REVIEW ARTICLE

Recent Developments in Self-microemulsifying Drug Delivery System: An Overview

Navdeep Gahlawat, Ravinder Verma, Deepak Kaushik

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

Abstract

Self-microemulsifying drug delivery system (SMEDDS) has emerged as a distinctive approach for the improvement of low bioavailability, high intra- and inter-subject changeability, and absence of dose proportionality difficulties associated with hydrophobic (water-repelling) drugs due to their incomparable potentials. SMEDDS is isotropic mixture of drug, surfactants, cosurfactants, and oil which have unique ability to form fine o/w microemulsion on slight shaking followed by dilution with fluid, such as gastrointestinal fluid. *In vitro* features such as concentration of surfactants, ratio of oil to surfactant, polarity of emulsion, zeta potential, and size of droplet play a vital role in drug absorption orally. It would be more accurate to say that it disperses out of oily droplets into gastrointestinal tract media, resulting in the development of equilibrium among outer dispersed media and the drugs dissolved in oily droplets in spite of saying that the drug is released from SMEDDS. This analysis is useful for the better understanding of SMEDDS for its recent advancements with an emphasis on absorption pathway of lipids, patents, and research work. The present article provides a discussion on recent developments such as self-microemulsifying mouth dissolving film, supersaturable, herbal, and sponges carrying SMEDDS.

Key words: Solid SMEDDS, Bioavailability, Self-emulsification, Application of SMEDDS, Herbal SMEDDS, Transportation of lipids

INTRODUCTION

About 40% of new drugs exhibit poor water solubility, resulting in lack of dose proportionality, high inter- and intra-subject variability, and low erratic oral bioavailability. For the pharmaceutical preparation to succeed in market, it should fulfill all the criteria such as stability, patient compliance, cost of product, and bioavailability.[1] There are several approaches for improvement in bioavailability such as use of crystal polymorphism, surfactants, salt formation, pulverization, size reduction of particles, solid dispersion, microemulsion, liposomes, complex formation, nano-particles, nano and micro-spheres, use of prodrugs and use of permeation enhancer.[2,3] Recently, preparation of formulations with lipid base to upsurge the oral bioavailability of drugs with poor aqueous solubility is in trend. Self-dispersing lipid formulations are classified into two categories: (1) Self-emulsifying drug delivery system (SEDDS) and (2) self-microemulsifying drug delivery system (SMEDDS).

SEDDS is the isotropic mixture of cosolvents/cosurfactants, solid or liquid surfactants, one or more hydrophilic solvents, and natural or synthetic oils. These result in the formation of o/w type emulsion or microemulsion in gastrointestinal tract (GIT) due to agitation which is provided by gastric and intestine motility during digestion which is necessary for self-emulsification.[4]

SMEDDS is homogeneous and isotropic mixture of drug, oil, surfactant, cosurfactant, and cosolvent. Dilution method and water titration methods are used to plot ternary phase diagram for the identification of best emulsifying region. SMEDDS is used to solve the problems of all Biopharmaceutical Classification System (BCS II) drug which possess issues of high molecular weight, low solubility, gastric irritation, enzymatic degradation, pre-systemic first pass-effect, low bioavailability and stability of drug.[2,3]

Address for correspondence:
Deepak Kaushik, Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak - 124001, India. Tel.: +91-9315809626.
E-mail: deepkaushik@rediffmail.com

Received: 11-12-2018
Revised: 01-03-2019
Accepted: 13-03-2019

MECHANISM OF SELF-EMULSIFICATION

In SMEDDS, the free energy formed may either be positive or very low or it may even be negative as a result of which thermodynamic spontaneous emulsification takes place. The interface between the continuous aqueous phase and oil is formed on the addition of a binary mixture (non-ionic surfactant/oil) to water. It has been found that self-emulsification take place due to the penetration of water into the Liquid Crystalline (LC) phase that is formed at the water-oil/surfactant interface into which water can penetrate easily, assisted by gentle agitation. After water penetration to a certain limit, it results in the disruption of interface and droplet formation takes place. According to the researches of Reiss, self-emulsification takes place when the entropy change favoring the dispersion is higher than the energy essential to increase the surface area of the dispersion. It can be expressed by:

$$\Delta G=\sum Ni\pi r2\sigma$$

Where,

ΔG – free energy accompanying the process (apart from the free energy of mixing),

N – Total number of droplets,

r – Radius of the droplets,

σ – Energy at the interface.[5]

COMPONENTS OF SMEDDS

Lipid

Lipids are responsible for the solubilization of hydrophobic drugs, fluidization of the intestinal cell membrane, enhancement of dissolution rate, and solubility in gastrointestinal (GI) fluids, and they further protect the drug from chemical and enzymatic degradation by altering pharmaceutical properties of drug. Most drugs used in SMEDDS are hydrophobic in nature and have greater solubility in triglycerides than surfactants. Hence, they are used in 40–80% concentration. Various lipids used in SMEDDS are summarized in Table 1.[6,7,12]

Surfactant

Surfactants play an important role in the enhancement of solubility of hydrophobic drug in oil, dispersion of liquid vehicle on dilution in GIT fluids, improvement of bioavailability by increasing permeability, prevention of precipitate formation within the GI lumen, and prolonging the presence of drug moiety in soluble form, which results in effective absorption, and 30–60% concentration is used. They concentrate at oil-water interface and settle at inner stage (internal phase) in emulsion and make more stable microemulsion. Various surfactants used in SMEDDS are summarized in Table 1.[8,18]

Cosurfactant

In SMEDDS, for the purpose of reducing interfacial tension, high concentrations of surfactants is required that may cause gastric irritation. Thus, cosurfactants are employed to lessen the concentration of the surfactant, to dissolve large amount of either lipophilic drug or hydrophilic surfactant in lipid base, and to decrease interface of oil/water which results in immediate formation of microemulsion. Cosurfactants ranging between hydrophile-lipophile balance (HLB) values

Table 1: List of various excipients used in SMEDDS formulation[6-18]

Lipids	Surfactants	Cosurfactants	Cosolvents
Labrafac CC	Tween 85	Hexanol	Ethanol
Isopropyl myristate	Span 20	Pentanol	PEG
Capmul MCM	Capryol 90	Octanol	Carbitol
Maisine 35-1	Lauroglycol 90	Ethanol	Transcutol P
Akoline MCM	Labrafil M 1944 CS	PEG 400	PG
Capmul MCM C-8	Cremophor EL	Labrasol	Glycerin
Capmul GMS-50K	Cremophor RH40	Transcutol P	Tetrahydrofurfuryl alcohol
Labrafil M 1944 CS	Acconon MC8	Capryol 90	Methoxy PEG
Brij	Tween 20	Capyrol PGMC	Isopropanol
Stepan GDL	Labrasol	PEG 300	Butanol
Caprol ET	Tween 80	PEG 600	Benzyl alcohol
Labrafac 1349	Pluronic F 127	PG-dicaprylate/dicaprate	PEG ether (glycofurol)
Labrafac PG	Pluronic L 64	Carbitol	Ethylene glycol
Labrasol	Tagat TQ	Akoline MCM	PG
Lauroglycol 90	Span 80	Tween 85	Glycerol

SMEDDS: Self-microemulsifying drug delivery system, PEG: Polyethylene glycol, PG: Propylene glycol

of 10–14 are widely used with the surfactant to reduce interfacial tension to a great extent to achieve transient negative value and to provide sufficient flexibility to interfacial film.[9-12] Various cosurfactants used in SMEDDS are enclosed in Table 1.

Cosolvents

Cosolvents used for oral dosage form are ethanol, polyethylene glycol (PEG), and propylene glycol as they helps in improvement of solubility of the drug or surfactants in a lipidic base, facilates in the dispersion process and starts earlier phases of dispersion and can perform action of co-surfactant in micro-emulsion system. Alcohol and other volatile solvents migrate into soft gelatin capsule shell and cause precipitation of lipophilic drug. However, lipophilic drug of alcohol-free products has limited dissolution ability. Hence, proper choice of solvent is done during the selection of components. Commonly used cosolvents in SMEDDS are summarized in Table 1.[11-17]

TRANSPORTATION OF LIPIDS

The GIT is richly supplied with both lymphatic and blood vessels. Hence, material or drugs that are absorbed through the epithelial cells of the small intestine possibly may enter either throguh blood capillaries or lymphatic. Majority of drugs or materials are transported into blood capillaries due to high flow rate (500-fold) higher than that of intestinal lymph. Lymphatic transport of drugs takes place when the drug shows high solubility in triglycerides (>50 mg/ml) and is highly lipophilic (logP >5).[18,19] These drugs are absorbed through intestinal lymph vessels by associating with developing lipoproteins in the enterocytes. Triglycerides are the most commonly used excipients in lipid-based drug delivery. When compared with long-chain glycerides, medium-chain glycerides show complete digestion with high solvent capacity. Monoglycerides and long-chain fatty acids (FAs) are reesterified to triglycerides within the intestinal cells, fused into the chylomicrons, and secreted out from the intestinal cells by exocytosis into the lymph vessels by resynthesized triglyceride accumulation within the Golgi apparatus. Chylomicrons are formed by the addition of proteins and phospholipids.

FACTORS INFLUENCING SMEDDS FORMULATION

Different factors affecting SMEDDS formulations are discussed as follows:

Nature and dosage of drug

For the preparation of high-dose formulations into SMEDDS, they need to have good solubility in at least one of the components of the formulation. Drugs having inadequate solubility in lipids are most difficult to be delivered by SMEDDS.[20]

Polarity of the lipophilic phase

This factor affects the drug release from emulsion or SMEDDS. Polarity of droplet depends on HLB value, degree of unsaturation and chain length of FAs, and molecular weight of micronized FAs.[16]

Charge on droplet of emulsion

Many physiological studies show that the potential of absorptive cells and all other cells in body are negatively (−ve) charged with respect to mucosal solution in lumen. Charge may be positive in some formulations.

Equilibrium solubility measurement

It is done to determine the possible cases of precipitate formation in the gut. Pouton's study found that formulation in which crystallization occurs may take 5 days to attain equilibrium and drug can continue to be in a supersaturated state for 1 day (24 h) after the early emulsification process.[21,22]

APPLICATION OF SMEDDS

Various applications of SMEDDS are discussed as follows:

Improvement in solubility and bioavailability

Multifold increase in bioavailability of BCS class-II drugs by improving solubility and dissolution rate of the drugs.

Protect drug from biodegradation

Many drug formulations are degraded in physiological fluids/system due to change in the pH around drug. Such as acidic pH in stomach leads to enzymatic or hydrolytic degradation, etc. SMEDDS formulation prevents drug from biodegradation by forming an obstacle among the drug and the degrading environment which is formed due to LC phase.[23]

No effect of lipid digestion process

This drug delivery system is unaffected from lipolysis because this system is not degraded by the action of pancreatic lipases and bile salts because these help in self-emulsification of formulation only.[2]

Enhance drug loading capacity

Formulation excipients provide high solubility of drug which results in high drug loading capacity of the formulation.[4]

SMEDDS for herbal drugs and traditional medicines

A large number of herbal drugs and traditional medicines are being exploited and used for the development of SMEDDS because most of them have volatile and fixed oils.[13,24]

Delivery of peptides

This drug delivery system provides protection from enzymatic degradation in GIT due to which this system is suitable for delivery of peptides, hormones, enzyme substrate/inhibitors.

Controlled release formulation

Polymer addition in composition of SMEDDS provides prolong/control release of medicament.[26-28]

RESEARCH WORK ON SMEDDS

SMEDDS is novel approach for enhancing bioavailability by avoiding dissolution step for all BCS class drugs. Many research works have been done on SMEDDS which is summarized in Table 2.

Patents on SMEDDS

The various patents on SMEDDS are summarized in Table 3.

RECENT TRENDS IN SMEDDS

Following is a brief discussion on the recent trend in SMEDDS.

Supersaturable SEDDS (S-SEDDS)

Higuchii T. proposed the potential for supersaturated drug formulations for the improvement of drug absorption. Polyvinylpyrrolidone and water-soluble cellulosic polymers such as hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), and hydroxyl propyl MC phthalate are useful in generating a supersaturatable state with a number of poorly water-soluble drug. A high payload S-SEDDS was deeply studied to improve the oral bioavailability of a drug candidate having poor water solubility, silybin. HPMC was employed as a precipitation inhibitor.[2]

Self-microemulsifying mouth dissolving film (SMMDF)

SMMDF was developed by Xiao *et al*. for water-soluble drugs. Indomethacin was produced by fusing

Table 2: Research works on SMEDDS[25,29-60]

Name of drug	Oil/lipid	Surfactant	Co-surfactant	Co-solvent	Carrier	Reference
Atorvastatin	Labrafil, estol, isopropyl myristate	Cremophor RH 40, cremophor EL	PG, PEG 400, transcutol	-	-	[25]
Simvastatin	Capryol 90	Cremophor EL	Carbitol	-	-	[25]
Seocalcitol	Viscoleo (MCT), sesame oil (LCT)	Cremophor RH	Akoline	-	-	[25]
Silmyrin	Ethyl linoleate	Tween 80	Ethyl alcohol	-	-	[25]
Acyclovir	Crodamol GTCC	Labrasol	Plurololeque CC 497	Macrogol 400	-	[29]
Oxyresveratrol	Capryol 90	Cremophor RH 40	Tween 80, labrasol	-	-	[30]
Nelfinavir mesylate	Maisine 35-1	Tween 80	Transcutol HP	-	-	[31]
Atorvastatin	Capmul MCM	Tween 20	Tetraglycol	-	Mannitol, lactose	[32]
Resveratrol	Ethyl oleate, castor oil, olive oil	Tween 80, triton X-100,	PEG 400, glycerol, glycol ether	-	-	[33]
Valsartan	Gelucire 44/14 (30%)	Solutol HS 15 (40%)	Transcutol *P* (30%)	-	-	[34]
Olmisartan Medoxidil	Acrysol EL 135	Tween 80 (33%v/v)	Transcutol *P* (33%v/v)	-	-	[35]

(*Contd..*)

Table 2: (*Continued*)

Name of drug	Oil/lipid	Surfactant	Co-surfactant	Co-solvent	Carrier	Reference
Buparvaquone	Capryol 90 (9.82%)	Cremophor EL (70.72%)	Labrasol (17.68%)	-	-	[36]
Bleomycin, ifosamide	Isopropyl myristate	Kolliphor RH 40 and labrasol	Capryol 90, transcutol HP	Cremophor RH 40	-	[37]
Leuprolein	Capmul MCM (30%m/m),	Cremophor EL (30%m/m)	Captex 355 (30%m/m)	-	-	[38]
Lovastatin	Capryol 90 (20%)	Cremophor RH 40 (40%)	Transcutol *P* (40%)	-	-	[39]
Danzaol	Capmul MCM	Tween 80	Transcutol HP	-		[40]
Paeonol and borneol	Ethyl oleate (20%)	Cremophor EL (45%)	Transcutol *P* (35%)	-	-	[41]
Mangiferin phospholipid	Cremophor EL 35 (48%)	Labrasol (32%)	-	-	-	[42]
Resveratrol	Castor oil/Capmul MCM (1:1)	Kolliphor RH 40/Kolliphor EL (1:1)	-	-	-	[43]
Clopidogrel napadisilate	Paceol	Cremophor RH 60	Transcutol HP	-	-	[44]
Apigenin	Capryol 90 (10%)	Cremophor EL (60%)	Transcutol HP (30%)	-	-	[45]
Domperidone	Labrafac CC (25%)	Tween 80 (55%)	Transcutol HP (20%)	-	-	[46]
Candesartan cilexetil	Capryol 90 (5%)	Tween 80 (35%)	Tetraglycol (60%)	-	Neusilin and fujicalan	[47]
Paeony glycoside	Ethyl oleate (16.27%)	Cremophor RH 40 (43.34%)	Transcutol P (18.70%)	-	-	[48]
Dutasteride	Capryol 90 (39.25%)	Cremophor EL (25.90%)	Transcutol HP (34.3%)	-	-	[49]
Lovastatin	Capryol 90 (20%)	Cremophor RH (40%)	Transcutol HP (40%)	-	-	[50]
Fenofibrate	Lauroglycol FCC (60%)	Solutol HS 15 (27%)	Transcutol P (13%)	-	-	[51]
Telmisartan	Paceol (28.93%)	Labrasol (80%)	Transcutol (28.08)	-	-	[52]
Lornoxicam	Labrafil M 1994 CS	Kolliphor HS 15	Transcutol HP	-	-	[53]
Atorvastatin	Coconut oil and isopropyl myristate	Tween 80	PEG 400 and glycerin	-	-	[54]
Ritonavir	Imwitor 988	Cremophor EL/Cremophor RH 40 (1:1)	Capmul GMS K-50	-	-	[55]
25-OCH3-PPD	Labrafil M 1944 (30%)	Cremophor EL (50%)	Glycerin (20%)	-	-	[56]
Oleanic acid	Ethyl oleate (15)	Cremophor EL (35)	Ethanol (50)	-		[57]
Sirolimus	Labrafil M 1944 CS	Cremophor EL	Transcutol P	-	MCC, Na- MCC, lactose	[58]
Lurasidone HCl	Capmul MCM (18%)	Cremophor RH 40 (14%)	Soluphor P (68%)	SMEDDS		[59]
Naproxen	Peceol (12%)	Miglyol 812, Gelucire 44/14	Solutol HS 15	S-SMEDDS	HPMC	[60]

SMEDDS: Self-microemulsifying drug delivery system, PG: Propylene glycol, HPMC: Hydroxypropyl methylcellulose, MCC: Microcrystalline cellulose

Table 3: Patents on SMEDDS[61-78]

U.S. Patent/ application no.	Inventors	Type	Drug/active ingredient	Remarks	Reference
14/802,837	Hassan (2017)	SMEDDS	Mitotane	In this invention, a method was developed which will enhance the bioavailability of a poorly water soluble drug using a surfactant and a polar lipids wherein the formulation is free of a polar sovent	[61]
7815933	Holmberg and Klaveness (2016)	SMEDDS/SNEDDS/ SEDDS	-	Prepared coated tablet and capusules using 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), polysorbate 20 (15–35%)	[62]
9278070	Coulter (2016)	Dried o/w emulsion (mini beads)	Cyclosporin A (8.0–12.0%)	Mini beads were prepared using 2 (2ethoxyethoxy) ethanol (15.0–19.0%); polyethoxylated castor oil (8.0–12.0%); caprylic/capric triglyceride (2.0–6.0%); sodium dodecyl sulfate (1.0–4.5%); Dsorbitol (3.0–8.0%); and gelatin (45.0–55.0%)	[63]
8728518	Liu (2014)	SMEDDS	Butylphthalide (1%–65%)	10%–65% of an emulsifying agent and 0%–64.7% of excipients were used	[64]
8652803	Kram (2014)	Microemulsion-based tissue treatment	Paraffin-embedded biological samples	Deparaffinizing was done	[65]
20110160168	Dhingra (2011)	SMEDDS	Testosterone	Formulation enhanced solubility, stability, absorption, and metabolism of lipophilic drug by preparing with sterol/sterol esters which results in enhancement of bioavailability of drug	[66]
20100331356	Legen and Igor (2010)	SMEDDS	Imwitor 308	Microemulsion and SMEDDS enhanced solubility of formulation, containing an oil, surfactant, cosurfactant, and cosolvent	[67]
7588786	Khan *et al.* (2009)	SNEDDS	Coenzyme Q_{10}	SNEDDS formulations were based on eutectic mixture which contained pharmacologically effective drug and essential oils. This SNEEDS was further converted to s-SMEDDS using copolymer of vinyl pyrrolidine and vinyl acetate, maltodextrin, and MCC	[68]
20080319056	Zhentao *et al.* (2008)	SEDDS	Butylphthalide	SEDDS formulation improved absorption of drug by increasing contact area between butylphthalide and mucous membrane of GIT	[69]
20070190080	Friedman (2007)	SMEDDS	-	This invention gave composition of BCS II class drug, dispersed low crystalline form in emulsion type composition of oily-solvent and water soluble solvent, emulsifier in small amount and emulsion of 1 μ mean droplet size is obtained on dilution with physiological fluids. This formulation particularly facilitates biological activity or improves clinical activity	[70]

(Contd..)

Table 3: (*Continued*)

U.S. Patent/ application no.	Inventors	Type	Drug/active ingredient	Remarks	Reference
20060275358	Lin and Jing (2006)	SMEDDS	Coenzyme Q_{10}	This SMEDDS formulation contained hydrophilic surfactant and lipophilic cosurfactant. HLB value of surfactant should be greater than 12 and HLB value of cosurfactant should be less than 8, respectively, which improve bioavailability many times	[71]
20040248901	Lee and Jin (2004)	SMEDDS	Itraconazole	This formulation contained itraconazole drug, oil, and surfactant. Drug was dissolved to form mucoid phase, and mucoid phase is dissolved in water to form microemulsion which greatly improves bioavailability	[72]
6652865	Benameur *et al*. (2003)	SMEDDS	Simvastatin	A method of reducing effect of intestinal metabolism on drug using other excipients in formulation	[73]
6436430	Mulye and Nirmal (2002)	SEDDS	Cyclosporin A	This formulation used lipophilic drug (cyclosporine) with pharmaceutical carrier (PG esters of Csub. 6–Csub. 18 FA) and non-ionic surfactant which improved bioavailability	[74]
6312704	Farah and Denis (2001)	SMEDDS	-	This formulation contained mixture of C_8-C_{18} polyglycolized glycerides and cosurfactant was selected from group comprising lauric esters of PG, oleic esters of polyglycerol, and ethyl diglycol	[75]
6309665	Barthelemy and Benameur	Sustain release Micro-emulsion	-	Extended release of active moiety	[76]
6890547	Takada and Murakami	Self-emulsifying suppository	Glycyrrhizin	Improved absorption of drug due to enhancement in surface area	[77]
6057289	Mulye and Nirmal (2000)	SEDDS	Cyclosporin A	This formulation contained lipophilic drug (cyclosporine) with effective amount of fatty acids having 6–22 carbon atoms and non-ionic surfactant	[78]

SMEDDS: Self-microemulsifying drug delivery system, SEDDS: Self-emulsifying drug delivery system, HLB: Hydrophile-lipophile balance, PEG: Polyethylene glycol, PG: Propylene glycol, MCC: Microcrystalline cellulose, s-SMEDDS: Solid SMEDDS, SNEDDS: Self-nanoemulsifying drug delivery system

self-microemulsifying segments with a solid carrier (microcrystalline cellulose [MCC], low-substituted HPMC, and hypromellose). The SMMDF break inside within 20 sec. and discharged medicament completely within 5 min in the disintegration medium with globule size of 28.81 ± 3.26 nm. Measurement units were according to criteria of the Chinese Pharmacopeia 2010 for consistency parameters. Pharmacokinetic parameters such as T-max, C-max, and area under the curve (AUC) compared between SMMDF and fluid SMEDDS were measured. C-max and AUC for SMMDF were found to be considerably higher than that of normal mouth dissolving film or tablet, and T-max of SMMDF was found to be essentially diminished. Results concluded that SMMDF is another promising dosage form that has remarkable attributes of accommodation, rapid action, and improved oral bioavailability of a poorly water-soluble drug.[10]

Formulations of lecithin-linker for SE delivery of nutraceuticals

Chu *et al*. studied lecithin-linker microemulsions in which soybean lecithin is blended with lipophilic and hydrophilic linkers. Lecithin-linker creates self-emulsification with β-sitosterol and β-carotene. The grouping of the sorbitan monooleate (lipophilic linker) was done to reduce the development of fluid precious stones. Grouping of hydrophilic linkers, i.e., PEG-6- caprylic/caprylic glycerides and decaglyceryl caprate/caprylate, was steadily checked until clear microemulsions were formed. The single stage clear microemulsions were weakened, and a stable emulsion was created with droplet size near 200 nm. Pseudoternary stage charts were used to assess the procedure of weakening of microemulsion pre-concentrates (blends of lecithin, oil, and linkers with practically no water) with fed-state simulated intestinal fluid (FeSSIF). It was resolved that self-emulsification is acquired when the early phases of the weakening produce a single stage microemulsions. Numerous stages were developed to avoid production of insecure emulsions with substantial size drop in early stages. An *in vitro* porousness study directed that steady emulsions with size of droplet ranging from 150 to 300 nm create substantial and irretrievable penetration of β-carotene to digestive system of sheep. Dialyzer chamber is used to isolate precarious emulsions.[10]

Sponges carrying SMEDDS

Josef *et al*. fabricated sponges carrying SMEDDS for improving solubility of lipophilic drugs but their liquid nature was one limitation to their wide application. Their expansion in sponge produced using a hydrophilic customary polymer is another system for plan of SMEDDS. The nanosponge structures focused on inspecting in electron microscopy and little edge X-pillar diffusing. The oil beads were dried and SMEDDS of size 9 nm in the dried sponge was found. The sponge was rehydrated, and the presence of SMEDDS in the rehydrated sponge was affirmed. SMEDDS containing Nile red (soluble in all rehydrated and dry sponges) discharges drop-wise from the nano-sponge at rate that contingent on the method used for drying. It was discovered that the drying plan incredibly influences the water take-up of the nanosponge. The mix of sponge and SMEDDS might be a way to give a solid structure for SMEDDS that can deal with use of the delivery of hydrophobic medicament.[10]

Herbal SMEDDS

SMEDDS provided fluids that filled hard gelatin capsules, which were taken into consideration for formulating a safe and stable dosage forms for herbal extracts. The solubility of the herbal extracts in a number of vehicles was determined. Pseudoternary phase diagrams were drawn to study the microemulsification existence area. Dissolution method investigated the release rate of herbal extract. SMEDDS was considered for precipitation, particle size distribution, and clarity. Development and screening of formulations were done on the basis of the results of solubility and phase diagram. Warke *et al*. used the improved preparation for *in vitro* dissolution which comprised of Cremophor RH 40 (40%), Plurol Oleique (30%), and herbal extract (30%) and showed complete discharge in 10 min. SMEDDS successfully passes the stability testing under storage conditions as per ICH guidelines for 3 months. From SMEDDS, improved dissolution profiles of herbal extracts were established. SMEDDS appeared as an amazing approach to increase the bioavailability and solubility of herbal drugs.[10,79-82]

Self-double-emulsifying drug delivery system (SDEDDS)

SDEDDS has the ability to instantly emulsify to double emulsions, i.e., water-in-oil-in-water (w/o/w) in the mixed aqueous GI surroundings in which drug is enclosed (encapsulated) in internal phase which is water of double emulsions. SDEDDS was used to enhance the oral absorption of a peptide-like drug and pidotimod with relatively high solubility and low permeability.[83]

Positively charged SEDDS

One of the most common difficulties faced by the scientists in formulation was to discover the methods for the improvement of oral bioavailability of drugs with poor water solubility. This positively charged SEDDS results in increase in the bioavailability than the SEDDS having negative charge. Cationic lipids are used in these types of systems. For example, positively charged SMEDDS of meloxicam was prepared using the oil components (ethyl oleate, arachis oil, and sunflower oil), a cationic lipid (oleylamine), and surfactants (combination of tween 80 and span 80).[83]

Self-microemulsifying floating dosage form

Drug having low solubility, undergoing pre-systemic metabolism and irregular absorption of drug throughout the GIT, faces low oral bioavailability. Floating system increases residence time of drugs in the stomach which results in prolonged release of the drugs. The new floating formulation of Furosemide prepared by its adsorption onto a blend of high functionality excipients, matrix forming polymers such as HPMC E50 LV and HPMC K4M and $NaHCO_3$ (a gas-generating agent) to attain a floating matrix with controlled release drug profile.[2] In another experiment, floating beads of alginate containing SEDDS of tetrahydrocurcumin were developed to enhance solubility of drug and extend the time of gastric residence. Using different proportions of calcium chloride, water-soluble pore former and sodium alginate in formulation of beads gave different effects on their ability to float and rates of the release of drugs *in vitro*.[84]

SE phospholipid suspension (SEPS)

SEPS contains a large amount of phospholipids that help the drug to stay solubilized under *in vivo* conditions, which is necessary for bioavailability improvement. Phospholipids are endogenous lipids with effcient *in vivo* emulsification ability. This formulation requires lesser quantity of cosurfactant/surfactant and thus is comparatively safe and does not cause any serious health complication.[84]

SE capsules

In conventional SE formulations, if permanent phase separation of the microemulsion happens, enhancement in absorption of drug cannot be anticipated. For management of this problem, sodium dodecyl sulfate was used in SE preparations. Supersaturatable SEDDS was designed for a parallel purpose using small amounts of HPMC (and/or other polymers) in the formulation to avoid the precipitation of drug by producing and retaining a supersaturated state *in vivo*. The resulting preparation contained reduced amounts of surfactant, thus minimiging side effects of drug in GIT. Liquid self-emulsifiable materials can also be filled into the capsule shells in solid or semisolid states obtained by the addition of solid carriers such as polymers and adsorbents. For example, the presence of a solid PEG matrix neither interfered with the self-microemulsification process nor with the drug solubility. These are usually prepared either as liquids or encapsulated in soft gelatin capsules.[85]

The conventional liquid SMEDDS had some drawbacks in the process of manufacturing, leading to high costs of productions. These were difficult to use and also had problems with physical incompatibility with the shells of soft gelatin capsules. They presented storage problems as well. Physical incompatibilities of liquid SMEDDS can be prevented with filling S-SMEDSS in the capsules. In case of semisolid, excipients are first melted and then filled into capsules. Contents of the capsule then solidify at room temperature.[3] Oral administration of SE capsules improved patient obedience when compared to the earlier used route, i.e., parental. For example, low molecular weight heparin (LMWH) was available clinically only through the parental route for the management of venous thromboembolism. Oral LMWH therapy was explored by Ito Y which was filled in hard gelatin capsules. LMWH was dispersed into the SMEDDS and the mixture was then solidified to powders using three types of adsorbents, i.e., magnesium aluminum silicate (Neusilin™ US2), silicon dioxide (Sylysia™ 320), and microporous calcium silicate (Florite™ RE). Finally, these solids were packed into hard gelatin capsule shells. In another research, SE tablets of gentamicin (initially used parentally or topically) were prepared using such adsorbents.[85,86]

Capsule filling is the most common and simplest method for the encapsulation of solids, liquids, or semisolid SE preparations. Benefits of capsule are the simplicity of their production, high drug loading potential up to 50% w/w, and its suitability for low-dose drug high potency. For filling of liquid preparations, it mainly involves two steps: Filling of the preparation into the capsule shell followed by the sealing of cap and body of the capsule either by banding or microspray sealing.[84]

SOLID SMEDDS (S-SMEDDS)

This novel technology provides an effective substitute to the conventional liquid SMEDDS for drugs having poor solubility. S-SMEDDS is prepared by adding semisolid/liquid SE constituents into powders or nanoparticles. Different solidification methods such as spray drying, adsorption onto solid carriers, melt granulation, and melt extrusion techniques are used by which it is transformed into solid SE nanoparticles. These can be processed into other solid SE dosage forms such as capsules, solid dispersions, dry emulsions, microspheres, nanoparticles, suppositories, implants, beads, pellets, and tablets.[80]

SE solid dispersions

Serajuddin pointed out that problems associated with solid dispersions such as manufacturing and stability can be reduced using SE excipients. These excipients have the ability to improve the absorption of drugs with poor solubility. SE excipients such as Gelucire 1-50/02, Gelucire 1-44/14, Transcutol, Labrasol, and tocopheryl PEG 1000 succinate have been used extensively in such preparations.[86] They may also be filled directly into hard gelatin capsule shells in the molten state due to the availability of self-dispersing waxy semisolid excipients. Gelucire 44/14 and Gelucire 50/02 are employed for this purpose because these excipients are semisolid and can be filled directly into the capsules in liquefied state. Gelucire improves the

absorption of drug due to its high surface activity. Gupta *et al*. prepared SE solid dispersion granules using the hot melt granulation method for seven drugs, which includes four drugs containing carboxylic acid (-COOH) group, a hydroxyl group (-OH) containing drug, an drug containing amide group (phenacetin), and a drug with no proton donating groups (progesterone) in which Neusilin US2 was appointed as surface adsorbent, while Gelucire 50/13 was hired as the dispersion carrier.[85]

Dry emulsions

These are the powdered solid dosage forms which instantly get emulsified on the addition of water in the formulation. They can be obtained by emulsifiable glass system, freeze drying, and spray drying. The most interesting outcome in this field is the recently formulated enteric coated dry emulsion preparation of amlodipine with dextrin as a carrier for the transport of peptide and protein drugs orally by Toorisaka *et al*. The preparation consisted of a vegetable oil, surfactant, and pH responsive polymer.[10] Lately, Cui *et al*. formulated dry emulsions by spreading liquid o/w emulsions on a flat glass, drying them, and then triturating it to powders.[4] Bamba *et al*. described the use of amorphous cryoprotectants for freeze drying of o/w emulsion. Vyas *et al*. prepared a dry emulsion of griseofulvin using mannitol as the cryoprotectant. Corveleyn *et al*. prepared formulation of lyophilized dry emulsion tablets and studied parameters that affect the addition of amorphous cryoprotectants and a slow cooling rate have the utmost stabilizing effects, while heat treatment before liquefying causes reductions the stabilizing effects.[10]

Myers and Shively developed solid-state glass emulsions. In this method, drug dissolved in a vegetable oil is mixed with sucrose solution. Such emulsifiable glasses have the benefit of not needing any surfactants in the formulation. Dry foam was produced by rotator evaporation of mixture under vacuum. Emulsion is produced by addition of this dry foam. Cyclosporine A was tried to deliver through this method. Spray drying technique is most often used in the preparation of dry emulsions. The o/w emulsion was prepared, and to eliminate the aqueous phase, the emulsion was spray dried.[86]

SE sustained-release microspheres

Quasi-emulsion solvent-diffusion process of the spherical crystallization technique was used to prepare sustained release microspheres of a traditional Chinese medicine and zedoary turmeric oil by You *et al*. The microspheres were prepared using HPMC acetate succinate and aerosil 200. After oral administration of such microspheres to rabbit's plasma, concentration-time profiles were attained with resulting bioavailability of 135.6% with respect to the conventional liquid SEDDS.[85]

Self-nanoemulsifying drug delivery system/SE nanoparticles

Techniques used in the production of SE nanoparticles are solvent injection technique, sonication, and emulsion–diffusion–evaporation. In the solvent injection technique, lipid, drugs, and surfactants are all liquefied together and added drop by drop into the agitated non-solvent. The final SE nanoparticles were strained and dried completely. The approach gave nanoparticles of about 100 nm with a high drug loading capacity of the approximately 74%.[85] In other studies, drug and excipients were melted all together and introduced into a solution of non-solvent. Nanoparticles were then separated by centrifugation and lyophilization. Goat fat and Tween 65 were used for the development of self-nanoemulsifying formulations. Paclitaxel nanoparticles were prepared using glyceryl monooleate (GMO) having SE property along with chitosan. Chitosan acted as bioadhesive for nanoparticles, while 100% drug loading and entrapment effciencies were achieved due to SE property of GMO. These benefits aided in the achievement of an effcacious therapeutic window with lower doses of paclitaxel, thereby reducing the adverse effects related to the chemotherapeutics of paclitaxel.[84]

SE implants

Self-emulsified carmustine (1, 3-bis (2-chloroethyl)-1-nitrosourea) was fused into PLGA wafer and used as an implant. SEDDS formulation reduced the contact of BCNU from the aqueous media. *In vitro* release of BCNU from SE PLGA wafers was extended up to 7 days. Such wafers had higher *in vitro* antitumor activity and were less prone to hydrolysis than those wafers without SE systems. The formulation contained Cremophor RH 40, tributyrin, Labrafil MC 1944, and carmustine. Then, SE carmustine was incorporated into wafers with a horizontal and even surface by compression molding. Eventually, SE system improved the *in vitro* half-life of carmustine up to 2 h 10 min.[83-86] Loomis invented copolymers having a bioresorbable region, a hydrophilic region, and at least two cross-linkable functional groups per polymer chain which showed SE properties without incorporating emulsifying agent. These copolymers can be used as good sealants for implantable prostheses.[4]

SE SUPPOSITORIES

Kim and Ku (2000) found that s-SMEDDS resulted in increase in vaginal/rectal adsorption.[83] Hae *et al*. used C6-C18 FA glycerol ester, and C6-C8 FA macrogol esters were used in the formulation of SE suppositories of glycyrrhizin. The resulting formulation reported good absorption of drug which was indicated by high plasma drug levels when given through rectal/vaginal route. However, its efficacy was hindered by its short half-life.[10]

SE tablets/control release tablets

Eutectic-based SE tablets were formulated by Nazzal *et al*. which inhibited the unalterable precipitation of the drug within the formulation. Drug and suitable semisolid oil were used in the formulation in combination. Based on the melting point depression method, the drug contained in the oil phase melts at body temperature, i.e., 37°C, which produces the droplets of emulsion in nanometer size range. During the formulation of these tablets, maltodextrin, modified povidone, and MCC were employed as carriers (additional excipients). Nazzal and Khan estimated the effects of certain processing factors such as colloidal silicates-P1, time of mixing magnesium stearate-P2, and force of compression-P3 on hardness and coenzyme Q10 on dissolution of tablets of eutectic-based SMEDDS. Face-centered cubic design adjusted the conditions (P1 = 1.06%, P2 = 2 min, and P3 = 1670 kg) to significantly reduce the quantities of solidifying excipients essential for the conversion of SEDDS into solid dosage forms. Patil *et al*. developed a gel-based SEDDS uaing colloidal silicon dioxide (Aerosil 200) as a gelling agent for the oil-based systems, which facilitated the dual purpose of decreasing the quantity of solidifying excipients and in slowing down the rate of drug release by adjusting the size of the molecule of MCC. Nazzal *et al*. formulated a self-nanoemulsified tablet of ubiquinone. First, ubiquinone contained in the self-nanoemulsion system was formulated which was then absorbed onto a granular substance and then compressed to form tablets. Polyethylene oxide successfully demonstrated its suitability for the controlled-release matrix. Subsequent SE tablets constantly maintained a higher concentration of active ingredients in blood plasma over the same time frame when compared to a non-emulsifying tablet. A number of potent drugs have low oral bioavailability due to their poor solubility in water or pre-systemic metabolism. Carvedilol (antihypertensive drug) has low solubility, low bioavailability, and pre-systemic metabolism. SE tablets are of great utility in escaping the adverse effect, as revealed by Schwarz in a patent. The novel self-emulsifying osmotic pump tablet (SEOPT) containing carvedilol has many advantages over the commercial carvedilol tablet such as stable plasma concentrations, controllable rate of release of drug, and bioavailability of approximately 156.78%.[85] Addition of indomethacin (or other hydrophobic NSAID) into SE tablets may upsurge its penetration efficacy through GI mucosal membranes, possibly reducing the bleeding of GI membranes.

SE beads

Patil and Paradkar invented porous polystyrene beads (PPB) for delivering SEFs using the solvent evaporation method. They are inert and stable over a wide range of pH and extreme conditions of humidity and temperature. Copolymerization of styrene and divinyl benzene was done for the preparation of beads. The formulation was poured into microchannels of the beads through capillary action. Size of beads and structure of pores of PPB affected the loading efficiency and *in vitro* release of drug from SE system filled with PPB. Studies concluded that PPB is a potential carrier for the solidification of SE system, with considerably high SES to PPB ratios required to obtain the solid form.[83] In another study, SEDDS of tetrahydrocurcumin contained in floating alginate beads was developed to enhance solubility of drug and prolong its gastric residence time. Using different quantities of sodium alginate, calcium chloride, and water soluble pore former (polyvinyl alcohol polyethylene glycol co-polymer) in bead preparations results in variation on the floating abilities and in-vitro release rate of drug.[84]

SE-controlled/sustained release pellets

Pellets are unit dosage forms with advantages of ease of manufacturing, reduced inter- and intra-subject irregularities of plasma profiles, and minimized irritation of GIT without affecting the bioavailability of the drug.[82] The pellets are characterized for their shape, size, friability, and surface characteristics.[83] Serratoni *et al*. formulated SE-controlled release pellets by adding drugs into SE system that improved the rate of release of the drug and then covering it with a water-insoluble polymer that reduced the release rate of drug. Spherical pellets were prepared by extrusion/spheronization with low friability that has two water-insoluble model drugs (methyl and propyl parabens) and SE system that contained mono-di-glycerides and polysorbate 80.

SE sustained release matrix pellets were successfully prepared with glyceryl behenate (Gelucire 70/02) and glyceryl palmito stearate (Gelucire 54/02).[85] Thus, it is very interesting to combine the benefits of pellets with those of SEDDS by formulating SE pellets. The combination of coating and SE system controlled *in vitro* release of drugs by providing different release rate profiles and the presence of the SEDDS did not influence the ability of the polymer film to control dissolution of the drug. In some investigations, s-SMEDDS was prepared by wet granulation method on a laboratory scale using a high shear mixer to increase the rate of dissolution of a drug having poor aqueous solubility. The conventional liquid granulation binder was substituted with an o/w type of microemulsion, containing the drug.[85]

The most common technique used for the preparation of s-SMEDDS was spray drying along with the use of a solid carrier. Solid carriers such as gelatin, dextran, aerosol 200, and lactose have been successfully used in the preparation of s-SMEDDS of drugs such as flurbiprofen, curcumin, nimodipine, dexibuprofen, and docetaxel with improved oral bioavailability. In his study for alternative method of s-SMEDDS preparation, Agarwal *et al*. adopted simply triturating the liquid SMEDDS with a solid adsorbent in a mortar until a uniform mixture was formed to prepare a powdered SE lipid formulation of meloxicam. It could be a cost-effective technique for the preparation of s-SMEDDS of poorly water soluble drugs overcoming the drawbacks of the

conventional liquid SMEDDS preparations. However, certain features of s-SMEDDS such as physical aging associated with glyceride, oxidation of vegetable oils, and interaction between drugs and excipients must be taken into consideration while preparation of s-SMEDDS. In a study, the drawbacks of s-SMEDDS were listed such as strong adsorption and physical interaction between the drug and the carriers causing improper or partial release of the drug from s-SEDDS. In the same study, immediate release SE tablets of ibuprofen were designed using an acid-soluble powdered carrier, Fujicalin® (granulated dibasic calcium phosphate) to aid the process of release of drug in the stomach. It suggested a novel approach for the preparation of immediate release s-SMEDDS.[3,8]

FUTURE PERSPECTIVE

SMEDDS could be an effective way to overcome the issue of solubility of drugs with relatively lesser solubility in the fluids of GIT. Role of intestinal lipids on solubilization of lipid-based formulations could be better understood using the combinations of *i in vitro* dispersion and digestion methodology. This *in situ* emulsion formulation has high stability which can be taken as an emulsion prefix. In future, development of SMEDDS will remove all the complications related to the delivery of drugs with poor solubility. Still, a long way has to be covered, before launching more SMEDDS products in the market because SMEDDS needs further exploitation including researches about bioavailability and development of *in vitro*, *in vivo* correlation (IVIVC) and other dosage forms.[8,10] The novel SEOPT needs more exploitation.[85]

CONCLUSION

SMEDDS is a great and useful approach for the preparation of drug compounds with poor solubility, pre-systemic first-pass effect, high molecular weight, gastric irritation, enzymatic degradation, low rate of dissolution, and lesser bioavailability. This approach is suitable for all drugs of BCS because prepared emulsion provides faster absorption, faster dissolution rates, and high bioavailability due to solubilization of drug in lipidic excipients which avoids the dissolution step. This approach needs more exploitation in field of SEOPT formulations and other dosage forms. They lack IVIVC which needs to be extensive and continuous comparison of these studies in foreseeable future using biorelevant media such as fasting state stimulated intestinal fluid (FaSSIF) media, FeSSIF media, and FaSSGF media which gives more accuracy of *in vivo* results in the formulations.

REFERENCES

1. Rahman MA, Hussain A, Hussain MS, Mirza MA, Iqbal Z. Role of excipients in successful development of SMEDDS/SEDDS. Drug Dev Ind Pharm 2013;39:1-19.
2. Ingle LM, Wankhade VP, Udasi TA, Tapar KK. New approaches for development and characterization of SMEDDS. Int J Pharm Sci Res 2013;3:7-14.
3. Agrawal S, Giri TK, Tripathi DK, Alexander A. A review on novel therapeutic strategies for enhancement of solubility for hydrophobic drugs through lipid and surfactant based SMEDDS: A novel approach. Am J Drug Disc Dev 2012;2:1-41.
4. Chaus HA, Chopade VV, Chaudhri PD. Self-emulsifying drug delivery system: A review. Int J Pharm Chem Sci 2013;2:34-44.
5. Ganesh K. SMEDDS o/w microemulsion for BCS II drugs: An approach to enhance oral bioavailability. Int J Pharm Sci 2011;3:1-3.
6. Reddy S, Katyayani T, Navatha T, Ramya G. Review on self-microemulsifying drug delivery systems. Int J Pharm Res Pharm Sci 2011;2:382-92.
7. Pooja M, Rajni B, Nimrata S. Lipid based SMEDDS for lipophilic drugs: A acquainted review. Int Res J Pharm 2011;2:75-80.
8. Shah I. Development and Characterization of o/w Nano-Emulsions form Self-Microemulsifying Mixture-Thesis. 2011. p. 1-25.
9. Khan A, Khan H, Mohamad T, Rasul A. Basics of SMEDDS. J Pharm Altern Med 2012;1:13-20.
10. Talele SG, Gudsoorkar VR. Novel approaches for solidification of SMEDDS. J Pharm Bio Sci 2015;4:90-101.
11. Thakare P, Mogal V, Borase P, Dusane J, Kshirsagar S. A review on self-emulsifying drug delivery system. Pharm Biol Eval 2016;3:140-53.
12. Parmar B, Patel U, Bhimani B, Sanghavi K. SMEDDS: A dominant dosage form which improve bioavailability. Am J PharmTech Res 2012;2:54-72.
13. Jinalbahen B, Patel M. Self-microemulsifying drug delivery system: A review. World J Pharm Pharm Sci 2016;2:2215-32.
14. Prachi S, Prajapati SK, Shipra S, Ali A. A review on SMEDDS: An approach to enhance oral bioavailability of poorly water soluble drugs. Int J Pharm Res 2016;3:1-6.
15. Kumar A, Nanda A. Novel approaches of SMEDDS. J Chem Pharm 2016;8:149-57.
16. Parul J, Geeta A, Amanpreet K. Bioavailability enhancement of poorly water soluble drugs by SMEDDS: A review. J Drug Del Ther 2013;3:98-109.
17. Drasika C. Self-emulsifying drug delivery system: A capsulization. J Pharm Sci Res 2016;8:121-4.
18. Reddy LH, Murthy RS. Lymphatic transport of orally administered drugs. Ind J Exp Biotechnol 2012;40:1097-109.
19. Gadhave A. Determination of hydrophilic-lipophilic balance value. Int J Sci Res 2014;3:2319-7064.
20. Bragagni M, Mennini N, Maestrelli F, Cirri M, Mura P. Comparative study of liposomes, transfersomes and ethosomes as carriers for improving topical delivery of celecoxib. Int J Pharm Sci 2012;6:202-10.
21. Vilas PC, Nayan G, Bhusahan R, Sunil P. A review on

self-emulsifying drug delivery system. Pharm Sci Monit 2013;4:3628-48.
22. Chandra A, Abblu K, Hyma P. Formulation nand evaluation of telmisartan self-emulsifying drug delivery system. Int J Pharm Sci 2014;6:120-5.
23. Khamkar GS. Self-emulsifying drug delivery system o/w microemulsion for BCS II drugs: An approach to enhance oral bioavailability. Int J Pharm Sci 2011;3:1-3.
24. Mahapatra AK, Murthy PN, Swadeep B, Swain RP. Self-emulsifying drug delivery systems (SEDDS): An update from formulation development to therapeutic strategies. Int J Pharm TechRes 2014;6:546-68.
25. Pandya BD, Shah SH, Shah N. Bioavailability enhancement of poorly water soluble drugs by SMEDDS: A review. J Pharm Sci Res 2015;2:187-206.
26. Lalawani JT, Vaishali T, Patel HV. Enhancement of oral bioavailability of ezetimibe by novel solid self-emulsifying drug delivery systems. Int J PharmTech Res 2013;5:513-22.
27. Wadhwa J, Nair A, Kumri R. Selfemulsifying therapeutic system: A potential approach for delivery of lipophilic drugs. Braz J Pharm Sci 2011;47:1-16.
28. Sarpal K, Pawar YB, Bansal AK. Self-emulsifying drug delivery systems: A strategy to improve oral bioavailability. CRIPS 2010;11:42-55.
29. Jankovic J, Ljilijana D, Vladimir D. Evaluation of critical parameters in design and differentitation of self-emulsifying drug delivery systems for oral delivery of acyclovir. Int J Pharm 2016;497:301-11.
30. Sangsen SK. Influence of surfactants in self-emulsifying formulations on enhancing bioavailability of oxyresveratrol. Int J Pharm 2016;498:294-303.
31. Kamboj S, Rana V. Quality by design based development of SMEDDS to reduce effect of food on nelfinavir mesylate. Int J Pharm 2016;501:311-25.
32. Yeam DW. Development of self-emulsifying drug delivery systems for atorvastatin calcium with improved dissolution and bioavailability. IntJ Pharm 2016;506:302-11.
33. Chen Y, Zhang H, Yang J, Sun H. Improved antioxidant capacity of optimization of a self-microemulsifying drug delivery system for resveratrol. Molecules 2015;20:21167-77.
34. Anand UK, Kisan RJ, Vilasrao JK. Self-emulsifying drug delivery system: Review. J Pharm Res 2010;3:75-83.
35. Prajapati ST, Joshi HA, Patel CN. Preparation and characterization of SMMEDDS of olmesartan medoxomil for bioavailability improvement. J Pharm 2013;7:1-9.
36. Venkatesh G, Majid MI, Mansor SM, Nair NK, Croft SL. *In-vitro* and *in vivo* evaluation of SMEDDS of buparvaquone. Drug Dev Ind Pharm 2010;36:735-43.
37. Zoltan U, Azin KK, Miklos V, Eszter R. The enhanced inhibitory effect of different antitumor agents in self-emulsifying drug delivery systems on human cervical cancer HeLa cells. Molecules 2015;20:13226-39.
38. Hintzen F. Self-emulsifying drug delivery systems to improved oral bioavailability. Int J Pharm 2014;472:20-6.
39. Goyal U, Arora R, Aggarwal G. Formulation design and evaluation of SMEDDS of lovastatin. Acta Pharm 2012;62:357-70.
40. Alinaghi A, Tan A, Rao S, Prestidge CA. Impact of solidification on performance of lipid based colloidal carriers: Oil-based versus selfemulsifying systems. Curr Drug Deliv 2015;12:16-25.
41. Lu FQ, Li H, Xu W, Huang MQ. Preparation of SMEDDS of mixture of paeoneol and borneol based on Xingbi Fangi. Yao Xue Xue Bao 2013;48:1602-10.
42. Xuan XY, Wang YJ, Tian H, Pi JX, Sun SZ, Zhang WL, *et al.* Study on prescription of self-microemulsifying drug delivery system of mangiferin phospholipid complex. Zhong Yao Cai 2012;35:1508-11.
43. Seljak KB, Berginc K, Trontejlj J, Zvonar A. A SMEDDS to overcome intestinal resveratrol toxicity and presystemic metabolism. J Pharm Sci 2014;103:3491-500.
44. Kim DW, Kwon MS, Yousaf AM, Park JH, Kim DS, Lee BJ, *et al*. Comparision of solid SMEDDS and solid dispersion for enhanced stability and bioavailability of clopdogrelnapadisilate. Carbohydr Polym 2014;1:365-74.
45. Zhao L, Zhang L, Meng L, Zhai G. Design and evaluation of SMEDDS for apigenin. Drug Dev Ind Pharm 2013;39:662-9.
46. Jakki R, Afzal SM, Kandai P, Veerabrahma K. Development of SMEDDS of domperidone: *In-vitro* and *in vivo* evaluation. Acta Pharm 2013;63:241-51.
47. Sohn Y, Lee SY, Lee GH, Na YJ. Devlopment of self self microemulsifying bilayer tablets for pH-independent fast release of candesartan cilexetil. Pharmazie 2012;67:917-24.
48. Chen LJ, Liu Y, Li Y, Gao F. Enhanced bioavailability of total paeony glycoside by self-emulsifying drug delivery systems. Yao Xue Xue Bao 2012;47:1678-86.
49. Choo GH, Park SJ, Hwang SJ, Kim MS. Formulation and *in vivo* evaluation of by self-emulsifying drug delivery systems of dutasteride. Drug Res(Stuttg) 2013;63:203-9.
50. Verma R, Mittal V, Kaushik D. Quality based design approach for improving oral bioavailability of valsartan loaded SMEDDS and study of impact of lipolysis on the drug diffusion. Drug Deliv Lett 2018;8:130-9.
51. Cho YD, Park YJ. *In-vitro* and *in vivo* evaluation of self-emulsifying drug delivery systems for poorly soluble drug fenofibrate. Acta Pharm 2014;37:193-203.
52. Sermkaew N, Ketjinda W, Boonme P. Liquid and solid self-emulsifying drug delivery systems for improving oral bioavailabilty of andrographolide from crude extract of andrographispaniculata. Eur J Pharm Sci 2013;50:459-66.
53. Cho HJ, Lee DW, Marasini N, Poudel BK. Optimization of self-emulsifying drug delivery systems for telmisartan using box-behnken design. J Pharm Pharamacol 2013;65:1440-50.
54. Cho W, Kim MS, Kim JS, Park J, Park HJ. Optimized formulation of self-emulsifying sirolimus delivery

systems. Int J Nanomed 2013;8:1673-82.
55. Deshmukh A, Kulkarni S. Solid self-emulsifying drug delivery system of ritonavir. Drug Dev Ind Pharm 2014;40:477-87.
56. Abdalla A, Mader K. Preparation and characterization of a self emulsifying pellet formulation. Eur J Pharm Biopharm 2007;66:2206.
57. Rui Y, Xin H, Jinfeng D. Self-emulsifying drug delivery systems to improved oral bioavailability of olmisartan medoxidil. Design and evaluation. Int J Nanomed 2013;8:2917-26.
58. Hu X, Lin C, Chen D, Zhang J, Liu Z, Wu W, *et al*. Sirolimus solid self-microemulsifying pellets: Formulation development, characterization and bioavailabilty evaluation. Int J Pharm 2012;438:122-33.
59. Foram J, Vaishali L. Solubility enhancement of lurasidone hydrochloride by preparing SMEDDS. Int J Pharm 2015;7:283-8.
60. Čerpnjak K, Zvonar A, Vrečer F, Gašperlin M. Development of a solid self-microemulsifying drug delivery system. SMEDDS for solubility enhancement of naproxen. Drug Dev Ind Pharm 2015;41:1548-57.
61. Hassan E. Self Micro-Emulsifying Drug Delivery System with Increased Bioavailability (SMEDDS). US Patent: 14/802837; 2017.
62. Holmberg A, Klaveness K. Self Emulsifying Drug Delivery System. US Patent: 7815933; 2016.
63. Coulter. Composition Comprising Oil Drops. United States Patent: 9278070; 2016.
64. Liu Z. Butylphathalide Self-Emulsifying Drug Delivery System, its Preparation, Method and Application. United States Patent: 8728518; 2014.
65. Kram BH. Methods and Compositions for a MicroemulsionBased Tissue Treatment. United States Patent: 8652803; 2014.
66. Dhingra O. U.S. Patent Application No. 12/983,216; 2011.
67. Legen Y, Ignor J. Self-Microemulsifying Drug Delivery Systems. Us Patents Applications: 20100331356; 2010.
68. Khan M, Nazzal A, Sami H. Eutectic-Based Self-Nanoemulsifieddrug Delivery System. US Patents Application: 7588786; 2009.
69. Zhentao L, Yang J, Liying Y. Butylphthalide Self-Emulsifying Drug Delivery Systems, its Preparation Method and Application. US Patents Application: 20080319056; 2008.
70. Friedman D. Nonaqueous Compostions for Oral Delivery of Insoluble Bioactive Agents. US Patents Application: 20070190080; 2007.
71. Lin J, Jing L. Self-Emulsifying Dosage Forms of Low Solubility Active Ingredients such as Coenzyme Q10. US Patents Application: 20060275358; 2006.
72. Lee Y, Jin X. Compostions Containing Itraconazole and their Preparation Methods. US Patents Application: 20040248901; 2004.
73. Benameur H, Jannin V, Roulot A. Method and Formulation for Decreasing Statin Metabolism. US Patents Application: 6652865; 2003.
74. Mulye H, Nirmal S. Self-Emulsifying Compostions for Drugs Low Solube in Water. US Patents Application: 6436430; 2002.
75. Farah N, Denis K. Orally Administrable Compositions Capable of Providing Enhanced Bioavailability When Ingested. US Patents: 6312704; 2001.
76. Barthelemy P, Benameur H. Compostion with Sustained Release Active Principle Capable of Forming Microemulsion. US Patent: 6309665; 2000.
77. Takada K, Murakami M. Glycyrrhizin Preparations for Transmucosal Absorption. US Patent: 6890547; 2000, 2005.
78. Mulye S, Nirmal S. Pharmaceutical Composition Comprising Cyclosporine in Association with Carrier in Self-Emulsifying Drug Delivery System. US Patent: 6057289; 2000.
79. Ghosh PK, Majithiya RJ, Umrethia ML, Murthy RS. Design and development of micro-emulsion drug delivery system of acyclovir for improvement of oral bioavailability. Am Assoc Pharm Sci 2006;7:1-6.
80. Paresh K, Patel MR, Patel KR. Design and development of self-microemulsifying drug delivery system of febuxostat. Int J Univ Pharm Biol Sci 2014;3:1211-8.
81. Tejeswari N, Harini CV, Hyndavi T, Jyotsna Y, Gowri Y, Raju P. Lipid based drug delivery system for enhancing oral bioavailability-a contemporary review. J Glob Trends Pharm Sci 2014;5:2074-82.
82. Kaushik D, Mittal V, Khatkhar A, Raina M, Chouhan N. Self-emulsifying drug delivery system(SEDDS) for phytoconstituents: A review. Curr Drug Deliv 2015;12:244-53.
83. Deokate UA, Shinde N, Bhingare U. Novel approaches for development and characterization of SMEDDS: Review. Int J Curr Pharm Res 2015;5:5-12.
84. Gupta S, Kesarla R, Omri A. Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems. Int J Pharm 2013;5:16-32.
85. Milind PW, Singh PK, Chaudhari CS, Khairnar DA. Solid self-emulsifying drug delivery system: Preparation techniques and dosage forms. Int J Biopharm 2014;5:101-8.
86. Kaushik Y, Preethi S. Approaches to development of solid-self micron emulsifying drug delivery system: Formulation techniques and dosage forms: A review. Int J Pharm Sci Res 2012;3:3550-8.

Source of Support: Nil. **Conflict of Interest:** None declared.