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Lipid Based Drug Delivery Systems

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Abstract
The formulation of lipid-based nanomedicines against various diseases has been hypothesized to improve drug localization into the in-target site and to increase the efficacy of conventional drugs, while minimizing their systemic adverse effects. Most of the treatments lack specificity, the treatment affects both target cells and their normal counterparts, many potent agents are highly toxic, and a number of chemotherapeutics are highly hydrophobic, which limits their utility in various therapies. As a result of these deficiencies, many current treatments lead to side effects, noncompliance, and patient inconvenience due to difficulties in administration. The improvement of bioavailability of drugs with such properties presents one of the greatest challenges in drug formulations. Oral lipid-based formulations are attracting considerable attention due to their capacity to increase the solubility, facilitating gastrointestinal absorption and reduce or eliminate the effect of food on the absorption of poorly water soluble, lipophilic drug and thus increasing the bioavailability. The present review outlines the recent findings on self-emulsifying drug delivery system (SEDDS), self-micro/nanoemulsifying drug delivery system (SMEDDS/SNEDDS) and evaluation of these formulations published over the past decade. The application of lipid-based formulations as a promising system for the oral delivery of many therapeutic agents. This review is about self-emulsifying lipid-based systems.

Keywords
Lipid based drug delivery systems, Lymphatic systems, surfactants, oils etc.

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1.INTRODUCTION
As a result of deficiencies from many current treatments which is leading to side effects, noncompliance and patient inconvenience due to difficulties in administration and low therapeutic efficacy. Lipid-based drug delivery systems have emerged as interesting vectors for oral application because of their potential to improve solubility, absorption of poorly water-soluble drugs and lipophilic drugs, slowing down drug chemical as well as enzymatic degradation, and thereby improving oral bioavailability. It is a fact that chemotherapy agents have little specificity for cancer cells, this leading to low concentrations into the target site and severe side effects on healthy tissues. The formulation of lipid-based nanomedicines against various diseases has been hypothesized to improve drug localization into the target tissue and to increase the efficacy of conventional drugs, while minimizing their systemic adverse effects[1][2][3].

Drawbacks to intravenous administration, including extravasation of drug or blood, catheter infections, and thrombosis can be prevented by administering the drug orally, making the oral delivery the most popular route of administration. Nonetheless, oral administration is limited by problems related to physicochemical properties of the drug, including poor solubility, low permeability, instability, and rapid metabolism, all of which decrease oral bioavailability [4].

With the advent of drug design, various molecules have been created that have a potential for therapeutic action. But most of the newly discovered

chemical entities are of high molecular weight and belong to biopharmaceutical classification system (BCS) – II, with poor aqueous solubility and high membrane permeability. Hence these two characteristics limit the bioavailability of orally administered drugs. These drugs have low solubility which leads to low dissolution and limits absorption [5][6].

In order to formulate such drugs in a safe and efficacious form, a balance must be maintained between bioavailability, toxicity and disposition within the body. The availability of novel lipid excipients with acceptable regulatory and safety profiles coupled with their ability to enhance oral bioavailability has helped in the development of lipid-based formulations as a means for drug delivery. Lipid-based drug delivery (LBDDS) systems have gained much importance in the recent years due to their ability to improve the solubility and bioavailability of drugs with poor water solubility. The absorption of drug from lipid-based formulation depends on numerous factors, including particle size, degree of emulsification, rate of dispersion and precipitation of drug upon dispersion [7][8]. Lipid-based formulations may include oil solution or suspensions, emulsions, self-micro or self-nano emulsifying drug delivery systems (SMEDDS/SNEDDS), Vesicular systems and lipid particulate systems [9].

2. Various types of lipid-based drug delivery systems

LBDDS is an umbrella term for numerous delivery systems. Various lipid-based drug delivery systems which efficiently delivers the drugs are divided into three categories. They are a) Emulsion systems b) Vesicular systems c) Lipid particulate systems [9][10][11][12]. The lipid systems are further division is shown in the Figure 1. The advantages of LBDDS over other dosage forms are drug release in controlled and targeted way, Pharmaceutical stability, High and enhanced drug content, Feasibilities of carrying both lipophilic and hydrophilic drugs, Biodegradable and biocompatible, Excipients versatility and Formulation versatility[13][6].

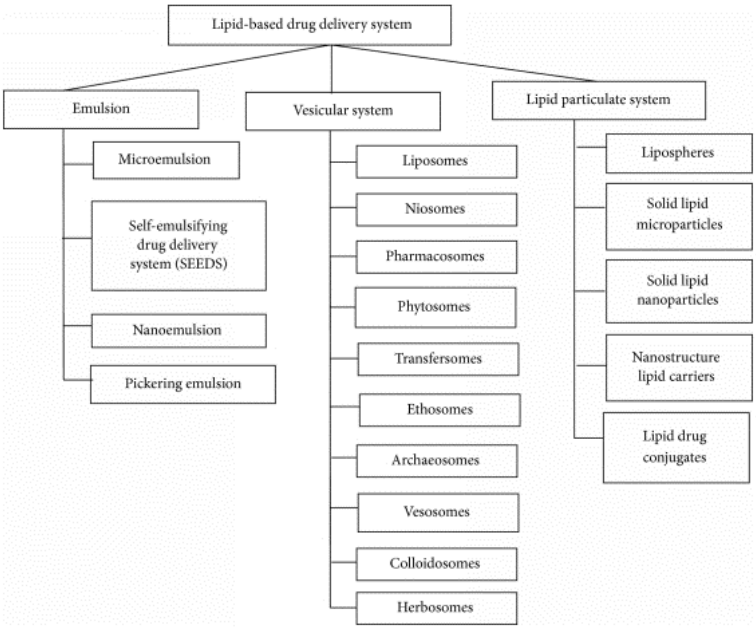

Fig-1: Various types of lipid-based drug delivery systems

2.1. The Lipid Formulation Classification System

LBBDS are typically composed of oils, surfactants and/or cosolvents solubilizing lipophilic drugs at high concentration and preventing precipitation during the gastrointestinal passage. Dilution, lipid digestion, and diffusion of water-soluble components after administration may change the composition and alter their solubilizing properties. Lipids are capable of inhibiting both pre-systemic drug metabolism and drug efflux by the gut wall mediated by p-glycoprotein. It is well known that lipids are capable of enhancing lymphatic transport of hydrophobic drugs, thereby reducing drug clearance resulting from hepatic first-pass metabolism [12][14]. Pouton proposed a lipid formulation classification system (LFCS) and related characteristics as described in Table-1.

LFCS Type	Materials	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (e.g. tri-, di-and monoglycerides)	Non-dispersing, requires digestion	GRAS status, simple, excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water-insoluble Surfactants	SEDDS without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2.0 µm)
Type III	Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS formed with water-soluble components	Clear or almost clear dispersion, drug absorption without digestion	Possible loss of solvent capacity on dispersion, less easily digested
Type IV	Water-soluble surfactants and colsolvents (no oils)	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion, may not be digestible

Table-1: The Lipid Formulation Classification System

2.1.1. Type I systems

These systems are mixtures of lipophilic materials which have little or no solubility in water. They are blends of food glycerides derived from vegetable oils, which are safe for oral ingestion, rapidly digested and absorbed completely from the intestine. They do not contain surfactant and have very limited ability to self-disperse in water. Mixture of mono and di-glycerides blends are used in Type I formulations. Type I formulations are excellent option if the drug is sufficiently soluble in mixed glyceride oils [12].

2.1.2. Type II systems

These systems are formulated with oils, polar oils and water-insoluble surfactants. Self-emulsifying systems are formed when the surfactant concentration exceeds 25%w/w and the optimum concentration range being 30-40% of surfactant. The performance of these formulation relies on the formation of a dispersed lamellar liquid crystalline phase at low water contents (5-10%), which aids further penetration of water causing interfacial disruption. These are formulated with long chain glycerides and these systems produce coarser emulsions by self-dispersion [12].

2.1.3. Type III systems

These systems contain water soluble surfactants and a significant amount of lipid components. Such formulations have the potential to disperse quickly to form fine submicron dispersions, often fine enough to form transparent dispersions. The key to successful formulation of type III systems is to avoid formulations that are so hydrophilic that they lose a considerable proportion of their solvent capacity on dispersion [12].

2.1.4. Type IV systems

These are pure surfactants or mixtures of surfactants and cosolvents. There are two problems using pure surfactants. The first, surfactants often take considerable amount of time to dissolve, because of formation of viscous crystalline liquid phases at the surfactant-water interface. The second, pure surfactants can be irritant and poorly tolerated in the gastrointestinal tract and the adhesion of a partially dissolved viscous mass rich in surfactant to the wall of the gastro-intestinal track could cause local damage[12].

2.2. Lipid excipients

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, sometimes including cosolvents, which emulsify under conditions of gentle agitation, like those which would be encountered in the gastro-intestinal tract. Hydrophobic drugs can often be dissolved in SEDDS allowing them to be encapsulated as unit dosage forms for peroral administration [15][16][17]. When such a formulation is released into the lumen of the gut it disperses to form fine emulsion, so that the drug remains in solution in the gut, avoiding the dissolution step which frequently limits the rate of absorption of hydrophobic drugs from the crystalline state[18][19]. Generally, this can lead to improved bioavailability, and/or more consistent temporal profile of absorption from the gut.

2.2.1. Oils

Oil solubilizes the hydrophobic drug and aids in self-emulsification. Lipid tends to increase the fraction of drug transported via intestinal lymphatic system and thus increasing lipophilic drug absorption from the GI tract [17][20]. The molecular structure of oil is responsible for emulsification property of oil. **Table-2** gives idea about commonly used oil in SMEDDS/SNEDDS.

Type of oil	Examples
Fixed oils (long-chain triglycerides)	Soybean oil, arachis oil, aastor oil, cottonseed oil, maize (corn) oil, hydrolyzed corn oil, olive oil, sesame oil, sunflower oil, palm oil, peanut oil, triolein
Medium-chain triglycerides and related esters	Caprylic/capric triglycerides (Akomed E, Akomed R, Miglyol 810, and Captex 355, Neobee M5®, Crodamol GTCC®), fractionated coconut oil (Miglyol 812), Captex 300, Labrafac CC, Triacetin
Medium-chain mono and di-glycerides	Mono and diglycerides of capric/caprylic acid. (Capmul MCM and Imwitor)
Long-chain mono glycerides	Glycerylmonooleate (Peceol, Capmul GMO), glycerylmonolinoleate (Maisine -35)
Propylene glycol (PG) fatty acid esters	PG Diester of caprylic/capric acid (Labrafac PG), PG monocaprylic ester (Sefsol-218) PG monolaurate (Lauroglyc FCC, Lauroglycol90, Capmul PG-12) PG dicaprylate (Miglyol 840)
Caprylic/capric/diglyceryl succinate	Miglyol 829
Fatty acids	Oleic acid (Crossential O94), Caprylic acid
Fatty acid esters	Ethyl Oleate (Crodamol EO), Ethyl butyrate, Isopropyl myristate, Isopropyl palmitate
Vitamins	Vitamin E
Mineral oil	Liquid paraffin

Table-2: List of Oils for SMEDDS/SNEDDS

2.2.2. Surfactants

Surfactants are commonly used in lipid formulations to enhance drug solubility and self-emulsifying properties of vehicle itself to minimize dependence on a patients digestion factors. Surfactants are important components of SMEDDS/SNEDDS systems as they are responsible for forming a stable emulsion upon dilution and stabilize the internal phase in an emulsion. A surfactant with an HLB value of more than 12 is necessary. Surfactants used in lipid-based drug delivery are usually polyethoxylated lipid derivative. Emulsifiers of natural origin are not widely used because of their poor self-emulsification property. Generally, non-ionic surfactants have lower toxicity compared to ionic surfactants [21][22]. LBDDS formulations usually contain non-ionic surfactants and possess good emulsion stability. Usually the surfactant concentration ranges between 30 and 60% w/w to form stable emulsions. Extremely small droplet size produced in case of SNEDDS promotes rapid gastric emptying and low local concentration of surfactant, thereby reducing the gastric irritation. Increase in surfactant concentration causes a decrease in droplet size thus surfactant molecules stabilize at the oil-water interface and if surfactant concentration is less then it causes enhanced water penetration into oil droplets leading to breakdown of oil droplets[23][24][25]. Thus, surfactant is also responsible for total solubility of the drug in SMEDDS, preventing drug precipitation upon aqueous dilution and keep the drug in solubilized form in GI tract. **Table-3** gives idea about commonly used surfactant in SMEDDS/SNEDDS.

General class	Examples	Commercial name
Polysorbates	POE-20-sorbitan monooleate	Tween® 80, Crillet 4
	POE-20-sorbitan monolaurate	Tween 20, Crillet 1
Sorbitan esters	Sorbitan monooleate	Span® 80, Crill 4
	Sorbitan monolaurate	Span 20, Crill 1
	Sorbitan monostearate	Span 60, Crill 3
PEO–PPO– block copolymers	Poloxamer 188	Pluronic®/Lutrol F 68
	Poloxamer 407	Pluronic/Lutrol F 127
POE castor oil	POE-35-castor oil	Cremphor® EL, Etocas 35 HV
POE hydrogenated castor oil	POE-40-hydrogenated castor oil	Cremophor RH 40, HCO-40, Croduret™ 40 LD
	POE-60-hydrogenated castor oil	Cremophor RH 60, HCO-60
POE-stearate	PEG-660-12-hydroxystearate	Solutol HS 15®
POE-vitamin E	Tocopheryl-PEG 1000-succinate	Vitamin E TPGS
Sucrose esters	Sucrose laurate	
	Sucrose palmitate	
Polyglycolyzed glycerides	Linoleoyl macrogol glycerides	Labrafil® 2125 CS
	Oleoyl macrogol glycerides	Labrafil 1944 CS
	Caprylocaproyl macrogol glyceride	Labrasol®
	Polyglyceryl oleate	Plurol® oleique CC 497
	Lauroyl macrogol glycerides	Gelucire® 44/14
	Stearoyl macrogol glycerides	Gelucire 50/13
Phospholipids	Soybean lecithin	

Table:3 List of surfactants used in SMEDDS/SNEDDS

2.2.3. Co-solvents

Co-solvents such as propylene glycol and ethanol are used to increase drug solubilization but also serve to enhance the dispersion rate of lipid formulations and are often included in SEDDS and SMEDDS. However, upon dispersion in the GI fluids, they rapidly partition into the aqueous phase and reduce the solvent capacity of the formulation often leading to drug precipitation [26].

3.DRUG ABSORPTION

LBDDS increase absorption from the gastrointestinal tract by accelerating the dissolution process, facilitating the formation of solubilized phases changing drug uptake, efflux and disposition by altering enterocyte-based transport and enhancing drug transport to the systemic circulation *via* intestinal lymphatic system[27][28].

3.1. Lymphatic system

The lymphatic system plays an important role in the transport of drugs to the systemic circulation, given its extensive drainage network throughout the body. In addition, fatty acid chain length has a crucial role in the spot of absorption. Fatty acids with C-14 to C-18 chains promote lymphatic absorption [29][30]. Some of the advantages of lymphatic transport of drug are avoidance of first-pass metabolism and targeting of specific diseases which are known to spread *via* lymphatics, such as certain lymphomas and HIV [31][32][33].

The promising mechanisms are facilitating transcellular absorption due to increased membrane fluidity, allowing paracellular transport by opening tight junctions, increased intracellular concentration and residence time by surfactants due to inhibition of P-gp and/or CYP450, lipid stimulation of lipoprotein/chylomicron production[34][35]. The mechanism of intestinal drug transport from lipid-based formulations is explained in Fig-2.

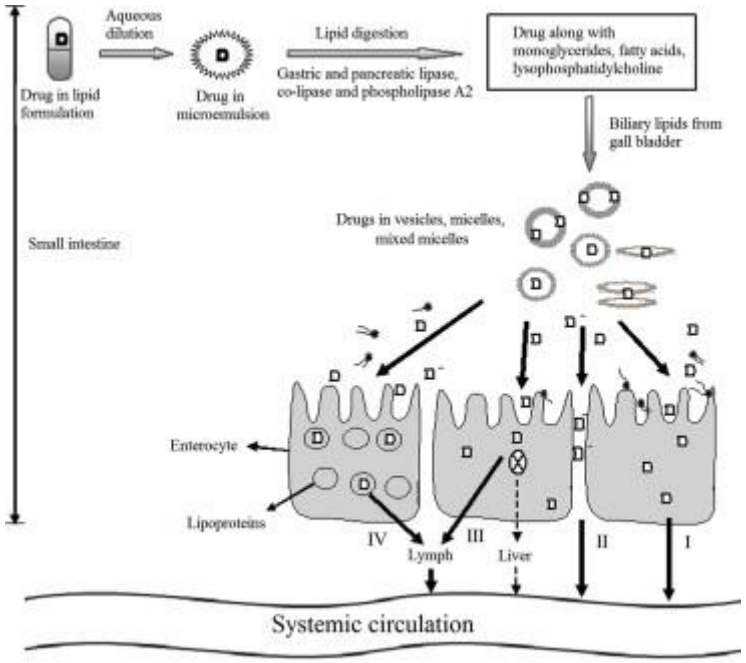

Fig:2 Schematic diagram of mechanisms of intestinal drug transport from lipid-based formulations

3.2. Digestion and Solubilization

The balance between a drug's solubility in the aqueous environment of the gastrointestinal lumen and its permeation across the lipophilic membrane of enterocytes determines its rate and extent of absorption. After oral administration of lipid-based formulations, gastric lipase initiates the digestion of exogenous dietary triglyceride (TG). Simultaneously, the mechanical mixing (propulsion, grinding and retropulsion) of the stomach facilitates formation of a crude emulsion (comprised of aqueous gastric fluid and lipid digestion products). Later in the small intestine, TG is broken down to diglyceride, monoglyceride and fatty acids by pancreatic lipase together with its cofactor co-lipase, acting primarily at the sn-1 and sn-3 positions of TG to produce 2-monoglyceride and free fatty acid[36][37][38].

Pancreatic phospholipase A2 digests the formulation-derived or biliary-

derived phospholipids (PL) by hydrolysing at the sn-2 position of PL to yield lysophosphatidyl choline and fatty acid. The presence of exogenous lipids in the small intestine stimulates the secretion of endogenous biliary lipids from the gall bladder, including bile salt (BS), PL and cholesterol. Previously formed monoglycerides, fatty acids, and lysophospholipid (products of lipid digestion) are subsequently incorporated into a series of colloidal structures, including micelles and unilamellar and multilamellar vesicles in the presence of bile salts [39][40]. The solubilization and absorptive capacity of the small intestine for lipid digestion products and drugs (D) is significantly enhanced due to these formed lipid metabolites. In Fig-3. The oil droplet in the intestine is represented in different colors to indicate undigested TG in the core (orange) and digested products such as fatty acid (blue) and monoglyceride (green) on the surface of the droplet. Lipid digestion and drug solubilization process in the small intestine is represented in Fig-3.

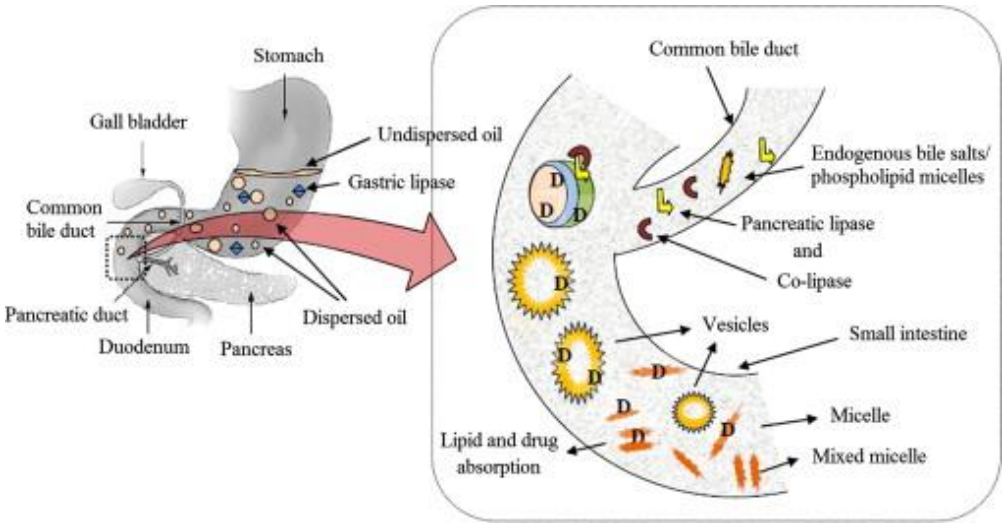

Fig: 3 Lipid digestion and drug solubilization process in the small intestine.

4.STABILITY

Maintaining adequate chemical and physical stability of lipid-based drug formulations delivery systems can also present challenges like unsaturated lipid components which can undergo lipid per oxidation. This can be minimized by use of saturated medium chain (C6-C12) triglycerides and by use of appropriate antioxidants. Phenol-based antioxidants such as Vitamin E (*α*-tocopherol), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and propyl gallate can act synergistically with oxygen scavengers such as ascorbic acid and its lipid-soluble counterpart, ascorbyl palmitate[41][42][2].

5.REGULATORY ASPECTS

In the Code of Federal Regulations, the FDA has published a list of substances that are generally recognized as safe (GRAS). Apart from this, it also maintains a list of excipients entitled inactive ingredient guide (IIG) that are approved and can be incorporated in marketed products [43][44]. This guide provides the list of maximum amounts allowed for excipients, which can be used for a specific route of administration. Once an inactive ingredient has been approved for a product through a particular route of administration. The formulator can take the information from both GRAS and IIG when developing a new formulation. More studies should be conducted to facilitate a better understanding of the pharmaceutical characteristics of lipid formulations and interactions between lipid excipients, drug, and physiological environment. To better understand the fate of a drug after oral administration in a lipid-based formulation, research must be developed for *in vitro* methods to assess the performance of LBDDS during dispersion and digestion, which are critical parameters.

6.FUTURE PROSPECTS

To better understand the fate of a drug after oral administration in a lipid-based formulation, research must be developed for *in vitro* methods to assess the performance of LBDDS during dispersion and digestion, which are critical parameters. More consideration needs to be paid to the characteristics of various lipid formulations available, so that guidelines and experimental methods can be established that allow identification of candidate formulations at an early stage. Methods need to be sought for tracking the solubilization state of the drug *in vivo*, and there is a need for *in vitro* methods for predicting the dynamic changes, which are

expected to take place in the gut. Attention to the physical and chemical stability of drugs within lipid systems and the interactions of lipid systems with the components. The present there is a great potential in the use of lipid formulations.

7.CONCLUSION

Lipid-based drug delivery systems showed great potential in overcoming problems of low bioavailability of poorly soluble drugs. This review provides a summary of lipid-based formulations which may be helpful for the advancement of this technology to obtain a safer, more stable and efficacious drug products.

8.REFERENCES

[1] S. Kalepu, M. Manthina, and V. Padavala, "Oral lipid-based drug delivery systems – an overview," *Acta Pharm. Sin. B*, 2013, doi: 10.1016/j.apsb.2013.10.001.

[2] H. Shrestha, R. Bala, and S. Arora, "Lipid-Based Drug Delivery Systems," *J. Pharm.*, 2014, doi: 10.1155/2014/801820.

[3] H. Mu, R. Holm, and A. Müllertz, "Lipid-based formulations for oral administration of poorly water-soluble drugs," *International Journal of Pharmaceutics*. 2013, doi: 10.1016/j.ijpharm.2013.03.054.

[4] C. W. Pouton and C. J. H. Porter, "Formulation of lipid-based delivery systems for oral administration: Materials, methods and strategies," *Advanced Drug Delivery Reviews*. 2008, doi: 10.1016/j.addr.2007.10.010.

[5] C. M. O'Driscoll and B. T. Griffin, "Biopharmaceutical challenges associated with drugs with low aqueous solubility-The potential impact of lipid-based formulations," *Advanced Drug Delivery Reviews*. 2008, doi: 10.1016/j.addr.2007.10.012.

[6] A. Charalabidis, M. Sfouni, C. Bergström, and P. Macheras, "The Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS): Beyond guidelines," *International Journal of Pharmaceutics*. 2019, doi: 10.1016/j.ijpharm.2019.05.041.

[7] C. J. H. Porter, N. L. Trevaskis, and W. N. Charman, "Lipids and lipid-based formulations: Optimizing the oral delivery of lipophilic drugs," *Nature Reviews Drug Discovery*. 2007, doi: 10.1038/nrd2197.

[8] J. Wadhwa, A. Nair, and R. Kumria, "Emulsion forming drug delivery system for lipophilic drugs," *Acta Poloniae Pharmaceutica - Drug Research*. 2012.

[9] K. Čerpnjak, A. Zvonar, M. Gašperlin, and F. Vrečer, "Lipid-based systems as a promising approach for enhancing the bioavailability of poorly water-soluble drugs," *Acta Pharm.*, 2013, doi: 10.2478/acph-2013-0040.

[10] K. Hadinoto, A. Sundaresan, and W. S. Cheow, "Lipid-polymer hybrid nanoparticles as a new generation therapeutic delivery platform: A review," *European Journal of Pharmaceutics and Biopharmaceutics*. 2013, doi: 10.1016/j.ejpb.2013.07.002.

[11] G. Cevc, "Lipid vesicles and other colloids as drug carriers on the skin," *Adv. Drug Deliv. Rev.*, 2004, doi: 10.1016/j.addr.2003.10.028.

[12] C. W. Pouton, "Lipid formulations for oral administration of drugs: Non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems," 2000, doi: 10.1016/S0928-0987(00)00167-6.

[13] D. J. Hauss, "Oral lipid-based formulations," *Advanced Drug Delivery Reviews*. 2007, doi: 10.1016/j.addr.2007.05.006.

[14] C. W. Pouton, "Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system," *Eur. J. Pharm. Sci.*, 2006, doi: 10.1016/j.ejps.2006.04.016.

[15] C. W. Pouton, "Formulation of self-emulsifying drug delivery systems," *Advanced Drug Delivery Reviews*. 1997, doi: 10.1016/S0169-409X(96)00490-5.

[16] Ş. Akkuş Arslan and F. Tirnaksiz, "Self-emulsifying drug delivery systems," *Fabad Journal of Pharmaceutical Sciences*. 2013, doi: 10.1201/9781315364353-1.

[17] R. N. Gursoy and S. Benita, "Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs," *Biomed. Pharmacother.*, 2004, doi: 10.1016/j.biopha.2004.02.001.

[18] K. Kohli, S. Chopra, D. Dhar, S. Arora, and R. K. Khar, "Self-emulsifying drug delivery systems: An approach to enhance oral bioavailability," *Drug Discovery Today*. 2010, doi: 10.1016/j.drudis.2010.08.007.

[19] B. Singh, S. Bandopadhyay, R. Kapil, R. Singh, and O. P. Katare, "Self-emulsifying drug delivery systems (SEDDS): Formulation development, characterization, and applications," *Critical Reviews in Therapeutic Drug Carrier Systems*. 2009, doi: 10.1615/critrevther drug carrier syst. v26.i5.10.

[20] S. Gupta, R. Kesarla, and A. Omri, "Formulation Strategies to Improve the Bioavailability of Poorly Absorbed Drugs with Special Emphasis on Self-Emulsifying Systems," *ISRN Pharm.*, 2013, doi: 10.1155/2013/848043.

[21] K. Balakumar, C. Vijaya Raghavan, N. Tamil Selvan, and S. M. Habibur Rahman, "Self-emulsifying drug delivery system: Optimization and its prototype for various compositions of oils, surfactants and co-surfactants," *J. Pharm. Res.*, 2013, doi: 10.1016/j.jopr.2013.04.031.

[22] A. Singh, V. Singh, D. Juyal, and G. Rawat, "Self-emulsifying systems: A review," *Asian Journal of Pharmaceutics*. 2015, doi: 10.4103/0973-8398.150031.

[23] M. H. Andrade Santana, "Self-Emulsifying Drug Delivery Systems (SEDDS) in Pharmaceutical Development," *J. Adv. Chem. Eng.*, 2015, doi: 10.4172/2090-4568.1000130.

[24] B. K. Nanjwade, D. J. Patel, R. A. Udhani, and F. V. Manvi, "Functions of lipids for enhancement of oral

bioavailability of poorly water-soluble drugs," *Scientia Pharmaceutica*. 2011, doi: 10.3797/scipharm.1105-09.

[25] P. P. Constantinides, "Lipid Microemulsions for Improving Drug Dissolution and Oral Absorption: Physical and Biopharmaceutical Aspects," *Pharmaceutical Research: An Official Journal of the American Association of Pharmaceutical Scientists*. 1995, doi: 10.1023/A:1016268311867.

[26] D. Mobarak, S. Salah, and M. Ghorab, "Improvement of dissolution of a class II poorly water-soluble drug, by developing a five-component self-nanoemulsifying drug delivery system," *J. Drug Deliv. Sci. Technol.*, 2019, doi: 10.1016/j.jddst.2018.12.018.

[27] A. A. Khan, J. Mudassir, N. Mohtar, and Y. Darwis, "Advanced drug delivery to the lymphatic system: Lipid-based nanoformulations," *International Journal of Nanomedicine*. 2013, doi: 10.2147/IJN.S41521.

[28] Q. Yang and L. Forrest, "Drug Delivery to the Lymphatic System," in *Drug Delivery: Principles and Applications: Second Edition*, 2016.

[29] S. M. Caliph, W. N. Charman, and C. J. H. Porter, "Effect of short-, medium-, and long-chain fatty acid-based vehicles on the absolute oral bioavailability and intestinal lymphatic transport of halofantrine and assessment of mass balance in lymph-cannulated and non-cannulated rats," *J. Pharm. Sci.*, 2000 doi:10.1002/1520-6017(200008)89:8<1073:AID-JPS12>3.0.CO;2-V.

[30] C. Imada *et al.*, "Improvement of oral bioavailability of n-251, a novel antimalarial drug, by increasing lymphatic transport with long-chain fatty acid-based self-nanoemulsifying drug delivery system," *Pharm. Res.*, 2015, doi: 10.1007/s11095-015-1646-x.

[31] N. L. Trevaskis, L. M. Kaminskas, and C. J. H. Porter, "From sewer to saviour-targeting the lymphatic system to promote drug exposure and activity," *Nature Reviews Drug Discovery*. 2015, doi: 10.1038/nrd4608.

[32] H. Nakamura and H. Maeda, "Cancer chemotherapy," in *Fundamentals of Pharmaceutical Nanoscience*, 2013.

[33] J. D. McAllaster and M. S. Cohen, "Role of the lymphatics in cancer metastasis and chemotherapy applications," *Advanced Drug Delivery Reviews*. 2011, doi: 10.1016/j.addr.2011.05.014.

[34] I. Singh, R. Swami, W. Khan, and R. Sistla, "Lymphatic system: A prospective area for advanced targeting of particulate drug carriers," *Expert Opinion on Drug Delivery*. 2014, doi: 10.1517/17425247.2014.866088.

[35] X. Y. Zhang and W. Y. Lu, "Recent advances in lymphatic targeted drug delivery system for tumor metastasis," *Cancer Biology and Medicine*. 2014, doi: 10.7497/j.issn.2095-3941.2014.04.003.

[36] A. Bernkop-Schnürch, A. Müllertz, and T. Rades, "Self-emulsifying drug delivery systems (SEDDS) – The splendid comeback of an old technology," *Advanced Drug Delivery Reviews*. 2019 doi: 10.1016/j.addr.2019.08.002.

[37] T. Tran, T. Rades, and A. Müllertz, "Formulation of self-nanoemulsifying drug delivery systems containing monoacyl phosphatidylcholine and Kolliphor® RH40 using experimental design," *Asian J. Pharm. Sci.*, 2018, doi: 10.1016/j.ajps.2017.09.006.

[38] M. Grove and A. Mullertz, "Liquid self-microemulsifying drug delivery systems.," *Drugs Pharm. Sci.*, 2007.

[39] T. Tran, S. D. V. S. Siqueira, H. Amenitsch, A. Müllertz, and T. Rades, "In vitro and in vivo performance of monoacyl phospholipid-based self-emulsifying drug delivery systems," *J. Control. Release*, vol. 255, no. March, pp. 45–53, 2017, doi: 10.1016/j.jconrel.2017.03.393.

[40] D. G. Fatouros *et al.*, "Structural development of self-nano emulsifying drug delivery systems (SNEDDS) during in vitro lipid digestion monitored by Small-angle X-ray scattering," *Pharm. Res.*, 2007, doi: 10.1007/s11095-007-9304-6.

[41] G. Pifferi and P. Restani, "The safety of pharmaceutical excipients," *Farmaco*, 2003, doi: 10.1016/S0014-827X (03)00079-X.

[42] J. B. Cannon, "Chemical and physical stability considerations for lipid-based drug formulations," *American Pharmaceutical Review*. 2008.

[43] M. L. Chen, "Lipid excipients and delivery systems for pharmaceutical development: A regulatory perspective," *Advanced Drug Delivery Reviews*. 2008, doi: 10.1016/j.addr.2007.09.010.

[44] GATTEFOSSÉ, "GATTEFOSSÉ," *Compritol® 888 ATO*, 2010.