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Lipid nanoparticles for the delivery of poorly water-soluble drugs

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Abstract

Objectives This review discusses important aspects of lipid nanoparticles such as colloidal lipid emulsions and, in particular, solid lipid nanoparticles as carrier systems for poorly water-soluble drugs, with a main focus on the parenteral and peroral use of these carriers.

Key findings A short historical background of the development of colloidal lipid emulsions and solid lipid nanoparticles is provided and their similarities and differences are highlighted. With regard to drug incorporation, parameters such as the chemical nature of the particle matrix and the physicochemical nature of the drug, effects of drug partition and the role of the particle interface are discussed. Since, because of the crystalline nature of their lipid core, solid lipid nanoparticles display some additional important features compared to emulsions, their specificities are introduced in more detail. This mainly includes their solid state behaviour (crystallinity, polymorphism and thermal behaviour) and the consequences of their usually non-spherical particle shape. Since lipid nanoemulsions and -suspensions are also considered as potential means to alter the pharmacokinetics of incorporated drug substances, some underlying basic considerations, in particular concerning the drug-release behaviour of such lipid nanodispersions on dilution, are addressed as well.

Conclusions Colloidal lipid emulsions and solid lipid nanoparticles are interesting options for the delivery of poorly water-soluble drug substances. Their specific physicochemical properties need, however, to be carefully considered to provide a rational basis for their development into effective carrier systems for a given delivery task.

Keywords lipid drug carrier systems; parenteral fat emulsions; poorly soluble drugs; solid lipid nanoparticles; solubilisation

Introduction

A large fraction of established and, in particular, newly developed drug substances are poorly water soluble. This leads to pharmaceutically important consequences such as poor peroral bioavailability or difficulties with developing parenteral, especially intravenous, formulations. There is thus an urgent need for adequate options to deliver such drugs to the patient. One interesting possibility is the use of colloidal lipid dispersions as drug carrier systems. Compared to many other materials used as drug carriers, in particular to polymers, lipids are regarded as a more physiological option and a high biocompatibility is expected. Naturally, lipophilic drugs in particular should benefit from an incorporation into the lipophilic matrix of lipid carriers. A broad variety of different colloidal lipid dispersions may be used as drug carrier systems and some of them have already been successfully marketed. Important examples are liposomes (Ambisome, Caelyx), colloidal lipid emulsions (Diprivan, Stesolid), self (micro)emulsifying systems (Sandimmun), micellar dispersions (Konakion MM) and solid or liquid crystalline lipid nanoparticles.

This review will focus on lipid emulsions and, in particular, solid lipid nanoparticles. Such particles consist of a continuous core of either a liquid (emulsions) or a solid lipid (solid lipid nanoparticles) which is surrounded by an emulsifier shell stabilising the particles against coagulation and coalescence. The nanoparticle dispersions are usually polydisperse with a mean particle size between about 50 and 500 nm. Depending on their composition and particle size, these lipid dispersions can be used for different routes of administration. As the systemic route is the most challenging for the administration of poorly water-soluble substances the main focus in this article will be on dispersions for parenteral and peroral use.

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Colloidal fat emulsions

Colloidal fat emulsions used to supply caloric energy and essential nutrients to intensive care patients by intravenous infusion can be regarded as the prototype of lipid nanoparticles as drug carrier systems. Such emulsions were introduced to the market in Europe in the early 1960s and have developed into an indispensable component of parenteral nutrition (marketed as products such as Intralipid, Lipofundin, Lipovenös etc.).[1–4] They contain highly purified qualities of triglyceride oils (e.g. soybean oil, medium chain triglycerides) and egg phospholipids as stabilisers. The resulting particles bear some resemblance to chylomicrons, the physiological carriers of triglycerides and other lipid components in the bloodstream.[5,6] Since colloidal fat emulsions for parenteral nutrition are administered by intravenous infusion with the potential risk of embolism by large particles, particular attention needs to be given to their particle size distribution.[3] The mean particle size is usually around 200–500 nm, and there are strict limitations concerning the presence of microparticulate contaminants. High pressure homogenisation is the standard technique to obtain emulsions that meet these specifications.

The oil droplets of lipid emulsions represent comparatively non-polar compartments within an aqueous environment and may thus be used to solubilise poorly water-soluble drugs. The drug carrier potential of colloidal lipid emulsion droplets has been investigated almost since the market introduction of parenteral feeding emulsions.[4,6] Several commercial preparations, for example containing diazepam, propofol or etomidate, have since become available, most of them intended for parenteral, usually intravenous, administration (see Table 1 for examples). A major advantage of nanoparticulate lipid carriers such as emulsion droplets is that their solubilisation capacity is retained on administration. In contrast, formulations based on more conventional solubilisation approaches, such as the use of cosolvents or surfactant micelles, partially lose their solubilisation potential on dilution with aqueous media. For example, paclitaxel may precipitate out of the dilutions of Taxol that are prepared prior to administration.[7]

Different aspects have to be considered when developing lipid emulsions (and lipid nanoparticles in general) for the delivery of poorly water-soluble drugs. Of great importance is the fact that poorly water-soluble drugs do not necessarily display a high solubility in lipids. Lipid nanoparticles are thus not a universal delivery approach for all poorly water-soluble drugs. They are mainly useful for substances which have a poor water solubility due to their inability to interact with water molecules. Drugs which display very strong intermolecular binding forces resulting in a high crystal lattice energy are often neither very soluble in water nor in oil. Drug substances of the latter type usually have a high melting point whereas drugs successfully formulated in emulsions are often characterised by a rather low melting temperature (Table 1). The incorporability of drugs into lipid particles can often be improved by the formation of lipophilic prodrugs like fatty acid esters, a technique which is usually accompanied by a considerable decrease of the melting point (e.g. from 262°C for dexamethasone to less than 100°C for dexamethasone palmitate).

Very non-polar oils such as long chain triglycerides have a lower solubilisation capacity for many drug substances than oils of more polar nature, for example castor oil or medium chain triglycerides.[8,9] Mixtures with comparatively polar lipid components, like medium chain triglycerides or diacetylated monoglycerides, are thus used in some commercial emulsion formulations (Table 1). The use of nonglyceride oils may also be considered in order to overcome solubility limits as, for example, described for vitamin E derivatives (tocols) for the preparation of paclitaxel-containing emulsions.[10]

When determining the solubilisation capacity of an emulsion formulation, not only the solubility in the oil but also partitioning of the drug between the oil and the aqueous phase has to be taken into consideration. If partitioning into the water phase leads to a drug concentration exceeding the aqueous solubility of the drug, the drug will precipitate, although the concentration in the oil phase may be well below the solubility limit. To avoid this complication, the partition coefficient of the drug should be sufficiently high.

On the positive side, the presence of a large interfacial area between oil and water in colloidal emulsions may provide a further site of localisation for the drug. In this way, solubilisation of amphiphilic drugs that are neither very soluble in water nor in oil (e.g. amphothericin B) may be enhanced.[11] Since many drugs are surface active to some extent it can be assumed that the interface of the oil droplets is a potential site of localisation for drugs (at least for a fraction of them) that are well soluble in the oil phase. Migration of the drug into the emulsifier layer can

Table 1 Examples of commercial drug loaded colloidal emulsions for parenteral administration[89]

Drug	Melting point (°C)[a]	Concentration (mg/ml)	Product examples	Oil phase
Diazepam	125–126	5	Stesolid	Soybean oil + acetylated triglycerides
			Diazepam-Lipuro	Soybean oil + MCT
Propofol	18	10, 20	Disoprivan	Soybean oil
			Propofol-Lipuro	Soybean oil + MCT
Etomidate	67	2	Etomidat-Lipuro	Soybean oil + MCT
Dexamethasone palmitate	60–65	4	Lipotalon	Soybean oil
Lipophilic vitamins			Vitalipid Infant/Adult	Soybean oil

MCT, medium chain triglycerides. Melting points were obtained from DrugBank[20] or from SciFinder Scholar[90] (for dexamethasone palmitate).

compromise the stability of the emulsions. For example, weak acids or bases can dissociate in contact with water and the resulting charge at the interfacial layer may interact with the stabilisation regime of the emulsion. This is a concern in particular for electrostatically stabilised emulsions.[12]

In addition to their solubilisation capacity for lipophilic drugs, emulsions can have other potential advantages in drug formulation. Localisation within the lipid droplets may decrease local side effects of irritating drugs and can also increase stability against chemical degradation, in particular by hydrolysis. Association with a nanoparticulate carrier may also modify the pharmacokinetics of a drug, since the biodistribution of colloidal particles differs from that of a molecule in aqueous solution.[4,6] Particle-bound drugs cannot, for example, be eliminated by renal filtration and cannot cross endothelia by simple passive diffusion. On the other hand, the drug-carrying particles may be taken up by phagocytic cells. The modification of the pharmacokinetics of nanoparticulate drug carriers such as liposomes and polymer nanoparticles, in particular by surface modification, is well established and may also be used for lipid emulsions.[6,13–15] In this way, a longer circulation time or accumulation in certain organs or tissues (drug targeting) may become possible.

The advantages of a modified biodistribution can, however, only be therapeutically exploited when the drug remains associated with the nanoparticles for a sufficient period of time. Many drugs rapidly dissociate from emulsion droplets after dilution or administration.[16–19] This is not a problem when drug solubilisation is the only aim and may even be a prerequisite for the formulation of drugs which require a rapid onset of action (e.g. on general anaesthesia with propofol or etomidate). The extent and rate of drug release from lipid emulsions under sink conditions appears to be closely related to the partition coefficient of the drug. Accordingly, it has been proposed that only drugs with a very high partition coefficient (e.g. >9) may be suitable for drug targeting with lipid emulsions.[17] Such high values are, however, quite uncommon for drug substances, even for those with low water solubility (e.g. logP ~3 for ciclosporin and paclitaxel).[20] Also in this regard, the use of lipophilic prodrugs may be helpful but is again not a universal approach. Moreover, the increase in logP by lipophilic modification is not necessarily very high (e.g. the logP value of paclitaxel is increased only from ~3 to 3.9 by transforming the drug to paclitaxel oleate).[19] As drug targeting with emulsions will thus be possible only in special cases, lipid nanoparticles with a solid core have been developed with the aim of overcoming this limitation.

Solid lipid nanoparticles

Development and preparation

A major idea behind the development of solid lipid nanoparticles was the hypothesis that a solid lipid nanoparticulate carrier would offer the potential for sustained or controlled drug release by immobilisation of the drug within a solid matrix. The physical and chemical stability of such particles might also be increased due to the presence of a solid particle core. Such a carrier system would thus combine the advantages of fluid-like lipid-based colloidal particles (good biocompatibility of ingredients and ease of production) with those of polymeric nanoparticles (solid matrix).[21]

After preliminary efforts from the group of Speiser,[22] the successful development of solid lipid nanoparticle dispersions started at the beginning of the 1990s. Gasco *et al*. described a microemulsion-based approach for the preparation of nanoparticles consisting of solid fatty acids.[23] Two German groups developed a preparation process based on high-pressure homogenisation allowing the preparation of nanoparticles with a composition more closely related to that of colloidal fat emulsions.[24,25] To allow processing of solid lipids, both types of preparation procedure are carried out at elevated temperatures (usually above the melting point of the matrix lipid of the nanoparticles) with a subsequent cooling step to solidify the lipid. These two preparation principles are, with variations, still the most often employed for the preparation of solid lipid nanoparticle dispersions. Alternative ways of preparation have also been developed, for example homogenisation of solid lipids and various solvent diffusion or evaporation processes.[25–30] With regard to large-scale production, high-pressure homogenisation of the lipid melt in a hot surfactant-containing aqueous phase with subsequent cooling and recrystallisation of the resulting nanoparticles is probably the most convenient manufacturing procedure. This process can easily be performed on a large scale with established methods, avoids the use of organic solvents and can be conducted with a comparatively low quantity of surface-active stabilisers. After preparation of the liquid nanosuspensions different approaches, such as freeze or spray drying, can be used to transform them into solid dosage forms.[31–35]

Solid lipid nanoparticles can be based on a broad range of solid lipids with quite different degrees of polarity, ranging from the rather non-polar triglycerides and waxes through glyceride mixtures to fatty acids and emulsifying wax. Their preparation requires the use of surfactants as stabilisers, which include natural substances such as phospholipids and bile salts but also many other kinds of surface active agents, for example non-ionic surfactants such as poloxamers, polysorbates, etc. The composition of the dispersions has to be adapted to the intended way of administration (e.g. only a very limited number of excipients can be used in parenteral formulations) but also depends on the preparation method.[36]

Physicochemical characteristics

Lipid emulsion particles always represent spherical liquid droplets bearing an emulsifier shell. Apart from differences in chemical composition (which may, for example, lead to different solubilisation capacities for drugs) they are thus mainly characterised by their particle size distribution and their surface properties, which are important for stability against coalescence (Ostwald ripening is usually not significant in colloidal fat emulsions). The distribution of single components within the emulsion system, in particular that of the emulsifier between the droplet interface and the aqueous phase, may also be important.[5,37,38]

For solid lipid nanoparticles, the situation is much more complex since the solid state of the particle core causes several additional phenomena. The lipids used for the preparation of solid lipid nanoparticles are crystalline

substances, which means that the particles will also crystallise on solidification. Thus, they will show all the features of crystalline materials. This includes a solid–liquid transition at a certain temperature and the occurrence of various crystalline modifications if polymorphic raw materials are used which is often the case for lipids (e.g. triglycerides).[39,40] The experimental techniques most often used to study these phenomena are differential scanning calorimetry and X-ray diffraction.[41] Polymorphic substances usually form metastable modifications on crystallisation and a time- and temperature-dependent transition into more stable forms (e.g. on storage of the nanoparticle dispersions) has to be taken into consideration.[42–45] The course of polymorphic transitions depends on the type of matrix lipid and can be modified by other components of the dispersions such as emulsifiers or incorporated drugs.[45–50] Polymorphic transitions may involve profound alterations of lipid packing and thus of the internal structure of the nanoparticles, which might have negative consequences for drug loading.[47,51] Problems with the stability of the dispersions have also been related to alterations caused by polymorphism and increase in crystallinity.[43] Moreover, the particles may change their shape during polymorphic transitions.[48,52]

As a further complication, the material properties of the core lipids can be drastically modified by the small size of the dispersed particles. It is a common observation that lipid nanoparticles prepared by high-pressure melt-homogenisation display a lower crystallisation tendency (i.e. higher supercooling) than the bulk material and thus may not readily recrystallise after preparation.[42,46,47,53] This phenomenon depends greatly on the core material used. It is particularly pronounced in nanoparticles made from short-chain monoacid triglycerides. For example, core materials like trimyristin or trilaurin may form long-term stable emulsions of supercooled melts if not adequately cooled to induce crystallisation after melt-homogenisation. Polymorphic transitions after crystallisation usually proceed faster in nanoparticles than in the bulk material.[42,47] Both the crystallisation behaviour and the kinetics of polymorphic transitions can be modified by the type of emulsifier used for the stabilisation of the nanoparticles.[45,48,54] For comparatively small glyceride nanoparticles, a pronounced dependence of the melting behaviour on particle size can be observed. The melting point of smaller particles is shifted to lower temperatures and dispersions containing smaller particles display a broader melting transition, sometimes containing several sharp transition events.[55,56]

Solid lipid nanoparticles are often referred to as spherical particles. Although a spherical shape has unambiguously been demonstrated in some cases,[44,48,52] a globular form is quite uncommon for crystalline materials, which should rather be expected to preferably exist in edged geometries. Unfortunately, the topic of particle shape is elusive for solid lipid nanoparticles due to the specificities of common characterisation techniques. The most common method for shape determination is transmission electron microscopy (TEM), which usually leads to a two-dimensional projection of the three-dimensional shape of the nanoparticles. It is thus difficult to distinguish between spherical (globular) particles and round-shaped platelets, particularly as sample preparation techniques such as negative staining may lead to orientation effects that favour display of the largest surfaces in the electron microscopic images.[57] Very careful investigation, preferably using different sample preparation techniques (e.g. cryoelectron and freeze-fracture TEM in addition to TEM of negatively stained samples), is thus necessary to get a true impression of the particle shape. The use of other imaging techniques (such as atomic force microscopy)[58] or completely different methods like viscometry[59] may also be very helpful in this regard. Solid (tri)glycerides in the stable β-modification seem to always form platelet-like particles.[27,60–64] The particle shape does, however, depend on the core material (triglycerides with shorter chains apparently leading to less anisometric particles[59] while long chain glycerides can form very extended platelets[63]) and is also influenced by the emulsifier (e.g. particles stabilised with polyvinyl alcohol are less anisometric than those stabilised with a combination of phospholipids and bile salts).[44,52]

The particle shape may influence several pharmaceutically important features of the nanoparticles. Due to their larger specific surface area, more anisometric particles will require a higher amount of emulsifier for stabilisation but they could also provide more space to accommodate pharmaceutically active substances with surface localisation. If substances are incorporated within the solid core of the particles, diffusion pathways to the particle surface (or the required time for degradation) will be shorter in thin platelets and thus drug release would be expected to be more rapid. The rheology of the dispersion will be highly affected by the particle shape. It has, for example, been observed that an increase in viscosity and gel formation, particularly in highly concentrated dispersions, is associated with a (more) anisometric shape of the particles.[59,65] Anisometric particles may also self-assemble in stacks without gel formation, as observed for triglyceride nanodispersions.[61,66] Last but not least, the interaction with the physiological environment may differ between particles of different shape. For example, the adsorption to mucosa or endothelium might be different and there are indications that the cell compatibility of solid, platelet-shaped particles is different from that of liquid, spherical emulsion droplets.[67]

The development and quality control of solid lipid nanoparticle dispersions thus require the investigation of more parameters than emulsions. Apart from the common techniques, such as particle size characterisation, the particle shape and, in particular, the solid state properties (in particular the crystalline status and melting behaviour) need to be carefully monitored.

Drug incorporation

A broad range of drugs, mainly with lipophilic properties, has already been incorporated into dispersions of solid lipid nanoparticles, including, for example, cytostatics, immunosuppressants, corticoids and lipophilic vitamins (for examples, see Table 2). Incorporated substances interact in specific ways with the physicochemical behaviour of the nanoparticles. Considering the usually crystalline nature of the matrix lipids in the solid particles, it has to be assumed that there is very limited space for the incorporation of foreign substances inside the particle core. The drug-loading

Table 2 Examples of poorly water-soluble drugs loaded into solid lipid nanoparticles dispersions (not exhaustive)

Class	Examples
Anticancer drugs	Camptothecin[75]
	Docetaxel[88]
	Etoposide[91]
	Idarubicin[92,93]
	Paclitaxel[81,86,87,94–96]
	Tamoxifen[97]
Immunosuppressants	Ciclosporin[50,76,98]
Glucocorticoids	Betamethasone valerate[73]
	Clobetasol propionate[29]
	Prednicarbate[73]
	Prednisolone[28]
Lipophilic vitamins and related substances	Menadione[46,47]
	Retinoids[35,47,51,68,74]
	Ubidecarenone[42,47,49,53]
Miscellaneous	Bromocriptine[64]
	Cloricromene[83]
	Clozapine[77]
	Diazepam[33,44,47,99]
	Estradiol[100]
	Etomidate[28,32]
	Indometacin[101]
	Nifedipine[102]
	Tetracaine[28,32]
	Triptolide[103]
	Vinpocetine[78]

capacity of lipid nanosuspensions (the amount of incorporated drug related to the content of matrix lipid or to the content of dispersed material) is indeed quite low (<5–10%) in most cases. It can be determined by incorporating increasing concentrations of drug during suspension preparation until the drug phase separates from the particles or other instability phenomena of the dispersion are observed.[28,68] This procedure requires that the drug-loaded lipid nanodispersions are carefully examined for drug precipitation after preparation. Unfortunately, precipitated drug is not always easy to detect and drug precipitation may occur in a highly retarded manner,[47] which can lead to an overestimation of the drug loading capacity. Alternative methods are thus currently under evaluation for their suitability to determine the true loading capacity of lipid nanodispersions.[69] For some drugs (e.g. ubidecarenone or ciclosporin), distinctly higher drug loads than commonly observed have been reported. In the case of ubidecarenone this is due to a specific interaction with the nanoparticles that involves the formation of a separate liquid compartment attached to the single nanoparticles at higher drug loads.[47,49] Ciclosporin also seems to interact strongly with the core lipid of the nanoparticles.[50] Alterations of the physicochemical behaviour, for example in terms of melting, crystallisation and polymorphic transition of the nanoparticles as a result of drug loading, have frequently been reported, in particular when higher amounts of drug could be loaded to the nanoparticles. For example, a decrease in melting and crystallisation temperature and increased rate of transformation into the stable β-modification is observed when ubidecarenone is loaded into triglyceride nanoparticles.[49] Incorporation of high amounts of ciclosporin also leads to a decrease in melting temperature but retards the transition into more stable modifications.[50]

In spite of its presumably high relevance for the pharmaceutical performance of solid lipid nanoparticle dispersions (e.g. with regard to drug stability and drug release) there is still only limited knowledge of the interaction of incorporated drugs with the carrier nanoparticles, particularly concerning their localisation within the single particles. This subject is difficult to address experimentally and corresponding results are thus scarce. Moreover, the interactions may be quite specific for a given drug/carrier combination. As incorporation of drug molecules into the tightly packed crystalline cores of the nanoparticles seems to be unfavourable, at least in most cases, it has to be assumed that at least a large fraction of drug is frequently localised at the surface of the particles instead of being incorporated within the particle core. There is increasing experimental evidence for this scenario[28,35,49,70–74] but exceptions may exist and this subject will require much more detailed investigation in the future.

Drug release

Solid lipid nanoparticles were originally developed with the aim of achieving controlled release of poorly water-soluble substances from colloidal lipid carriers and some of their intended applications, in particular drug targeting after intravenous administration, essentially rely on this property. Hitherto, there has been, however, not much experimental evidence that the solid lipid particle matrix does provide a universal platform to control drug release. Particularly if drugs are localised on the particle surface, controlled drug release should be difficult to achieve; at least, release cannot be expected to be slower than from corresponding emulsion formulations. In spite of this, slow release from such formulations is often claimed and deduced from release experiments.[74–78] A slow appearance of drug in the release medium can, however, be an artificial result of an inadequate experimental setup rather than a true property of the suspensions. Unfortunately, the release properties of colloidal lipid dispersions are more difficult to assess than those from, for example, solid oral dosage forms. The colloidal particles will usually not disappear from the release medium (e.g. due to dissolution or degradation) during the process of a release study. Their presence does, however, disturb most analytical processes and their separation from the release medium is usually required unless special analytical techniques, such as electrochemical methods, are used. Separation of small particles, for example by centrifugation or filtration, is not necessarily straightforward and may be time consuming. A high time resolution of the experiment is, however, required since the release from colloidal lipid particles can be extremely rapid.[16,18,79,80] As a further difference to normal release/dissolution studies, the remaining particles will always represent a potential localisation site for the drug and release of lipophilic substances will thus often remain incomplete.

In the context of drug-release studies on solid lipid nanoparticles, the intended use of the formulation needs to be

considered. It is particularly important to distinguish between modes of administration which do and do not lead to the dilution of the nanoparticle dispersion on administration. The former will always be the case on peroral and intravenous administration. This situation has to be mimicked in drug-release experiments on corresponding dispersions. Unfortunately, release experiments on lipid nanoparticle dispersions are often carried out with dialysis techniques (e.g. using dialysis bags or a Franz cell setup),[74–78,81] even where the dispersions are intended for peroral or intravenous use. These techniques are convenient to perform but they lead to distorted (artificially sustained) release profiles as they do not provide adequate dilution of the nanoparticles.[79,82] Experiments performed under more 'sink-like' conditions, employing, for example, filtration, centrifugation or electrochemical in-situ techniques, indicate that the release from solid lipid nanoparticles can be very rapid.[28,44,83] They often suggest that the drug-release process is mostly controlled by drug partition processes rather than by the hampering of the drug diffusion through the solid lipid matrix. First investigations involving the direct comparison of the release behaviour of dispersions of solid and liquid nanoparticles with the same composition and particle size distribution indicate that the velocity and extent of release from solid lipid nanoparticles is comparable or even higher than that from the corresponding emulsion systems.[84,85] On the other hand, there are several reports that describe the modification of bioavailability or pharmacokinetics by the use of solid lipid nanoparticles.[74,75,78,81] This whole field will thus require more attention in the future, in particular with regard to in-vitro–in-vivo correlations, in order to elucidate in detail all effects involved and to provide an adequate basis for appropriate carrier selection.

Application examples: solid lipid nanoparticles loaded with cytostatic drugs

Solid lipid nanoparticles have been investigated with regard to a broad variety of administration routes, including the peroral and the parenteral ones, but also, for example, dermal, ocular and pulmonary administration. A large fraction of the research dedicated to solid lipid nanoparticle suspensions is directed towards parenteral, especially intravenous, delivery, with a particular focus on cancer therapy. Prominent examples of drugs investigated in this regard are paclitaxel, camptothecin and related substances (Table 2). Besides solubilisation (and, in the case of camptothecin, protection against chemical degredation) issues like the extension of plasma half-life and a modified biodistribution with special regard to tumour targeting are particular matters of interest. It has been shown that the incorporation into solid lipid nanoparticles leads to an increased efficiency of paclitaxel in paclitaxel-resistant tumour models compared to treatment with Taxol.[86,87] Koziara *et al*. found an increased residence of paclitaxel in perfused rat brain after washout when the drug was administered in the form of lipid nanoparticles instead of Taxol.[86] Also for docetaxel a beneficial effect of the binding to nanoparticles compared to the conventional formulation was observed in a tumour model.[88] Camptothecin bound to lipid nanoparticles was shown to have a longer circulation time in plasma and an increased uptake into many organs (including the brain) than after administration of a drug solution.[75]

Conclusions

About 20 years after their first description in the pharmaceutical literature, a wealth of knowledge has been gathered on the properties and potential areas of application of solid lipid nanoparticles. The latter mostly refer to an improved administration of poorly water-soluble drugs and indicate some potential of this rather new type of carrier. Several questions do, however, still require more scientific attention in order to provide a rational basis for the further development of solid lipid nanoparticles. On the one hand, these are related to basic structural aspects, in particular the localisation of incorporated drug molecules within the single particles and specific drug/matrix lipid interactions. On the other hand, the parameters involved in in-vivo performance and their relationship to the physicochemical characteristics of the nanoparticles need to be elucidated in more detail.

Although solid lipid nanoparticles have now reached a more mature stage of development, a realistic assessment of their position among the different available types of lipid carrier systems is still difficult, even if only the delivery of poorly water-soluble substances and a systemic way of administration is considered. From the limited reliable data available so far, they do not seem to be much different from lipid emulsions with regard to their drug-release properties. Unfortunately, there is only very little comparative in-vitro and in-vivo data that could help to more precisely determine the specific advantages of the two different types of formulation. In any case, the possibility of preparing suspensions of lipid nanoparticles extends the spectrum of matrix materials that can be used for particle preparation. Moreover, solid lipid nanoparticles should be highly interesting carrier candidates for drug substances that localise at the particle surface since their often platelet-like shape offers much space for the association with such drugs. On the other hand, they usually display an even more complex physicochemical behaviour than lipid emulsions. Such aspects need to be carefully balanced in order to choose an optimal carrier system for a given delivery task.

Declarations

Conflict of interest

The Author(s) declare(s) that she has no conflicts of interest to disclose.

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