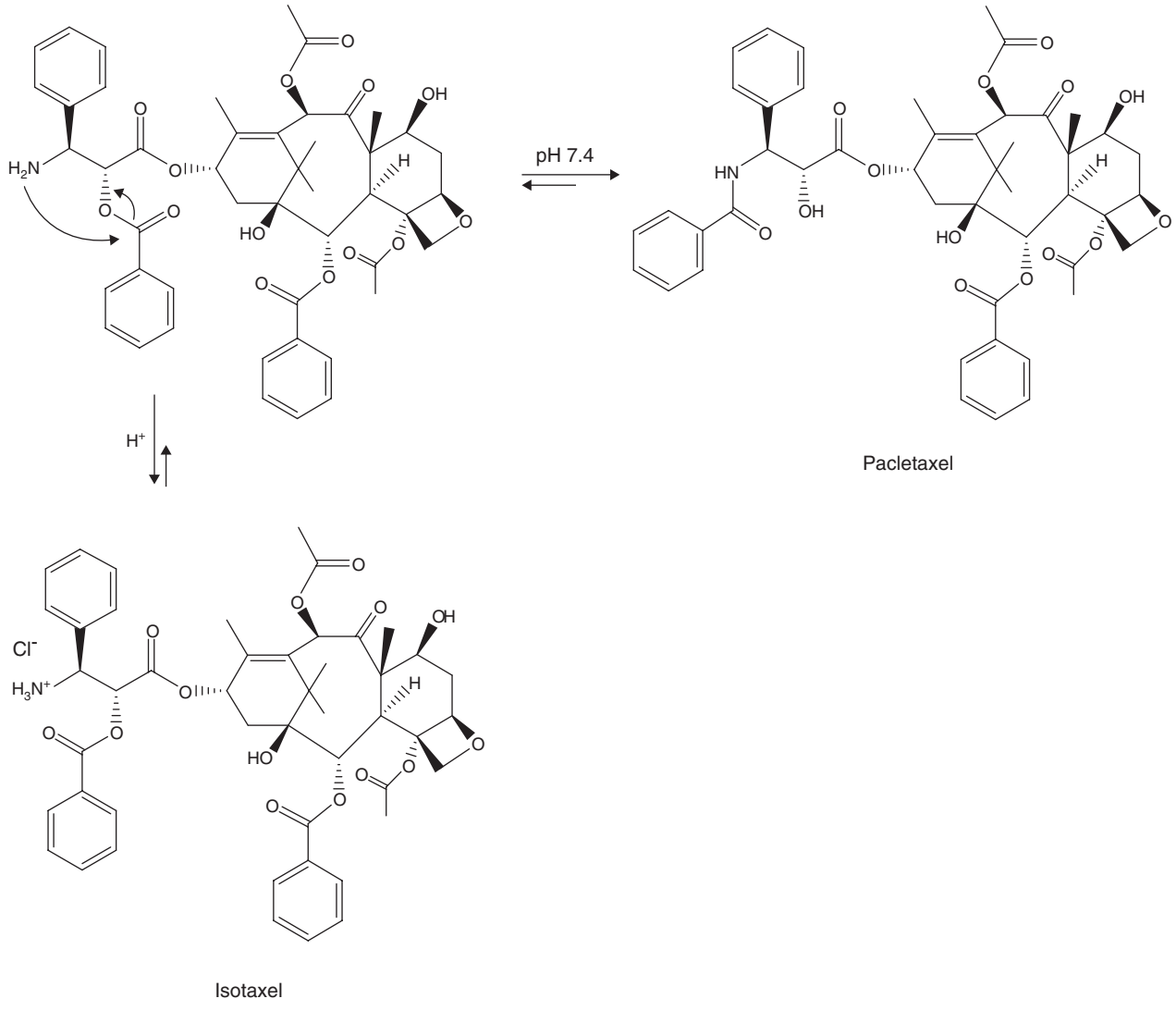

Figure 11. O→N acyl prodrug of paclitaxel.

solvent is used in the manufacturing of the product (i.e., lipid systems), strict requirements on solvent removal from the product, emission control, and recovery will also add to the final product manufacturing cost. Therefore, the manufacturing process complexity should be a key factor for comparison when evaluating different delivery systems.

Delivery systems involving a new carrier that has not been used in a FDA-approved product will meet with high regulatory scrutiny. This will normally require further preclinical safety studies and possibly more extensive clinical trials; both will lead to higher development cost and longer timeline. For these exact reasons, drug product developers are reluctant to choose such a new delivery system if other systems with a record of regulatory approval are still available. Apart from the concerns about the unproven safety profile of a carrier, the introduction of potential contaminants during product manufacturing also needs to be addressed. For example, when a fragmentation technology is applied for the generation of a nanosuspension, the solid proof of the absence of contaminations from the product contact parts of the processing equipment due to abrasion is a key quality assurance issue.

Declaration of interest

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