Review Article

A Review on Lipid Based Oral Drug Delivery Systems

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ABSTRACT

The main problem in oral drug formulations is low and erratic bioavailability, which is mainly due to poor aqueous solubility. This can lead to high inter- and intra-individual variability, lack of dose proportionality, and failure. Improving the bioavailability of drugs with such properties presents one of the greatest challenges in formulations. Oral lipid-based formulations are interesting considerable attention due to their ability to improve solubility, facilitate gastrointestinal absorption, and reduce or eliminate the effect of food on poor water absorption. soluble lipophilic drug and therefore increases bioavailability. This review describes recent findings on Potential Advantages of these Systems, Types of Lipid-Based Drug Delivery Systems, Guidelines for Design of Lipid-Based Formulations, problems solved by LBDDS, Characterization of Lipid-Based Drug Delivery Systems, Applications of lipid-based formulations, including traditional medicine (TM), new trends in LBDDS, Regulatory Aspects has also been examined in the current revision.

Keywords: Self-micro / nanoemulsifying drug delivery system (SMEDDS / SNEDDS), solubility, bioavailability, oral absorption, surfactant, co-surfactant.

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INTRODUCTION

In these modern days, many significant efforts have been made to utilize the potential of lipid-based drug delivery systems, as it provides the appropriate means for the delivery of drugs with different molecular weights, both small and large, both at specific sites as time-controlled. and also bioactive agents [1 2 3]. Poorly water-soluble drugs are a challenge for formulation scientists concerning solubility and bioavailability. Lipid-based drug delivery systems (LBDDS) have shown effective size-dependent properties, thus attracting much attention. Similarly, LBDDS has taken the lead due to the obvious advantages of a higher degree of biocompatibility and versatility. These systems are commercially viable for formulating pharmaceuticals for topical, oral, pulmonary, or parenteral administration. Lipid formulations can be modified in various ways to meet a wide range of product requirements depending on the disease state, the route of administration, and also the stability, toxicity, and efficacy of the cost product. Lipid-based vehicles are safe and efficient, which is why they are attractive candidates for the formulation of pharmaceuticals, as well as for vaccines, diagnostics, and nutraceuticals. [4]. Therefore, lipid-based drug delivery (LBDD) systems have gained much importance in recent years due to their ability to improve the solubility and bioavailability of drugs with poor water solubility.

Potential Advantages of these Systems Include [5]

1) Improved oral bioavailability allowing dose reduction,

2) More consistent time profiles of drug absorption,

3) Selective targeting of drugs towards a specific absorption window in the GIT,

4) Protection of the drug (s) from the hostile environment in the intestine,

5) Control of delivery profiles,

6) Reduced variability, including the effects of food,

7) Protection of sensitive pharmacological substances,

8) higher payloads of drugs.

Types of Lipid-Based Drug Delivery Systems [6]

1. Emulsion:

a. Microemulsion
b. Self-emulsifying drug delivery system
c. Nanoemulsion
d. Pickering emulsion

2. Vesicular System:

a. Liposomes
b. Neosomes
c. Pharmacosomes

d. Phytosomes
e. Transfersomes
f. Ethosomes
g. Archacosomes
h. Vesosomes
i. Colloidosomes
j. Herbosomes

3. Lipid Particulate system:

a. Lipospheres
b. Solid lipid microparticle
c. Solid lipid microparticle
d. Nanostructure lipid carrier
e. Lipid drug conjugates

Guidelines for Design of Lipid-Based Formulations[7]

While it is clear that lipid-based formulations will continue to be an important tool for formulating poorly soluble drugs, the design of these formulations can be challenging. In his outstanding review, he recently mentioned seven guidelines for designing lipid-based formulations, which are shortened below.

(1) It is essential to maintain the solubility of the drug in the formulation, after dispersion, and after digestion.

(2) The properties of the colloidal species formed after processing in the GI medium are probably more important than the properties of the formulation itself in improving absorption.

(4) Medium-chain triglycerides can provide greater solubility and stability of the drug in the formulation, but long-chain triglycerides facilitate more efficient formation of colloidal lipid species from bile salts and thus can provide greater bioavailability.

(5) Type IIIB Selfemulsifying drug delivery system (SMEDDS) formulations give lower droplet sizes after dispersion. Still, they are more dependent on the surfactant properties employed, and nondigestible surfactants generally give greater bioavailability.

(6) The dispersion of type IV formulations (surfactant/cosolvent) is probably more effective if two surfactants are used instead of just one.

(7) Type IV formulations can provide increased drug solubility but must be designed with care to ensure that the drug does not precipitate after dispersion.

These guidelines are important to consider when designing lipid-based oral formulations for poorly soluble medications. As more experience is gained with the design and use of these formulations and the database of successful formulations grows, it is to be expected that the design of these formulations will be less an empirical exercise and more rational in its approach. As this happens, the usefulness of lipid-based formulations can only grow.

PROBLEMS SOLVED BY LBDDS [8]

Solubilization of Poorly Water-Soluble Drugs

Hauss has reported that more than 70% of new drug candidates have low water solubility values [4]. Almost 40% of lipophilic drug candidates that shows good pharmacological activity do not reach the market because low aqueous solubility compromises bioavailability and leads to low pharmacokinetic result show and low exposure.[1] The trend is likely to continue No matter how promising a drug's pharmacological activity is, its inability to dissolve in the gastrointestinal tract renders it ineffective. However, lipid-based dosage forms can be used to salvage good therapeutic agents that have low water solubilities.

LBDDS provide the drug in a fully or partially solubilized state and, more importantly, hold the drug solution until it is absorbed. The drugs remain in a solubilized state because the LBDDS self-emulsify the emulsions after digestion. During digestion, the oils in LBDDS undergo lipolysis to form fatty acids and monoglycerides, which combine with components of gastrointestinal fluids to form mixed micelles that can help keep the drug in solution.[8]

Lipid formulations are classified in the Lipid Formulations Classification System by their formulation components, hydrophobicity, dispersibility, and digestibility (Table 1)[9]. A Type I formulation consists of triglycerides (oils), Type II adds insoluble surfactants In water and dispersible to oils, Type III incorporates water-soluble surfactants and hydrophilic cosolvents (Transcutol®, ethanol, PEG), and Type IV is oil-free and consists only of hydrophilic surfactants and cosolvents. Type I formulations cannot be dispersed in water and rely on the body's natural lipid digestion processes to form mixed micelles that act as a natural detergent for the drug. an emulsion formed through digestion of alpha-tocopherol quinone into a triglyceride. Type II formulations generally form run-in-water emulsions and are digested to form mixed micelles. Type III formulations spontaneously form as emulsions or micro / nanoemulsions upon dispersion in water and may rely on some digestion to aid or keep the drug in solution. Type IV formulations form micellar solutions upon dispersion in water and are less digestible. The common feature of Type I to Type IV formulations is solubilization by micellization *in-vivo*. This is in contrast to other approaches, such as solubilization by dissolving a drug in an organic cosolvent where large reductions in solubility are experienced upon dilution. The formulator necessity understand that category does not predict *in-vivo* performance; For example, Type I formulations may work better with low melting point highly lipophilic compounds, but such compounds will not work well if formulated with Type IV formulations. Therefore, the choice of the type of

formulation will depend on the molecule that is administered.

There are numerous examples in the literature that demonstrate the improved solubility and bioavailability that can be achieved with LBDDS; A non-exhaustive list of active ingredients includes progesterone, halofantrine, docetaxel, carvedilol, piroxicam, nifedipine, and curcumin[10-14].

A potential advantage of LBDDS is that the drug is delivered in solution to the gastrointestinal tract, avoiding the need for dissolution. The drug remains in solution by micellar solubilization caused by digestion and / or autoemulsification. The challenge for the formulator is to discern which excipient (s) and what proportion of them will solubilize the dose.

Alskar et al. Analyzed the solubilities of molecules in various lipid solvents and surfactants to establish predictive solubility relationships [15]. Some notable findings from this work are Lipophilic drugs with low melting points (<150 ° C) are often soluble in oils or oily vehicles. The solubility of a drug in a mixture of lipid excipients can be expressed as the sum of the solubilities of the drug in the individual excipients, each solubility value being weighted by the mass fraction of the excipient in the formulation. Lastly, the solubility values for a given molecule are similar in similar solvents; for example, a solubility value in PEG400 can be used as an estimate of solubility values in other ethoxylated solvents such as Transcutol®. This research provides a framework for estimating the solubilities of molecules in lipid excipients and facilitates the work of the preformulator and formulator to select excipient (s) and their ratios to allow for target drug loading.

Enhancement of Intestinal Permeability

To be absorbed into the systemic circulation, a drug molecule must cross the GI wall. The resulting colloidal dispersions caused by the digestion of LBDDS improve the affinity of the drug for the protective aqueous monolayer (or layer of water without shaking) that covers the light and facilitate the conditions for the permeability of the API.16 This effect is related to excipients such as caprylocaproyl polyoxyglycerides (Labrasol®), which improves drug transport through intestinal cell membranes and its effect on the opening of tight epithelial junctions [17-21].

Previous studies, based on the in vitro cell-based model, pointed to membrane fluidity and efflux inhibition as other possible mechanisms that drive intestinal permeability. However, lately, scientists are increasingly focusing on API supersaturation in GI light as the main mechanism for improving permeability. Recent studies suggest that initially, API supersaturation (an increase in the fraction of free drug) results from a decrease in the solubilization capacity of LBF after dispersion into gastric and intestinal fluids in the small intestine, creating pressure for the API [17,22,23]. An absorption the subsequent imbalance created between the initial concentration of the solubilized drug in GI fluids and the solubility of the drug in the colloidal species formed after dispersion and digestion is another factor that contributes to supersaturation of the API. Meanwhile, lipid metabolites are absorbed, contributing to a further reduction in the solubilization capacity of the remaining colloidal phases during digestion, thus promoting continuous supersaturation [22 23].

Protection From Enzymatic/Chemical Degradation

Hetenyi and colleagues revealed that the therapeutic peptides, leuprorelin, insulin, and desmopressin can be combined with docusate sodium and loaded into a SEDDS formulation.[24] Researchers exposed the formulated peptides to intestinal proteases (α-chymotrypsin, trypsin, and elastase). and glutathione. They observed that there was no degradation of peptides in the SEDDS formulation, which was consistent with the observation that proteases and glutathione were ≤ 0.1% soluble in the oily SEDDS. This work strongly suggests that an LBDDS can protect sensitive peptide APIs from water-soluble reagents and degradation mechanisms that require an aqueous environment.

Reduction of the First-Pass Metabolism

The triglycerides in an LBDDS are digested by the natural lipolysis process in the GI tract to form fatty acids and monoglycerides. Fatty acids can be absorbed by the hepatic and/or lymphatic routes, and the distribution between the routes depends on the length of the hydrocarbon chain. Fatty acids with hydrocarbon chains below 12 ° C tend to bind to albumin, making them soluble in water. As a result, they passively diffuse through the epithelial cells that line the intestine and are taken up into the bloodstream through the portal vein before being transferred to the liver.

Fatty acids with a chain length of 14C or more, due to their hydrophobicity, can be substrates for the transport of proteins to cells, where they can be resynthesized into lipoproteins (known as chylomicrons) for absorption by the lymphatic pathway.

Long-chain unsaturated fatty acids (LCFA), in particular, are known to stimulate chylomicron secretion and increase lymphatic uptake. They have been shown to improve the bioavailability of certain drugs, such as saquinavir, ontazolast, halofantrine, through preferential absorption through the lymphatic transport system, and consequently decrease the first-pass metabolism of API in the liver [25-27].

For the reason that absorption by lymph means bypassing the liver, co-formulation with LCFA may be a promising strategy for active drugs that are extensively metabolized in the liver. Enhanced lymphatic absorption is important in oral administration, mainly for highly lipophilic drugs (LogP> 5) with high solubility in triglycerides (Cs> 50 mg/ml), that is, APIs that are candidates for lymphatic absorption.

Table 1: Lipid Formulation Classification System

Types	Composition	Characteristics	Examples of Approved Drug Products
I	Oils (Triglycerides, mixed mono, and diglycerides)	Non-Dispersing, poor solvent capacity unless the drug is highly lipophilic. Required digestion to convert triglycerides to monoglycerides and fatty acids which combine with bile salt and lecithin to form bile salt mixed micelles.	Amitiza Rocaltrol
II	Oils, Low-HLB surfactants	SEDDS without water-soluble component, turbid O/W dispersion, unlikely to lose solvent capacity in dispersion.	Sandimmune Neoral
III	Oils, high-HLB surfactants Hydrophilic cosolvents	SEDDS/ SMEDDS with water-soluble/ dispersible components, clear or bluish dispersion, possible loss of solvent capacity on dispersion, less easily digested.	Xtandi Lipofen Kaletra
IV	Low-HLB surfactants, High-HLB surfactants, Hydroalcoholic cosolvents	Micellar solutions, good solvent capacity for many drugs, loss of solvent capacity on dispersion, least digestible formulation type.	Agenerase Norvir

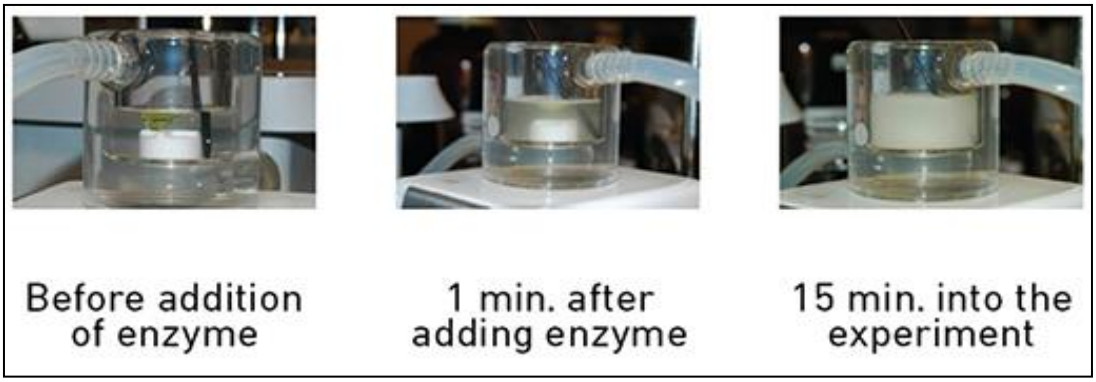

Figure 1: Enzymatic digestion of a type I lipid Formulation

Characterization of Lipid-Based Drug Delivery Systems

1. Appearance:

The appearance can be checked in a graduated glass cylinder or transparent glass container to check its uniformity and color in equilibrium [28].

2. Color:

smell, and taste. These characteristics are especially important in orally administered formulations. Variations in taste, especially of the active components, can often be attributed to changes in particle size, crystal habit, and subsequent dissolution of the particles. Changes in color, odor, and taste can also indicate chemical instability [29].

3. Density:

The specific gravity or density of the formulation is an essential parameter. A decrease in density often indicates trapped air within the structure of the formulation. Density measurements at a given temperature can be made using high precision hydrometers [29].

4. pH value:

The pH value of the aqueous formulation should be taken at a given temperature using a pH meter and only after the settlement equilibrium has been reached, to minimize "pH drift" and coating of the electrode surface with particles. in suspension. The electrolyte should not be added to the external phase of the formulation to stabilize the pH, because neutral electrolytes alter the physical stability of the suspension [29].

5. Self-dispersion and size of dispersions:

It is desirable to evaluate the dispersion rate and the resulting particle size of lipid-based systems, therefore attention has been paid to the measurement of the dispersion rate. Particle size measurement can be done by a light microscope using a compound microscope for

particles with measurement within microns. The particle size analyzer can be used to measure particle size.

6. Drop size and surface charge (Zeta potential):

The droplet size distribution of the microemulsion vesicles can be determined by electron microscopy or light scattering technique. Dynamic light scattering measurements are taken at 90 ° on a dynamic light scattering spectrophotometer using a 632 nm wavelength neon laser. Data processing is done on the computer built into the instrument. Recently, regarding the importance of particle size distribution in terms of particle characterization and physical stability testing of the product, there has been interested in new light scattering methods for particle detection called photon correlation spectroscopy (PCS). The surface charge is determined using a zeta potential (ZP) analyzer by measuring the zeta potential (ZP) of the preparations. Zeta Potential characterizes the surface charge of the particles and therefore provides information on the repulsive forces between particles and droplets. To obtain stable nanoemulsions by preventing flocculation and coalescence of the nano-droplets, ZP should typically reach a value greater than 30 mV [29].

7. Viscosity measurement:

A Brookfield type rotary viscometer can be used to measure the viscosity of lipid-based formulations of various compositions at different shear rates at different temperatures. Samples for measurement should be immersed in it before testing and the sample temperature should be kept at 37 ± 0.2 ° C using a thermal bath. The viscometer must be properly calibrated to measure the apparent viscosity of the suspension in equilibrium at a given temperature to establish the reproducibility of the suspension. Apparent viscosity, like pH, is an exponential term, and therefore logarithmic apparent viscosity is a good way to report results [29].

8. *In- vitro* studies:

In-vitro characterization of lipid-based drug delivery systems can be performed with the use of lipid digestion models. To evaluate the performance of an excipient during formulation development and predict *in-vivo* performance, it is necessary to design an in vitro dissolution test method. Journal of Pharmaceutics 7. This may be called a "simulated lipolysis release test" 30. The basic principle on which these system works requires maintaining a constant pH during a reaction that releases or consumes hydrogen ions. If any deviation is found, it is compensated with the addition of a reagent. The model consists of a temperature-controlled container (37 ± 1 ∘ C), which contains a model intestinal fluid, composed of digestion buffer, bile salt (BS), and phospholipid (PL). In this model, a fluid formulation based on lipids is added and pancreatic lipase and colipase were added to start the digestion process. As the digestion process begins, the release of fatty acids occurs, causing a transient drop in pH. This drop-in pH is quantified using a pH electrode. The pH electrode is coupled with a pH-stat meter controller and an automatic buret. An equimolar quantity of sodium hydroxide is added to titrate the fatty acids released by the automatic buret, to avoid a change in the pH of the digestion medium from a preset pH value. By quantifying the rate of addition of sodium hydroxide and considering the stoichiometric relationship between fatty acids and sodium hydroxide, the degree of digestion can be quantified. During the digestion process, samples can be extracted and separated into a sparsely dispersed oil phase, a highly dispersed aqueous phase, and a sediment phase precipitated by centrifugation. Quantitation of the drug in the highly dispersed aqueous phase indicates that the drug has not precipitated, so an assumption can be made regarding the *in-vivo* performance of the lipid-based formulation.

9. *In-vivo* studies:

The impact of excipients on the bioavailability and pharmacokinetic profile of drugs can be assessed by designing appropriate *in-vivo* studies. A comprehensive study of intestinal lymphatic absorption is mandatory since lipid-based formulations improve bioavailability by improving the intestinal absorption of the drug. Due to unsatisfactory clinical data and differences in the methods and animal models used, studies related to the transport of drugs through the lymphatic system have become difficult [31].

10. *In-vitro-in-vivo* correlation (IVIVC):

The *in-vitro-in-vivo* correlation will help maximize the potential for the development and commercialization of lipid-based formulations. A shorter drug development period and better product quality could be achieved by developing a model that correlates *in-vitro* and *in-vivo* data. Determination of solubility, dissolution, lipolysis of the lipid excipient, and intestinal membrane techniques (isolated animal tissue and cell culture models) are various *in-vitro* techniques that can be used to evaluate lipid-based formulations [32].

These techniques provide information on specific aspects of the formulation only. But it is important to know the interaction and *in-vivo* performance of these systems. Similar to enterocytes *in-vivo*, Caco-2 cells produce and secrete chylomicrons on exposure to lipids. More studies should be conducted on the choice of the most suitable *in-vivo* model to evaluate lipid-based formulations.

APPLICATIONS

(i) Until now, the design of successful lipid-based delivery systems have relied heavily on empirical experiences. Systematic physicochemical investigations of structure and stability not only help accelerate the development of new and improved formulations but can also help understand the complex mechanisms that govern the interaction between lipid carriers and living cells. Therefore, they sought to be safe, efficient, and specific carriers for the delivery of genes and drugs.

(ii) LBDDS can be used to deliver various types of drugs from new chemical entities to newer developments for proteins and peptides, nucleic acids (DNA, siRNA), and site-specific cellular delivery [33, 34, 35].

(iii) The utility of lipid-based formulations to improve the absorption of poorly water-soluble lipophilic drugs has been recognized for many years. Lipids are possibly one of the most versatile excipient classes currently available, providing the formulator with many potential options for enhancing and controlling the absorption of poorly water-soluble drugs. These formulation options include lipid suspensions, solutions, emulsions, microemulsions, mixed micelles, SEDDS, SMEDDS, thixotropic vehicles, thermosetting matrices, and liposomes.

(iv) Lipid-based formulations, which are by no means a recent technological innovation, have not only shown their usefulness in mitigating poor and variable gastrointestinal absorption of poorly soluble lipophilic drugs but have also, in many cases, shown the ability to reduce or eliminate the influence of food on the absorption of these drugs. Despite these realities, marketed oral pharmaceuticals employing lipid-based formulations are currently 25 to 1 outnumbered by conventional formulations. Some of the commercially available lipid-based formulations are shown in Table 2.

REGULATORY ASPECTS [36]

All excipients are not having inert substances and some can be toxic at increased concentrations 36. In the Code of Federal Regulations, the FDA has published a list of substances that are generally recognized as safe (GRAS). Separately from this, it also maintains a list of inactive ingredients for excipients entitled Inactive Ingredient Guide (IIG) that are approved and can be incorporated into commercially available products [37]. This guide provides the list of the maximum allowable amount for excipients, which can be used for the specific route of administration. Once an inactive ingredient has been approved for a product via a particular route of administration, it can be used in any new drug formulation and does not require extensive review. The formulator can take the information from both GRAS and IIG when developing a new formulation. Currently, the FDA does not have any process or mechanism to evaluate the safety of excipients on an individual basis. Instead, excipients are reviewed and approved as "components" of the drug or biological product in the application. Since excipients play an integral role in the formulation and cannot be reviewed separately from the drug formulation, the regulatory process is appropriate from a scientific point of view. From a regulatory point of view, quality and safety issues associated with preclinical and clinical studies are the main difficulties that can arise when launching a lipid-based pharmaceutical form on the market and, above all, manifestations of therapeutic efficacy. The overall stability of the drug and the absence of immunological reactions to oils or lipid excipients must be demonstrated. Sufficient details should be provided explaining the use of lipid excipients and the types of dosage forms, the drug release mechanism, and their manufacture to persuade regulatory authorities of their acceptability [38]. Safety assessment and the possible effect of biopharmaceutical factors in the Drug or lipid excipients need to be explored. It can be difficult to predict the *in-vivo* behavior of a lipid dosage form based on *in-vitro* results obtained by conventional dissolution methods given the complicated GI processing of lipid formulations. More mechanistic studies should be conducted to facilitate a better understanding of the pharmaceutical characteristics of lipid formulations and the interactions between lipid excipients, the drug, and the physiological environment. The lack of predictability in product quality and performance may be due to the nature of empirical and iterative processes traditionally employed [39].

To rationalize the design of the lipid formulation and better understand the fate of a drug after oral administration in a lipid formulation, a consortium has been created, made up of academics and industrial scientists (www.lfcsconsortium.org/). The consortium sponsors and researches to develop *in-vitro* methods to evaluate the performance of LBDDS during dispersal and digestion, which are critical parameters. The primary objective is to develop guidelines that streamline and accelerate the development of drug candidates through the identification of key performance criteria and the validation and eventual publication of universal standard tests and operating procedures. To establish approved guidelines, proper dialogue with pharmaceutical regulatory bodies (FDA, EMEA) is also foreseen.

NEW TRENDS IN LBDDS

Formation of Lipophilic Salts/Ion Pairs of Drugs for Solubilization in Lipidic Excipients:

Despite the wide range of excipients to allow the development of an LBDDS in which the drug is completely solubilized, some molecules will not dissolve in lipid excipients at the required unit dose. Although suspensions in LBDDS can provide good exposure and are commercially available, for example, CiproTM oral suspension, typically the best LBDDS exposure is achieved when the drug is fully solubilized in the dosage form. Additionally, formulating and manufacturing solutions present fewer challenges than suspensions that can be prone to aggregation and sedimentation. The inability to solubilize an active agent in lipid excipients has led formulators to discard LBDDS as a viable technology for the drug. This unfortunate circumstance has restricted the use of this highly versatile LBDDS approach to allow the formulation of drugs with high formulation barriers, including low bioavailability.

Recent work has been done to prepare lipophilic salts (or ion pairs) of drugs that allow for increased drug loadings and are completely solubilized in lipid excipients. Sahbaz and colleagues prepared docusate or decyl sulfate salts of itraconazole, cinnarizine, and halofantrine to form low-melting ionic liquids or solids that were miscible or could be solubilized in SEDDS composed of long- or medium-chain triglycerides, surfactants, and cosolvents [40 41]. Itraconazole

docusate or cinnarizine decyl sulfate was administered to rats in SEDDS formulations in which the dose was fully solubilized. The exposure of completely solubilized drugs in the SEDDS formulation (made possible by the synthesis of lipophilic salts of these drugs) was 2 times higher for cinnarizine and 20 times higher for itraconazole, relative to the control formulations of the forms free-base suspended drugs at the same dose This study demonstrated that the formation of lipophilic salts or ion pairs could allow the complete solubilization of drugs in lipid excipients and greatly improve their exposure. This major study should initiate a paradigm shift in which less water-soluble and more lipid-soluble salt forms or ion pairs of drugs are synthesized to allow the use of LBDDS for drug delivery.

REFERENCES

1. Thakkar H, Patel B, Thakkar S. A review on techniques for oral bioavailability enhancement of drugs. *International Journal of Pharmaceutical Sciences Review and Research.* 2010;4(3):203-223.
2. I. Brigger, C. Dubernet, and P. Couvreur, Nanoparticles in cancer therapy and diagnosis. Advanced Drug Delivery Reviews. 2002;54(5): 631–651.
3. J. Panyam and V. Labhasetwar, Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Advanced Drug Delivery Review. 2003;55(3):329–347.
4. R. H. Muller, M. Radtke, and S. A. Wissing, Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Advanced Drug Delivery Reviews. 2002;54(1):131–155.
5. E. B. Souto and R. H. Muller, Nanoparticulate Drug Delivery Systems. Informa Healthcare New York, USA. 2007;166:120
6. Hina Shrestha, Rajni Bala, and Sandeep Arora. Lipid-Based Drug Delivery Systems. Hindawi Publishing Corporation Journal of Pharmaceutics. 2014:1-10
7. C. J. H. Porter, C. W. Pouton, J. F. Cuine, and W. N. Charman. Enhancing intestinal drug solubilisation using lipid-based delivery systems. Advanced Drug Delivery Reviews. 2008; 60(6): 673–691.
8. Fatouros D, Bergenstahl B, Mullertz A. Morphological observations on a lipid-based drug delivery system during *in-vitro* digestion. European Journal of Pharmaceutical Sciences. 2007;31(2):85-94.
9. Pouton C. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. European Journal of Pharmaceutical Sciences. 2006;29(3-4):278-287.
10. Tuleu C, Newton M, Rose J et al. Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid form Compared with an Aqueous Suspension of Progesterone. Journal of Pharmaceutical Sciences. 2004;93(6):1495-1502..
11. Khoo S, Humberstone A, Porter C, Edwards G, Charman W. Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine. International Journal of Pharmaceutics. 1998;167(1-2):155-164.
12. Yin Y, Cui F, Mu C et al. Docetaxel microemulsion for enhanced oral bioavailability: Preparation and *in-vitro* and *in-vivo* evaluation. Journal of Controlled Release. 2009; 140(2):86-94.
13. Wei L, Sun P, Nie S, Pan W. Preparation and Evaluation of SEDDS and SMEDDS Containing Carvedilol. Drug Development and Industrial Pharmacy. 2005;31(8):785-794.
14. Jannin V, Chevrier S, Michenaud M et al. Development of self emulsifying lipid formulations of BCS class II drugs with low to medium lipophilicity. International Journal of Pharmaceutics. 2015;495(1):385-392.
15. Alskär L, Porter C, Bergström C. Tools for Early Prediction of Drug Loading in Lipid-Based Formulations. Molecular Pharmaceutics. 2016;13(1):251-261.
16. Porter C, Trevaskis N, Charman W. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nature Reviews Drug Discovery. 2007;6(3):231-248.
17. KOGA K, KUSAWAKE Y, ITO Y, SUGIOKA N, SHIBATA N, TAKADA K. Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate. European Journal of Pharmaceutics and Biopharmaceutics. 2006;64(1):82-91.
18. Rama Prasad Y, Eaimtrakarn S, Ishida M et al. Evaluation of oral formulations of gentamicin containing labrasol in beagle dogs. International Journal of Pharmaceutics. 2003;268(1-2):13-21.
19. Chang R, Shojaei A. Effect of a lipoidic excipient on the absorption profile of compound UK 81252 in dogs after oral administration. J Pharm Pharm Sci. 2004;7(1):8-12.
20. Rama Prasad Y, Minamimoto T, Yoshikawa Y et al. In situ intestinal absorption studies on low molecular weight heparin in rats using Labrasol as absorption enhancer. International Journal of Pharmaceutics. 2004; 271(1-2):225-232.
21. Sha X, Yan G, Wu Y, Li J, Fang X. Effect of self-microemulsifying drug delivery systems containing Labrasol on tight junctions in Caco-2 cells. European Journal of Pharmaceutical Sciences. 2005;24(5):477-486.
22. Williams H, Sassene P, Kleberg K et al. Toward the Establishment of Standardized *In-vitro* Tests for Lipid-Based Formulations, Part 1: Method Parameterization and Comparison of *In-vitro* Digestion Profiles Across a Range of Representative Formulations. Journal of Pharmaceutical Sciences. 2012;101(9):3360-3380.
23. Williams H, Trevaskis N, Yeap Y, Anby M, Pouton C, Porter C. Lipid-Based Formulations and Drug Supersaturation: Harnessing the Unique Benefits of the Lipid Digestion/Absorption Pathway. Pharmaceutical Research. 2013;30(12):2976-2992.
24. Hetenyi G, Griesser J, Moser M, Demarne F, Jannin V, Bernkop-Schnürch A. Comparison of the protective effect of self-emulsifying peptide drug delivery systems towards intestinal proteases and glutathione. International Journal of Pharmaceutics. 2017;523(1):357-365.
25. Hauss D, Fogal S, Ficorilli J et al. Lipid-Based Delivery Systems for Improving the Bioavailability and Lymphatic Transport of a Poorly Water-Soluble LTB4 Inhibitor. Journal of Pharmaceutical Sciences. 1998;87(2):164-169.

26. Charman W, Stella V. Transport of lipophilic molecules by the intestinal lymphatic system. Advanced Drug Delivery Reviews. 1991;7(1):1-14.
27. O'Driscoll C. Lipid-based formulations for intestinal lymphatic delivery. European Journal of Pharmaceutical Sciences. 2002;15(5):405-415.
28. C. J. H. Porter and W. N. Charman. *In-vitro* assessment of oral lipid based formulations. Advanced Drug Delivery Reviews. 2001;50(1):127–147.
29. L. Wei, P. Sun, S. Nie, and W. Pan, "Preparation and evaluation of SEDDS and SMEDDS containing carvedilol," Drug Development and Industrial Pharmacy. 2005;31(8): 785–794.
30. S. Prabhu, M. Ortega, and C. Ma, "Novel lipid-based formulations enhancing the *in-vitro* dissolution and permeability characteristics of a poorly water-soluble model drug, piroxicam," International Journal of Pharmaceutics. 2005;301(1-2): 209– 216.
31. G. A. Edwards, C. J. H. Porter, S. M. Caliph, S. Khoo, and W. N. Charman. Animal models for the study of intestinal lymphatic drug transport. Advanced Drug Delivery Reviews. 2001;50(1-2):45–60.
32. F. Seeballuck, M. B. Ashford, and C. M. O'Driscoll. The effects of Pluronic block copolymers and Cremophor EL on intestinal lipoprotein processing and the potential link with Pglycoprotein in Caco-2 cells. Pharmaceutical Research. 2003;20(7):1085–1092.
33. M. Rawat, D. Singh, S. Saraf, and S. Saraf. Lipid carriers: a versatile delivery vehicle for proteins and peptides. Yakugaku Zasshi. 2008;128(2):269–280.
34. A. J. Almeida and E. Souto. Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Advanced Drug Delivery Reviews. 2007;59(6):478–490.
35. W. Choi, J. Kim, S. Choi, J. Park, W. S. Ahn, and C. Kim, "Low toxicity of cationic lipid-based emulsion for gene transfer," Biomaterials. 2004;25(27):5893–5903.
36. Federal Register Rules and Regulations. 2000;65:182.
37. P. Maincent, "The regulatory environment: the challenges for lipid-based formulations," Bulletin Technique Gattefosse. 2007;100:47–49.
38. M. Chen, "Lipid excipients and delivery systems for pharmaceutical development: a regulatory perspective," Advanced Drug Delivery Reviews. 2008;60(6):768–777.
39. Sahbaz Y, Williams H, Nguyen T et al. Transformation of Poorly Water-Soluble Drugs into Lipophilic Ionic Liquids Enhances Oral Drug Exposure from Lipid Based Formulations. Molecular Pharmaceutics. 2015;12(6):1980-1991.
40. Griesser J, Hetényi G, Moser M, Demarne F, Jannin V, Bernkop-Schnürch A. Hydrophobic ion pairing: Key to highly payloaded self-emulsifying peptide drug delivery systems. International Journal of Pharmaceutics. 2017; 520(1-2):267-274.

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