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Lipid excipients and delivery systems for pharmaceutical development: A regulatory perspective ☆

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Abstract

The use of lipid-based dosage forms for enhancement of drug absorption or delivery has drawn considerable interest from pharmaceutical scientists. The unique characteristics of these dosage forms, however, present significant challenges to pharmaceutical industry and regulatory agencies in many ways. For example, safety assessment is necessary when the use of a new lipid excipient is considered. An important question for lipid formulation is whether the drug remains in solubilised form along the gastrointestinal (GI) tract after it is administered. Certain lipid excipients and surfactants have been reported to change intestinal permeability or interfere with enzyme/transporter activity, thereby affecting drug bioavailability. The potential influence of biopharmaceutical and/or pathophysiological factors on the drug or lipid excipient(s) needs to be explored. For a complex lipid-based dosage form, the conventional *in vitro* dissolution methods may not be appropriate for predicting *in vivo* performance in view of the convoluted GI processing of the lipid vehicle and formulation

Of paramount importance is to identify any gaps in the scientific understanding of lipid-based dosage forms so that regulatory issues can be addressed. More mechanistic studies should be encouraged to facilitate a better understanding of the pharmaceutical characteristics of lipid formulations and complex interactions between lipid excipient, drug and physiological environment. This review discusses some regulatory considerations in the use of lipid excipients and delivery systems for pharmaceutical development. Implications in the regulatory determination of pharmaceutical equivalence, bioequivalence and therapeutic equivalence are also illustrated.
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Keywords: Lipid-based dosage form; Lipid-based formulation; Modified release; Liposome; *In vitro* release; Therapeutic equivalence; Bioequivalence; Pharmaceutical equivalence; Food and Drug Administration

Contents

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1. Introduction

Lipid-based dosage forms represent a distinct class of drug products that have drawn considerable interest and attention from pharmaceutical scientists [1–23]. Most of the lipid-based drug delivery systems use lipid vesicles or excipients to solubilize lipophilic drugs that are poorly water-soluble in nature, thereby improving drug absorption in the body. In the case of water-in-oil emulsions or microemulsions, however, hydrophilic drugs are solubilized in the system and phase inversion usually takes place later *in vivo* [24]. The unique characteristics of lipid-excipients as well as lipid-based delivery systems have presented many challenges to pharmaceutical scientists in all stages of drug development. Similarly, from a regulatory perspective, apart from the multitudes of issues in chemistry, manufacturing and controls, several issues have arisen for these dosage forms in the area of biopharmaceutics as related to product quality and performance.

This paper provides regulatory considerations for science- and risk-based approaches in the use of lipid excipients and delivery systems for pharmaceutical development.

2. Regulatory status of lipid excipients

Historically, excipients were considered inert substances that would be used mainly as diluents, fillers, binders, lubricants, coatings, solvents, and dyes, in the manufacture of drug products [25]. Over the years, however, advances in pharmaceutical science and technology have facilitated the availability of a wide range of novel excipients. In some cases, known and/or unknown interactions can occur between an excipient and active ingredient, other inactive ingredient(s), biological surroundings, or even container closure system [26–40]. Accordingly, it is now recognized that not all excipients are inert substances and some may be potential toxicants [41].

In the United States, the Food and Drug Administration (FDA) has published listings in the Code of Federal Regulations (CFR) for GRAS substances that are generally recognized as safe [42]. Over the years, the Agency also maintains a list entitled *Inactive Ingredient Guide* (IIG) for excipients that have been approved and incorporated in the marketed products [43,44]. This guide is helpful in that it provides the database of allowed excipients with the maximum dosage level by route of administration or dosage form for each excipient. Both GRAS listings and IIG information can be used by industry as an aid in developing drug products. For new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and may require a less extensive review the next time it is included in a new drug product. For example, if a particular inactive ingredient has been approved in a certain dosage form with certain potency, a sponsor could consider it safe for use in a similar manner for a similar type of product.

In general, nonclinical and clinical studies are required to demonstrate the safety of a new excipient before use. In this context, the U.S. FDA has recently published a guidance document for industry on the conduct of nonclinical studies for the safety evaluation of new pharmaceutical excipients [41]. This guidance not only provides the types of toxicity data to be used in determining whether a potential new excipient is safe, but also describes the safety evaluations for excipients proposed for use in over-the-counter and generic drug products. The document also depicts testing strategies for pharmaceuticals proposed for short-term, intermediate, and long-term use. More importantly, this guidance highlights the importance of performing risk-benefit assessments on proposed new excipients in the drug products while establishing permissible and safe limits for the excipients. As illustrated, with proper planning, it is often possible to assess the toxicology of an excipient in a relatively efficient manner [41]. Existing human data for some excipients can substitute for certain nonclinical safety data. In addition, an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation with a full battery of toxicology studies [41].

There is no process or mechanism currently in place within the FDA to independently evaluate the safety of an excipient. Instead, for a drug or biological product subject to premarketing approval, their excipients are reviewed and approved as ‘components’ of the drug or biological product in the application. From a scientific standpoint, the regulatory process is appropriate since excipients play an integral part to the formulation and cannot be reviewed separately from the drug product. This is particularly true for lipid excipients in view of their distinct physicochemical properties and potential complex interactions with other ingredients or physiological environment that may occur *in vivo*.

3. Drug solubilization *in vivo*

As indicated, lipid-based formulations are mostly prepared for enhancing solubility and absorption of poorly water-soluble drugs. These formulations typically contain long- or medium-chain triglyceride lipids, long- or medium-chain mixed mono-

and di-glycerides, individual or mixed surfactants, and various hydrophilic surfactants [23]. Several approaches are available to incorporate active drug into lipid vehicles resulting in a variety of dosage forms, such as oils, surfactant dispersions, emulsions, self-emulsifying drug delivery systems (SEDDS), self-micro-emulsifying drug delivery systems (SMEDDS), self-nanoemulsifying drug delivery systems (SNE), solid lipid nanoparticles (SLN), and liposomes [3,12,13]. Hence, lipid-based dosage forms encompass a wide range of compositions and exhibit a broad character and functionality.

The use of lipid excipients for formulations is inevitably complicated, and thus has presented challenges to both pharmaceutical and regulatory scientists. Lipid excipients are able to solubilize hydrophobic drugs within the dosage form matrix. However, as with dietary lipids, these excipients can also be digested and dispersed in the GI tract. Therefore, one of the questions for a lipid-based oral formulation is whether the drug remains in solubilised form in the presence of changing phases of the formulation after it is administered [3,15,16,45–48]. This is a difficult question, which can be illustrated by a simplified phase diagram for an oily formulation dispersed in water and a surfactant. As shown in Fig. 1, various possible lipid assemblies can arise from the interplay of the three major components (i.e., oil, water and surfactant) present in the system [12]. These assemblies may include emulsion, micelle, water-in-oil microemulsion, oil-in-water microemulsion, and bicontinuous microemulsion. The phase of the lipid-formulation may be changing as it reaches the GI tract and is subject to the digestion, dispersion and transport process in the body. Accordingly, the solubilization status of the drug will vary as a function of time and the simultaneous lipid-digestion process *in vivo* [12].

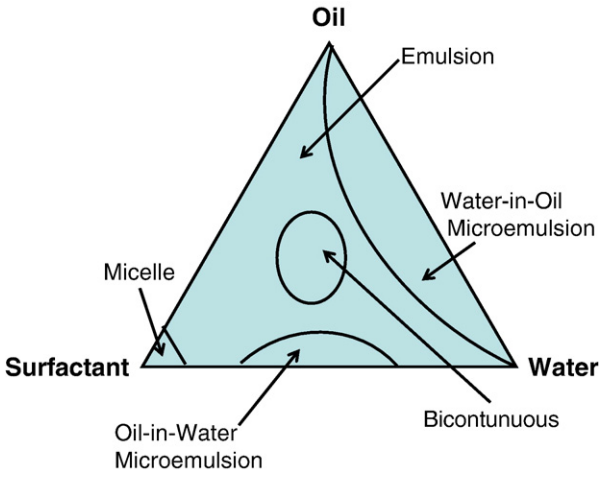

Fig. 1. A simplified phase diagram for an oily formulation dispersed in water and a surfactant [adapted from [12]].

4. Unique disposition of lipid delivery systems

4.1. Lipoprotein binding and transport

Lipid-based formulations can be transported by serum lipoproteins that play an important role in the intrinsic lipid pathway through the vascular and extravascular body fluids to the cells [49,50]. The content and composition of circulating lipoproteins can vary with age and gender [51]. Lipoprotein levels can also be influenced by disease states, diet or fat content, and co-administered compounds [49].

Literature information has suggested that the variability in response to several drugs may be due in part to the varying serum lipid levels within patient [49]. The binding of lipoproteins may also influence the efficacy or safety profile of a drug, especially when the drug is given to patients with abnormal lipid metabolism secondary to the disease state [49,50]. For example, it was observed that transplant patients receiving cyclosporine tended to develop dyslipidemia and the efficacy or toxicity of this drug would change depending on the triglyceride or cholesterol levels in the patients [52–54]. Another example is amphotericin B. This drug binds to serum lipoproteins, particularly low-density lipoprotein (LDL), a key carrier of cholesterol in the body [49,55]. The administration of amphotericin B formulation was found to cause an increased renal toxicity in the patients with high cholesterol levels. Yet, when complexed with lipid, the drug had a decreased binding to LDL and in turn, significantly reduced renal toxicity in these patients [49].

4.2. Lymphatic transport

The lymphatic system in the body comprises a network of lymphatic vessels and lymph nodes, which allow absorption of interstitial fluid containing macromolecules (proteins) and particulate cellular matter [56]. The route of entry to the lymphatic system has been utilized for targeting therapeutic agents to regional lymph nodes after local parenteral administration [56]. This can be exemplified by the use of colloidal systems such as liposomes for subcutaneous injection [57]. Some highly lipophilic drugs administered orally have also been shown to gain access to the systemic circulation via intestinal lymphatic transport, avoiding the hepatic first-pass metabolism and resulting in a higher drug bioavailability [58–60]. However, the role of intestinal lymphatic system in the processing of lipids and drugs from lipid-based oral dosage forms remains an area for further investigation.

4.3. Interplay of lipid excipients/surfactants with enzymes and transporters

Many hydrophobic drugs are primarily metabolized by cytochrome P450 (CYP) 3A isozymes [61], the major enzymes responsible for phase I metabolism [62–64]. Several of these drugs were also found to be the substrates and/or inhibitors of P-glycoprotein (P-gp) [61], an efflux transporter expressed along the GI tract and also in the liver, kidney, blood brain barrier and placenta [65,66]. Examples of such compounds are provided in Table 1. The involvement of P-gp transport further complicates the absorption of a hydrophobic drug that is formulated in the lipid delivery system. Moreover, several lipid-excipients and surfactants present in pharmaceutical formulations have also been reported to inhibit the CYP 3A metabolism or P-gp

Table 1
Selected examples of hydrophobic drugs that are primarily metabolized by CYP 3A, substrates or inhibitors of P-gp transport [61]

CYP 3A substrate	P-gp substrate	P-gp inhibitor
Amiodarone	−	+
Atorvastatin	+	+
Azithromycin	+	+
Carbamezapine	+	+
Cyclosporine	+	+
Indinavir	+	−
Itraconazole	+	+
Ketoconazole	−	+
Lanzoprazole	−	+
Lovastatin	+	+
Ritonavir	+	+
Saquinavir	+	+
Sirolimus	+	−
Tacrolimus	+	+
Tamoxifen	−	+

transport (Table 2). The interplay between certain excipients and enzymes/transporters has raised much concern about the predictability of drug absorption and bioavailability, as well as the possible drug–drug interactions when co-administered with other compounds. More studies are needed to elucidate these potential interactions during pharmaceutical development.

5. *In vitro* release testing for orally administered lipid formulations

In the context of oral solid dosage forms, it has generally been recognized that there are multiple roles for *in vitro* dissolution testing [74–80]. For example, it is employed to guide the drug development and selection of appropriate formulations for further *in vivo* studies. It is also used as a preliminary test for detection of possible bio*in*equivalence between products before and after changes in manufacturing and/or formulation. As a quality control tool, *in vitro* dissolution can be used to set specifications for batch release and ensure batch-to-batch consistency. With appropriate methods, *in vitro* dissolution can be further correlated with *in vivo* performance and employed as a surrogate for bioequivalence studies.

Despite all the advantages for solid oral dosage forms, a question has been raised regarding the usefulness of *in vitro* dissolution testing for lipid-based formulations [21–23]. The main issue seems to stem from the concern that the absorption mechanism for lipid-based oral formulations is so complicated that it may not be feasible to create a single *in vitro* dissolution environment that mimics the physiological conditions [21–23]. For liquid-filled capsules, some drug sponsors have argued that since the drug is already in solution, *in vitro* dissolution testing may not be necessary and a rupture test for capsules may be sufficient to assure drug release from the dosage form [81]. However, this argument may not be held in view of the complexity of a lipid formulation and convoluted dispersion/digestion/transport process that takes place *in vivo* after drug administration. As for microemulsions, one might contend that droplet size of the dispersed formulation could be more relevant and predictive of *in vivo* performance [82]. Indeed, based on the conventional methods, the role of *in vitro* dissolution for lipid-based dosage forms may be limited. The conventional dissolution method may be suitable for the establishment of a dispersion test for these products, but the focus should be on precipitation rather than dissolution [6].

For simple lipid formulations, the use of modified dissolution media, reflecting the physiological environment in the gut, may serve the purpose of predicting bioavailability of poorly water-soluble drugs in these formulations and assessing the effect of food on drug absorption [83–91]. Additionally, the USP two-tier dissolution testing can be employed for gelatine capsules in the event of gelatine cross-linking [92]. The conventional *in vitro* dissolution methods, however, may not be appropriate for predicting *in vivo* performance of a complex lipid-based formulation since dissolution of the drug and GI processing of the lipid vehicle (including digestion and dispersion) are intrinsically linked to each other. Ideally, the *in vitro* release testing should incorporate the dynamics of lipid digestion, formation of various intermediate colloidal products, and solubilization of the drug under study [15,16,22,23]. To date, considerable investigations have been undertaken in an attempt to develop proper *in vitro* models that mimic the dispersion and digestion phenomena observed *in vivo* for lipid-based oral formulations [22,93,94]. Undoubtedly, there is need for further research in developing more predictive *in vitro* methods for these formulations. From a regulatory perspective, it would be valuable to establish a standard protocol for developing such *in vitro* methods based on the distinct characteristics of various lipid-based formulations. In this regard, the use of a 'lipid classification system' may be a good starting point [6].

6. Lipid-based modified-release parenteral dosage forms

Lipid-based delivery systems given by parenteral route of administration are becoming increasingly utilized to deliver

Table 2
Examples of lipid excipients or surfactants that may interact with enzymes or transporters

Lipid excipients/ surfactants	Examples	Comments	References
Polyoxyethylated/pegylated			
Polyoxyl 35 caster oil	Cremophor	CYP3A and P-gp inhibitors	[2,31,32,67,68]
PEG-15-hydroxystearate	Solutol HS-15	CYP3A and P-gp inhibitors	[2,67]
Medium chain glycerol and PEG esters	Labrasol, Softigen 767, Acconon	P-gp inhibitor	[2]
Polysorbates	Tween 80, Tween 20	CYP3A and P-gp inhibitors	[2,67,68,69]
Sucrose esters	Sucrose monolaurate	P-gp inhibitor	[2]
Tocopherol esters	Vitamin E-TPGS [a]	P-gp inhibitor	[2,37,68,70]
Polymers	Pluronic block copolymers	CYP3A and P-gp inhibitors	[2,71,72,73]

[a] TPGS: D-alpha-tocopheryl polyethylene glycol 1000 succinate.

drugs and biologicals for treatment or prevention of a variety of diseases [95]. Injectable dispersed systems are often colloidal in nature and thus have been designed for sustained release and/or targeted delivery of drugs and biologicals [95]. These delivery systems improve the therapeutic response by providing more consistent and stable blood levels compared to the conventional release dosage forms. As a result of targeting and controlled characteristics, lipid-based parenteral products offer the advantages of lower dosing frequencies, greater patient compliance, and reduced adverse reactions [96].

Lipid-based modified-release parenteral dosage forms, however, are complex and have posed significant challenges in the development of standards and regulations. For example, over the past few years, the U.S. FDA has been working diligently to foster the development of regulatory approaches for ensuring the quality and performance of liposome drug products. In 2001, the agency convened an advisory committee meeting to discuss the scientific and technical issues surrounding these products [97] and subsequently published a draft guidance document for industry on the subject [98]. Several national and international workshops were also held to facilitate better understanding of chemistry, manufacturing and controls as well as the biopharmaceutic issues for sustained/controlled-release parenteral products [99–102]. For illustration purposes, this review will focus on some of the regulatory considerations relevant to lipid-based parenteral systems, using liposomes as an example.

6.1. Liposomes

Liposomes have been under extensive investigation as a drug delivery system for many years. However, pharmaceutical preparations did not become commercially available in U.S. until 1995 when the FDA approved the first liposome drug product, Doxil, a doxorubicin HCl liposome injection. Recognizing the importance of nomenclature for novel dosage forms in the regulatory setting, the U.S. FDA has defined liposomes and liposome drug products as follows [98]:

> Liposomes are microvesicles composed of one or more bilayers of amphipathic lipid molecules enclosing one or more aqueous compartment, and
>
> Liposome drug products are those drug products that contain drug substances encapsulated or intercalated in the liposomes.

It is noteworthy that based on these definitions, a drug–lipid complex will be differentiated from a true liposome drug product in that the former does not contain an internal aqueous compartment.

6.1.1. Chemistry, manufacturing and controls

Characterization is not normally expected for a conventional dosage form, but this is not the case for liposome drug products [98]. The physicochemical properties of a liposome drug product are critical to ensure product quality and performance [95,99–104]. Accordingly, the FDA guidance indicates that physicochemical characterization tests are necessary for these products to ensure batch-to-batch quality although not all of the characterization tests need to be included in the specification for batch release [98]. In addition, since the quality and purity of lipid(s) can affect the quality of the final product, the FDA requests that sponsors provide detailed information on chemistry, manufacturing and controls of the lipid component for a liposome product [98].

Stability is an important issue for all the lipid-based dosage forms, which is no exception with liposome drug products. The FDA guidance dictates that stability studies be conducted to address both physical and chemical stability of a liposome drug product, including the loaded and unloaded liposomes [98]. These products should also be evaluated for stability of the encapsulated drug substance and the lipid used to manufacture liposomes. In addition, a careful evaluation of *in vivo* integrity should be undertaken. Based on the FDA guidance, stress testing of liposome drug products and unloaded liposomes may be warranted to demonstrate possible degradation or other reaction processes unique to the liposomes [98]. The physical and chemical complexity of liposome drug products can present unique challenges to the sterilization process. In this context, product-specific validation studies are advised by the agency [98].

Liposome drug products are very sensitive to changes in the manufacturing conditions. Consequently, it is important to identify and evaluate critical manufacturing parameters during the development process [95,99–104]. As indicated, it may be necessary to assess the effect of each manufacturing change on the identity, strength, quality, purity, and potency of the liposome drug product [98]. *In vivo* studies may be warranted to demonstrate that the changed product is equivalent to the original product with respect to safety and efficacy [98].

6.1.2. Biopharmaceutics

Several drug applications for liposomes have been based on an approved drug product in the conventional dosage form given by the same route of administration. It appears that these liposomal products have been made to improve the therapeutic index of drugs by increasing their efficacy and/or reducing their toxicity [95,96,103,104]. Since both preparations contain the same active moiety, comparisons of product performance in terms of single-dose pharmacokinetics and mass balance profile are generally required [98]. Information obtained from the pharmacokinetic studies will be useful in determining the dose- (concentration-) response relationship and establishing dosage/dosing regimen for the liposome product. Accordingly, the FDA guidance further recommends a multiple-dose study and a dose-proportionality study for the liposome drug product under investigation [98]. Additional studies such as drug–drug interaction or studies in special populations may be needed to refine the dose or dosage regimen under different conditions [105–112].

To evaluate the pharmacokinetics of a liposomal formulation, it is pertinent to develop a sensitive and specific analytical method that can differentiate the encapsulated drug from unencapsulated drug. A difficult question, however, has been

whether the pharmacokinetic approach can be used for assessment of bioavailability or bioequivalence of liposome drug products. There is yet uncertainty with respect to when and where the drug is released from liposomes in most of the products that have been developed so far [95,97,99–102]. It is thus unknown if the drug concentration in the blood will reflect the drug concentration at the site of action [99–102]. Some have contended that the pharmacokinetic approach might be applied for liposome products that were primarily designed to avoid the uptake of mononuclear phagocytic system (MPS) in the body. The rationale behind this contention was based on the assumption that the liposome-encapsulated drug would circulate in the blood for a long period of time and all drug molecules would eventually become available at the site of action [99–102]. This assumption, however, may not be true as there is high possibility for some drug molecules to distribute to other tissues or organs. Furthermore, the uptake of MPS is by no means an all-or-none phenomenon and it would be difficult to demonstrate that an MPS-avoiding liposome formulation could shy away from MPS all the time after drug administration.

6.2. *In vitro* release testing

As with *in vitro* release testing for solid or lipid-based oral dosage forms, development of *in vitro* release testing is essential for assuring product quality and performance of lipid-based, modified-release parenteral formulations. From a regulatory viewpoint, an appropriate *in vitro* release test method should be capable of discriminating between 'acceptable' and 'unacceptable' batches so that it can be used for batch release and quality control. If an *in vitro–in vivo* correlation or association is available, the *in vitro* test can serve not only as a quality control tool for manufacturing process, but also as an indicator of product performance *in vivo*. The *in vitro* release method is thus best developed to simulate the physiological conditions and preferably on the basis of the mechanism of drug release from the product under study.

For products designed to release drug over a long period of time, it is better to have both long- and short-term *in vitro* release tests in place for quality control. The long-term release test (sometimes referred to as "real-time test") can be employed to monitor product release over the dosing interval. This test should be developed during the early stage of drug development. The short-term release test, "accelerated test", can be used for setting specifications for batch release. A logical approach to devising *in vitro* release testing for these modified release dosage forms is to first develop a real-time test using experimental conditions that simulate the *in vivo* environment, and then develop a short-term release test based on its relevance to the real-time test.

The ultimate goal of developing an *in vitro* release test is to link *in vitro* and *in vivo* performance such that the *in vitro* release test can be used as a tool to predict product behavior *in vivo* and further serve as a surrogate for *in vivo* studies if there are changes in formulation or manufacturing [74–80].

7. Therapeutic equivalence of lipid formulations

The U.S. FDA deems drug products *therapeutic equivalents* if they are pharmaceutical equivalents and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling [113]. In this setting, a major premise underlying the U.S. law is that evidence of *pharmaceutical equivalence* and *bioequivalence* provides the assurance of therapeutic equivalence, hence interchangeability. According to the FDA's Orange Book, pharmaceutically equivalent products should contain the same amount of active ingredient in the same dosage form, have the same route of administration, identical in strength or concentration, and meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity) [113]. However, the Orange Book also states that pharmaceutically equivalent products 'may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavours, preservatives), expiration time, and within certain limits, labeling' [113].

Traditionally, determination of pharmaceutical equivalence has been made by a qualitative and quantitative comparison of composition between formulations. While this approach may be appropriate for simple dosage forms or drug products, a question has been raised as to whether it is sufficient for complex drug delivery systems such as lipid-based formulations. Clearly, with all the unique characteristics described above for lipid-excipients/surfactants and lipid-based dosage forms, additional scrutiny of formulation and potential biopharmaceutical interactions are necessary for adequate evaluation of pharmaceutical equivalence and bioequivalence. A difference in the makeup of lipid formulations may result in a significant impact on the outcome of bioequivalence [81]. This can be illustrated by the case of cyclosporine. Indeed, the recall of a generic formulation of cyclosporine, SangCya^{R}, has been based on the evidence that the bioavailability of SangCya^{R} oral solution is low compared with the pioneer formulation, Neoral^{R} oral solution, when administered with apple juice [114]. It appears that Neoral^{R} forms a microemulsion while SangCya^{R} forms a microdispersion upon mixing with apple juice. Interestingly, however, the two formulations were found bioequivalent when mixed with chocolate milk [81].

8. The critical path for development of lipid-based delivery systems

Recently, there is growing concern that medical product development has not kept pace with the tremendous advancement in basic sciences and the expenditure of medical product development has increased dramatically over the past decade. To help address some of these concerns, the U.S. FDA launched a critical path initiative in 2004 to identify and prioritize pressing problems, and provide opportunities for acceleration of innovative medical therapies to the patients [115,116]. Similarly, the development of lipid-based products has been slow, which is probably due, in part, to the perceived problems of physical and chemical instability, as well as unpredictable

bioavailability and *in vivo* performance of these dosage forms [23]. The lack of predictability for product quality and performance may be attributed to the empirical and iterative processes traditionally employed for the design of these products. However, much has been learned about these dosage forms thus far. In concert with the FDA's critical path initiative, it is a good time to consider novel approaches for rational design of lipid-based formulations and use of better evaluation tools for assessment.

The rational design of lipid formulations will require a better understanding of formulation and manufacturing variables that may affect the quality of the products. The product and process performance characteristics will have to be scientifically designed to meet specific objectives and not merely empirically derived from performance of test batches [117]. These approaches coincide with the 'quality-by-design' principle that has been promoted by the agency [118]. Ideally, the approaches can be applied to all phases of pharmaceutical development, from the selection of drug substance, polymorphic form, and excipients, to the design, manufacturing and controls of a lipid-based product.

In parallel, the critical path for development of a lipid-based dosage form should encompass predictive *in vitro* methods that mimic the physiological environment, allowing for study of the kinetics and fate of the drug *in vivo*. To develop such *in vitro* methods, more mechanistic studies will need to be conducted to track the solubilisation state of the drug, as well as the potential interactions involved in the GI processing of lipid-based formulation. Concurrent with the FDA's critical path initiative [116], additional (bio)markers or tools may be developed to assess formulation design during pharmaceutical development, or evaluate product quality and performance after the final product is made.

9. Conclusions

The unique characteristics of lipid excipients and lipid-based delivery systems have presented several challenges during the drug development, as well as in the establishment of regulations and standards. Attention should be given to the distinctive pharmaceutical properties of lipid excipients and lipid-based dosage forms. More mechanistic studies are encouraged to track the drug solubilization status and study the complex interactions between the formulation-derived lipids, surfactant(s), incorporated drug and physiological environment. Rational design may be achieved using *in vitro* methods or other markers to better predict the dynamic changes of a lipid formulation *in vivo*. The recent FDA's critical path initiative offers an excellent opportunity for enhancing regulatory sciences and fostering development of novel dosage forms such as lipid-based delivery systems. Good product quality and product performance can be maintained with the rational design of a lipid-based dosage form.

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