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REVIEW ARTICLE

Self-emulsifying Drug Delivery System: A Review

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ABSTRACT

Drug development in the past used to be initiated after the identification of most active molecule. However, this approach leads to a number of drawbacks with the problems being that many molecules which are put into development had poor physicochemical such as solubility and stability and biopharmaceutical such as permeability and enzymatic stability properties, as a consequence of which about 40% of new chemical entities fail to reach the market place. At present, a number of technologies are available to deal with the poor solubility, dissolution rate, and bioavailability of insoluble drugs. However, much attention has been focused on lipid-based formulations, with particular emphasis on self-emulsifying drug delivery systems (SEDDSs). SEDDSs are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or one or more hydrophilic solvents and cosolvents/surfactants. On mild agitation followed by dilution in aqueous media, these systems can form fine oil-in-water emulsions or microemulsions (self-micro-EDDS [SMEDDS]). Self-emulsifying formulations spread readily in the gastrointestinal tract, the digestive motility of the stomach and intestine provides the agitation necessary for self-emulsification. SEDDSs produce emulsification with a droplet size between 100 and 300 nm, while SMEDDSs form transparent microemulsions with a droplet size of <50 nm. SEDDSs are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and the extent of absorption.

Keywords: Lipophilic drug, poor solubility, self-microemulsifying drug delivery system, self-emulsifying drug delivery systems

INTRODUCTION

In recent years, drug discovery program has dramatically undergone changes from "empirical-based" to "knowledge-based" rational drug design. Advances in biotechnology and combinatorial synthetic approaches, clubbed with high throughput screening for pharmacological activity, have resulted in increasing number of diverse new chemical entities (NCEs). However, this rational design of molecules does not necessarily mean rational drug delivery since the drug molecules do not always deliver themselves.[1] Drug development in the past used to be initiated after the identification of most active molecule. However, this approach leads to a number of drawbacks with the problems being that many molecules which are put into development had poor physicochemical (solubility and stability) and biopharmaceutical (permeability and enzymatic stability) properties, as a consequence of which about 40% of NCEs fail to reach the market place.[2] Many investigational new drugs fail during preclinical and clinical development, with an estimated 46% of compounds entering clinical development are dropped due to unacceptable efficacy and 40% due to safety reasons.[3] Oral delivery of such drugs is also frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality.[4] At present, a number of

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Table 1: The lipid formulation classification system: Characteristic features, advantages, and disadvantages of the four essential types of "lipid" formulations

Formulation 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	o/w-insoluble surfactants	SEDDS formed without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2 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 cosolvents (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

SMEDDS: Self-microemulsifying drug delivery system, SEDDS: Self-emulsifying drug delivery systems, o/w: Oil-in-water

Table 2: List of typical oil, fatty, and lipid compounds used in the formulation of SEDDS[24-28]

Category	Example
Fatty-acids, salts, and esters	Aluminum monostearate, ethyl oleate, calcium stearate, isopropyl myristate, isopropyl palmitate, magnesium stearate, oleic acid, polyoxyl 40 stearate, propionic acid, sodium stearate, stearic acid, zinc stearate
Fatty alcohols	Benzyl alcohol, butyl alcohol, cetyl alcohol, cetyl esters wax, lanolin alcohols, octyldodecanol, oleyl alcohol, stearyl alcohol
Oils and oils esters	Almond oils, castor oil, cod liver oil, corn oil, cottonseed oil, ethiodized oil injection, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, mono- and diglycerides, mono- and diacetylated monoglycerides, oil-soluble vitamins, olive oil, orange flower oil, peanut oil, peppermint oil, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil
Phospholipids	Lecithin and derivatives
Waxes	Carnauba wax, emulsifying wax, hard fat, hydrophilic ointment, hydrophilic petrolatum, microcrystalline wax, paraffin, rose water ointment, white wax, synthetic paraffin, yellow ointment, yellow wax

SEDDS: Self-emulsifying drug delivery system

Table 3: Some of the common excipients used to formulate SEDDS[29-31]

Oils	Surfactant	Cosurfactant
Oleic acid	Polysorbate 20 (Tween 20)	Ethanol
Castor oil	Polysorbate 80 (Tween 80)	Glycerin
Corn oil	Polyoxyl 35 castor oil (Cremophor EL)	PEG 300
Cottonseed oil	Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	PEG 400
Peanut oil	Polyoxyl 60 castor oil (Cremophor RH 60)	Poloxamer 407
Sesame oil	PEG 300 caprylic/capric glycerides (Softigen 767)	Propylene glycol
Soybean oil	PEG 400 caprylic/capric glycerides (Labrasol)	–
Medium-chain triglyceride	PEG 300 oleic glyceride (Labrafil M 1944CS)	–

SEDDS: Self-emulsifying drug delivery system, PEG: Polyethylene glycol

technologies are available to deal with the poor solubility, dissolution rate, and bioavailability of insoluble drugs. Various formulation strategies reported in literature include incorporation of a drug in oils, solid dispersions, emulsions, liposomes, use of cyclodextrins, coprecipitates, micronization, nanoparticles, permeation enhancers, and lipid-based vehicles [Figure 1and Table 1].[5,6]

LIPID-BASED DRUG DELIVERY SYSTEM

Lipid-based drug delivery systems are experiencing a resurgence of interest lately since their introduction in 1974. However, much attention has been focused on lipid-based formulations, with particular emphasis on self-emulsifying drug delivery systems (SEDDSs), which were shown to improve the oral bioavailability of many drugs, namely progesterone.[7] Lipid formulations are a diverse group of formulations with a wide variety of properties and usually consist of a mixture of excipients, ranging from triglyceride oils through mixed glycerides, lipophilic surfactants, hydrophilic surfactants, and cosolvents. Lipid-based formulations can decrease the intrinsic limitations of slow and incomplete dissolution of poorly water-soluble drugs by facilitating

Table 4: Currently marketed oral lipid-based formulation products[32-38]

Molecule/trade name/ company	Indication	Dose	Type of formulation/ strength	Lipid excipients and surfactants
Amprenavir/Agenerase®/ GlaxoSmithKline	HIV antiviral 1200 mg (8 capsules) B.I.D Soft gelatin capsule, 50, 150	HIV antiviral 1200 mg (8 capsules) B.I.D Soft gelatin capsule, 50, 150	HIV antiviral 1200 mg (8 capsules) B.I.D Soft gelatin capsule, 50, 150	HIV antiviral 1200 mg (8 capsules) B.I.D Soft gelatin capsule, 50, 150
		Pediatrics > 4 years old, <50 kg at 17 mg/kg (1.1 ml/kg) T.I.D; >50 kgat1400 mg (~93ml)B.I.D	Oral solution, 15 mg/ml TPGS (~12%) PEG 400 (~17%), propylene glycol	Oral solution, 15 mg/ml TPGS (~12%) PEG 400 (~17%), propylene glycol
Bexarotene/Targretin®/ Ligand	Antineoplastic	300–750 mg (4–10 capsules) Q.D	Soft gelatin capsule, 75 mg	Polysorbate 20
Calcitriol/Rocaltrol®/ Roche	Calcium regulator	Adults: 0.25–0.5 mcg (1 capsule) Q.D	Soft gelatin capsule, 0.25–0.5 mcg	Fractionated triglyceride of coconut oil (MCT)
		Pediatrics: 10–15 ng/ kg (0.01–0.015 ml/kg) Q.D	Oral solution, 1 μg/ml	Fractionated triglyceride of palm seed oil
Ciprofloxacin/Cipro®/ Bayer	Antibiotic	Antibiotic 15 mg/kg B.I.D. not to exceed the adult dose of 500 mg per dose	Microcapsules for constitution to suspension, 5% or 10% in solid, 50 or 100 mg/ml in suspension	Bottle 1 - diluents: MCT, sucrose, lecithin, water, and strawberry flavor
Cyclosporin A/I. Neoral®/ Novartis	Immunosuppressant/ Prophylaxis for organ transplant rejection	2–10 mg/kg/day, B.I.D. (1–7 capsules)	Soft gelatin capsule, 10, 25, 50, 100 mg	dI-α-tocopherol, corn oil-mono-di- triglycerides, Cremophore RH 40
		2–10 mg/kg/day, B.I.D. (1–7 ml)	Oral solution 100 mg/ml	dI-α-tocopherol, corn oil-mono-di-triglycerides, cremophore RH 40
Cyclosporin A/II. Sandimmune®/Novartis		2–10 mg/kg/day, B.I.D. (1–7 capsules)	Soft gelatin capsule, 25, 100 mg	Corn oil, Labrafil M-2125CS
		2-10 mg/kg/day, B.I.D. (1-7 ml)	Oral solution 100 mg/ml	Olive oil, Labrafil M-2125CS
Cyclosporin A/III Gengraf®/Abbott		2–10 mg/kg/day, B.I.D. (1–7 capsules)	Hard gelatin capsule, 25, 100 mg	Cremophor EL, Polysorbate 80
Cyclosporin A/IV Cyclosporin®/Sidmak		1–9 mg/kg/day 70–700 mg, (1–7 capsules)	Soft gelatin capsule, 100 mg	Labrafac, dI-α-tocopherol glyceryl caprylate, Labrasol, Cremophor EL
Doxercalciferol/Hectorol® Bone care	Management of secondary hyperparathyroidism associated with chronic renal dialysis	10-20 mcg 3 times weekly (4–8 capsules)	Soft gelatin capsule, 0.5, 2.5 μg	Fractionated triglycerides of coconut (MCT)
Dronabinol/Marino®/ Roxane and Unimed	Anorexia or nausea	2.5–10 mg (1 capsule) B.I.D.	Soft gelatin capsule 2.5, 5, 10 mg	Sesame oil
Dutasteride/Avodart®/ GlaxoSmithKline	Treatment of benign prostrate hyperplasia	0.5 mg Q.D. (1 capsule)	Soft gelatin capsule, 0.5 mg	Mixture of mono- and diglycerides of caprylic/ capric acid
Isotretinoin/Accutane®/ Roche	Anticomedogenic	0.5–1.0 mg/kg/day subdivided in two doses (1–2 capsules)	Soft gelatin capsule, 10, 20, 40 mg	Beeswax, hydrogenated soybean oil flakes, hydrogenated vegetable oils, soybean oil
Lopinavir and ritonavir/ Kaletra®/Abbott	HIV antiviral	400/100 mg B.I.D. (2 tablets) or 800/200 mg Q.D. (4 tablets)	Tablet 200 mg lopinavir and 50 mg ritonavir	Sorbitan monolaurate
		400/100 mg B.I.D. (3 capsules)	Soft gelatin capsule. 133.3 mg lopinavir and 33.3 mg ritonavir	Oleic acid, Cremophor EL
		400/100 mg B.I.D. (5 ml)	Oral solution, 80 mg/ml lopinavir and 20 mg/ml ritonavir	Cremophor RH 40, peppermint oil
Progesterone/ Prometrium®/Solvay	Hormone replacement therapy	200–400 mg Q.D. (2–4 capsules)	Soft gelatin capsule, 100, 200 mg micronized	Peanut oil
Ritonavir/Norvir®/Abbott	HIV antiviral	Adults 600 mg (6 capsules) B.I.D.	Soft gelatin capsule, 100 mg	Oleic acid, Cremophor EL

(Contd...)

Table 4: *(Continued)*

Molecule/trade name/ company	Indication	Dose	Type of formulation/ strength	Lipid excipients and surfactants
		Pediatrics 250–450 mg/m2 up to a max. of 600 mg (<7.5 ml) B.I.D.	Oral solution, 80 mg/ml	Cremophor EL, sweetener, dye
Saquinavir/Fortovase®/ Roche	HIV antiviral	1200 mg capsule (6 capsules) T.I.D. without ritonavir, 1000 mg (5 capsules) B.I.D. with ritonavir	Soft gelatin capsule, 200 mg	Medium-chain mono- and diglycerides, dl-α-tocopherol
Sirolimus/Rapamune®/ Wyeth-Ayerst	Immunosuppressant	6 mg (6 ml) loading dose followed by 2 mg (2ml) Q.D.	Oral solution, 1 mg/ml	Phosal 50 PG (phosphatidylcholine, mono- and diglycerides, soy fatty acids, ascorbyl palmitate), polysorbate 80
Tipranavir/Aptivus®/ Boehringer Ingelheim	HIV antiviral	500 mg (2 capsules) with ritonavir 200 mg B.I.D.	Soft gelatin capsule, 200 mg	Cremophor EL, medium chain mono- and diglycerides
Tolterodine tartrate/ Detrol® LA/Pharmacia and Up John	Overactive bladder muscarinic receptor antagonist	2–4 mg Q.D. (1 capsule)	Extended-release hard gelatin capsule, 2, 4 mg	MCT, oleic acid
Tretinoin/Vesanoid®/ Roche	Antineoplastic	45 mg/m2 subdivided (8 capsules) B.I.D.	Soft gelatin capsule, 10 mg	Beeswax, hydrogenated soybean oil flakes, hydrogenated vegetable oils, soybean oil
Valproic acid/Depakene®/ Abbott	Antiepileptic	10–60 mg/kg/day (3–15 capsules)	Soft gelatin capsule, 250 mg	Corn oil

SEDDS: Self-emulsifying drug delivery system, PEG: Polyethylene glycol, MCT: Medium chain triglyceride, TPGS: Tocopheryl polyethylene glycol succinate

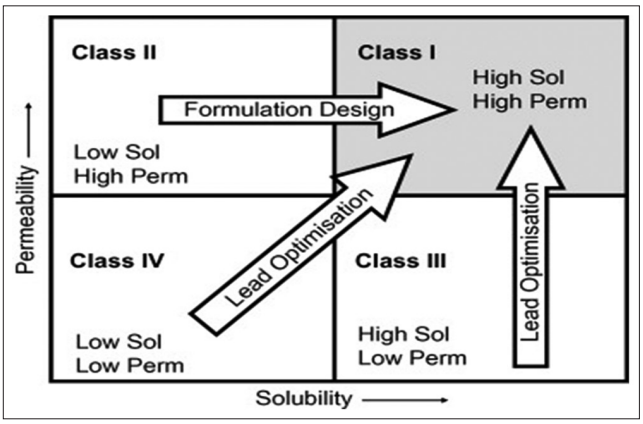

Figure 1: Biopharmaceutical classification system

the formation of solubilized phases from which absorption takes place.[8] The achievement of such phases will not essentially take place from the formulation itself, but alternatively from taking the advantage of the intraluminal processing to which lipids are subjected. The extent of drug absorption from lipid vehicles is significantly affected by the dispersibility of the administered lipid and drug. On the other hand, due to the inherent physical instability, the large volume of the two-phase emulsions, and the poor precision of dose, the use of conventional emulsions is problematic.[9] A formulation approach for avoiding such restrictive problems is the use of microemulsions or SEDDSs. The most famous example of a microemulsion-based system is the Neoral® formulation of Cyclosporine, which result in replacement of Sandimmune®.[10]

For high solubility and high permeability drugs and in some instance for high solubility and low permeability drugs, 85% dissolution in 0.1 N HCl in 15 min can ensure that the bioavailability of the drug is not limited by dissolution. If a drug has reasonable membrane permeability, then often the rate-limiting process of absorption is the drug dissolution step, this is the characteristic property of compounds which can be categorized as biopharmaceutical classification system Class II.[11] Formulation plays a major role in determining the rate and extent of absorption of such drugs from gastrointestinal tract (GIT). There are a number of drug strategies that could be used to improve the bioavailability of Class II drugs, either by increasing the dissolution rate or by presenting the drug in solution in the intestinal lumen. Modification of the physicochemical properties such as salt formation and particle size reduction of the compound can be done to improve the dissolution rate of the drug. Formulation strategies that have been adopted as described below.[12,13]

SEDDSS

SEDDSs are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or one or more hydrophilic solvents and cosolvents/ surfactants. On mild agitation followed by dilution in aqueous media, these systems can form fine oil-in-water emulsions or microemulsions (self-micro-EDDS [SMEDDS]).[14] Self-emulsifying formulations spread readily in the GIT, the digestive motility of the stomach and intestine provides the agitation necessary for self-emulsification. SEDDSs produce emulsification with a droplet size between 100 and 300 nm, while SMEDDSs form transparent microemulsions with a droplet size of <50 nm. SEDDSs are physically stable formulations that are easy to manufacture.[5,15] Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and the extent of absorption.[16]

Limitations

One of the obstacles for the development of SEDDSs and other lipid-based formulations is the lack of good predicative *in vitro* models for the assessment of the formulations. Traditional dissolution methods do not work because these formulations potentially are dependent on digestion in the gut, before release of the drug.[17] To mimic this, an *in vitro* model simulating the digestive processes of the duodenum has been developed. This *in vitro* model needs further refinement and validation before its strength can be evaluated. Further, development will be based on *in vitro-in vivo* correlations, and therefore, different prototype lipid-based formulations need to be developed and tested *in vivo* in a suitable animal model.[18,19]

Few other drawbacks are chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30–60%) which irritate GIT. Moreover, volatile cosolvents in the conventional self-microemulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.[20] The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent. At the same time, formulations containing several components become more challenging to validate.[21]

CLASSIFICATION OF LIPID-BASED DRUG DELIVERY SYSTEM[22-24]

Lipid system includes triglycerides, mono and diglycerides, lipophilic surfactants, hydrophilic surfactants and co-solvents; excipients with a wide variety of physicochemical properties. A classification system was introduced in 2000 to help identify the critical performance characteristics of lipid systems, it is called the lipid formulation classification system (LFCS) [Tables 2-4].

EVALUATION PARAMETERS FOR SEDDS[39-43]

Shape and morphology

Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) are very useful techniques to determine the shape and morphology of lipid nanoparticles. These techniques can also determine the particle size and size distribution. SEM utilizes electron transmission from the sample surface, whereas TEM utilizes electron transmission through the sample. In contrast to photon correlation spectroscopy (PCS) and laser diffraction (LD), SEM and TEM provide direct information on the particle shape and size.

Particle size/size distribution

Particle size/size distribution of solid lipid nanoparticles (SLN) may be studied using PCS, LD, TEM, SEM, AFM, scanning tunneling microscopy, or freeze-fracture electron microscopy. Among these, PCS and LD are the most commonly employed techniques for routine measurement of particle size.

Crystallinity and polymorphism

Determination of the crystallinity of the components of SLN/NLC formulations is crucial as the lipid matrix as well as the incorporated drug may undergo a polymorphic transition, leading to a possible undesirable drug expulsion during storage. Lipid crystallinity is also strongly correlated with drug incorporation and release rates. Thermodynamic stability and lipid packing density increase, whereas drug incorporation rates decrease in the following order: Supercooled melt, α-modification, β′-modification, and β-modification. However,

lipid crystallization and modification changes might be highly retarded due to the small size of the particles and the presence of emulsifiers. Differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) are two widely used techniques to determine the crystallinity and polymorphic behavior of the components of the SLNs/NLCs. DSC provides information on the melting and crystallization behavior of all solid and liquid constituents of the particles, whereas XRD can identify specific crystalline compounds based on their crystal structure. DSC utilizes the fact that different lipid modifications possess different melting points and melting enthalpies.

Polydispersity index (PI)

As SLNs are usually polydisperse in nature, measurement of PI is important to know the size distribution of the nanoparticles. Lower PI value indicates that the nanoparticle dispersion is uniformly distributed. Most of the researchers accept PI value <0.3 as optimum value. PI can be measured by PCS.

Zeta potential (ZP)

The ZP indicates the overall charge a particle acquires in a specific medium. Stability of the nanodispersion during storage can be predicted form the ZP value. The ZP indicates the degree of repulsion between close and similarly charged particles in the dispersion. High ZP indicates highly charged particles. In general, high ZP (negative or positive) prevents aggregation of the particles due to electric repulsion and electrically stabilizes the nanoparticle dispersion. On the other hand, in case of low ZP, attraction exceeds repulsion and the dispersion coagulates or flocculates. However, this assumption is not applicable for all colloidal dispersion, especially the dispersion which contains steric stabilizers. The ZP value of −30 mV is enough for good stabilization of nanodispersion. The ZP of the nanodispersions can be determined by PCS.

Drug content and drug entrapment efficiency

The total drug amount in the formulation was determined spectrophotometrically. Entrapment efficiency in the nanoparticles was determined by the following formula:

Wt. of the drug incorporated % entrapment efficiency = Wt. of the drug initially taken

In vitro release studies[44]

The dialysis bag diffusion technique was used to study the *in vitro* drug release of nanoparticles. The prepared nanoparticles are placed in the dialysis bag and immersed in dissolution media. The entire system was kept at 37 ± 0.5°C with the continuous magnetic stirring. Samples were withdrawn from the receptor compartment at predetermined intervals and replaced by fresh medium. The amount of drug dissolved was determined with UV spectrophotometer at maximum wavelength.

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