Review Article

Self-micro emulsifying drug delivery system of acyclovir for solubility enhancement: An updated review

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ABSTRACT

Solubility of orally administered drug is a major challenge of pharmaceutical industry as nearly 35–40% of newly launched drugs possess low aqueous solubility which leads to their poor dissolution and low bioavailability, resulting in high intra and intersubject variability and lack of dose proportionality. This can be increased by different methods such as salt formation, solid dispersion, and complex formation. Self-emulsifying drug delivery system (SEDDS) is gaining popularity for improving the solubility of lipophilic drugs. SEDDS is defined as isotropic mixtures of one or more hydrophilic solvents and cosolvents/surfactants that have a unique ability of forming fine oil-in-water microemulsions upon mild agitation followed by dilution in aqueous media, such as gastrointestinal fluids. The present review provides an updated account of advancements in SEDDS with regard to its composition, evaluation, different dosage forms, and newer techniques to convert liquid SEDDS to solid and also various applications.

Keywords: Acyclovir, solubility enhancement, emulsion, self-emulsifying drug delivery system

Introduction

Oral drug delivery system and absorption window

Oral bioavailability of drugs is affected by a variety of factors, which influence their absorption gastrointestinal tract (GIT). One determinant factor for absorption is drug dissolution, which influenced by solubility of drug in GI fluids.[1] A variety of methods have been developed over the years to improve the release and dissolution of such drugs. Various techniques are used to enhance oral bioavailability of poorly water-soluble drug. Oral route has been the major route of drug delivery for the chronic treatment of many diseases as it offers a high degree of patient compliance. However, oral delivery of 50% of the drug compounds is hampered because of the lipophilicity of the drug itself.[2] Nearly 40% of new drug candidates exhibit low solubility in water, which is a challenge in the development of optimum oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products. Many strategies have been used to overcome these problems either by means of modifying the solubility or maintaining the drug in dissolved form throughout gastric transit time. These strategies may include the use of surfactants, cyclodextrins, micronization, liquisolid techniques, salt formation, pH change, nanosize delivery, solid dispersions, and permeation enhancers. Bioavailability is a measurement of the extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action.[3,4] Bioavailability is mainly controlled by the delivery of drug as determined by its pharmaceutical formulation, solubility, and permeability through the gut wall. Bioavailability can be decreased by decomposition of drug in the GIT by the formation of non-absorbable complexes, by metabolization or by premature elimination. These limitations influenced by physiological parameters of the GIT or physiological properties of the drug and formulation. It is estimated that 40% of all new chemical entities (NCE) have poor bioavailability because of low aqueous solubility.[5] The percentage

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still increases due to combinatorial chemistry and the impact of lipophilic receptors. Attention has been focused particularly on orally administered drug delivery systems because of their ease of administration and low cost of manufacturing as compared to other dosage forms.[5,6]

Oral drug administration is a widely accepted route of administration. However, the therapeutic window of many drugs is limited by their low solubility and hence absorption through a defined GIT segment. Such limitations lead in many cases to design a special type system of these medications to achieve the required therapeutic effect. The phenomenon of absorption through a limited part of the GIT has been called as "narrow absorption window;" once the dosage form passes the absorption window, the drug will be neither bioavailable nor effective.[7] A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to increase the solubility of the drug in solution at its absorption area, that is, in the stomach and to release the drug completely. The need for dosage forms has led to extensive efforts in both academics and industry toward the development of such drug delivery systems.[7,8]

Solubility and Bioavailability of Drug

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substance to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction.[9] Drug solubility is the maximum concentration of the drug solute dissolved in a solvent under the specific condition of temperature, pressure, and pH. The drug solubility in a saturated solution is a static property, whereas dissolution is a dynamic property that relates more closely to the bioavailability rate.[10,11] Therapeutic effectiveness of a drug depends upon the bioavailability and ultimate upon the solubility of the drug molecule. An important prerequisite for the absorption of a drug by all mechanisms except endocytosis is that it must be present in aqueous solution. This, in turn, depends on the drug solubility aqueous and its dissolution rate.[12] Dissolution rate is defined as the amount of the solid substance that goes into the solution per time under a standard condition of temperature, pH, and solvent composition and constant solid surface area. Therefore, solubility is one of the important parameter to achieve the desired concentration of a drug in systemic circulation for pharmacological response to be shown. At present, only 8% of new candidates have both high solubility and high permeability.[12,13] As a matter of fact, more than one-third of the drug listed in the U.S Pharmacopoeia falls into poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that more than 41% of the failure in new drug development has been attributed to poor biopharmaceutical properties, including water insolubility, while it was still indicated recently that about 50% failure of drug candidates was due to poor "drug-like" properties. It was commonly recognized in the pharmaceutical industry that on average more than 40%of newly discovered drug candidates are poorly water-soluble.[13] Nearly 40% of new drug candidates exhibit low solubility in water, which is a challenge in the development of optimum oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products. Many strategies have been used to overcome these problems either by means of modifying the solubility or maintaining the drug in dissolved form throughout gastric transit time.[14] Much attention has focused on lipid solutions, emulsions and emulsion pre-concentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. With today's contemporary drug discovery techniques, innovating drug candidates without compromising on safety and efficacy is a challenge. Although there has been a remarkable success in the development of new drug candidates, there are still unmet needs in healthcare which need effective therapy predominantly NCE (about 40%) with potential therapeutic activity and other pharmacokinetic aspects are compromised as a result of poor solubility, concerns with permeability, rapid metabolism, and early elimination. Therefore, the pharmaceutical drug discovery phase for an NCE with appropriate biopharmaceutical properties is crucial for the successful development of the new drug.[14,15]

Newer Technologies to Overcome Solubility Problems

Hence, the significance of pharmaceutical technology[16] emerged to formulate bio-pharmaceutically competent drugs. Several strategies exist to deal with drug molecules with lipophilicity or permeability includes micronization of crystalline solids, amorphous formulation, and lipid-based formulations. Lipid-based formulations, especially self-emulsifying formulations; self-micro emulsifying drug delivery system; or self-nanoemulsifying drug delivery system (SMEDDS or SNEDDS) prominently gained great significance as a successful approach for poorly soluble drugs amid other approaches.[17,18] Liposomes, solid-lipid nanoparticle, SMEDDS, microemulsion, and macroemulsions mostly contribute to lipid-based formulations. In recent years, lipid-based formulation attained importance with significant emphasis on self-emulsifying drug delivery system (SEDDS).[19] Majority of the new drug candidates (almost 40%) being developed are water-insoluble. Such active pharmaceutical ingredient poses several problems while developing their formulations. Popular formulation techniques used for delivering a poorly water-soluble drug include (a) micronization of crystalline solids, (b) amorphous formulation or solid dispersions, and (c) lipid-based formulations. Among these approaches, lipid-microemulsion formulations, with a particular emphasis on SEDDS (SEDDS or SMEDDS), have gained great importance as a promising approach for poorly soluble drugs as well as for natural compounds.[20,21]

Microemulsions

The term microemulsion was first used by jack Shulman in 1953. A microemulsion is a four-component system composed of external phase, internal phase, surfactant, and cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike to the cosurfactant, results in the formation of an optically clear, isotropic, and thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is <0.1 μ

droplet diameter.[22] The formation of microemulsion is spontaneous and does not involve the input the external energy as in case of coarse emulsion. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsions. Nonionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hydrophilic-lipophilic balance, are often used to ensure the immediate formation of oil-in-water droplets during production.[23] SEDDS is used to solve low bioavailability issues of poorly soluble and highly permeable compounds. Hydrophobic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration. When SEDDS formulation is released in the lumen of the GIT, they come in contact with GI fluid and form a fine emulsion (micro/nano) so-called as *in situ* emulsification or self-emulsification, which further leads to solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect. This bioavailability enhancing property has been associated with a number of *in vivo* properties of the lipid formulations including:

1. Ability of certain lipid compounds and their metabolites to initiate changes in the GI fluid to favor improved drug absorption.
2. Inhibition of cellular efflux mechanisms, which keep drugs out of circulation.
3. Certain lipid excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism.

Recent Advancements in SMEDDS

Microemulsion

The microemulsion concept was introduced as early as the 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol Schulman *et al*. (1959) subsequently coined the term microemulsion, and it has since been defined and indeed redefined on many occasions. For the purposes of this review, however, the microemulsion definition provided by Danielsson and Lindman in 1981 will be used as the point of reference. Microemulsions are thus defined as "a system of water, oil, and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution." Microemulsions are clear, stable, isotropic mixtures of oil, water, and surfactant, frequently in combination with a cosurfactant. These systems are currently of interest to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicles by incorporating a wide range of drug molecules. The key difference between emulsions and microemulsions are that the former, while they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate.[24] Another important difference concerns their appearance; emulsions are cloudy while microemulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while microemulsions do not. It is also useful to note that under the dentition given, SMEEDS is not microemulsions, although they may be considered a closely related system. A SMEDD typically comprises a mixture of surfactant, oil, and drug (known as the concentrate) which when introduced into the body is rapidly dispersed to form droplets of approximately the same size range as those observed in microemulsion systems. Once dispersed, such systems would be expected to behave *in vivo* much the same way as oil-in-water (o/w) microemulsions. The attraction of o/w microemulsion systems lies in their ability to incorporate hydrophobic drugs into the polar oil phase, thereby enhancing their solubility. The dispersal of the drug as a solution in nanometer-sized droplets enhances the rate of dissolution into an aqueous contracting phase, and *in vivo* generally results in an increase in drug bioavailability. It is also noteworthy that the use of o/w microemulsions in drug delivery is more straight-forward than is the case with w/o microemulsions. This is because the droplet structure of o/w microemulsions is often retained on dilution by an aqueous biological phase, thereby permitting oral as well as parenteral administration.

Grovea *et al*. (2006) constructed ternary phase diagrams and found it was possible to identify two SMEDDS containing either medium-chain triglycerides (MC-SMEDDS) or long-chain triglycerides (LC-SMEDDS), with the same ratio between lipid, surfactant, and cosurfactant ended up having a composition of 25% lipid, 48% surfactant, and 27% cosurfactant, MC-SMEDDS: Viscoleo, cremophor RH40, akoline MCM, and LC-SMEDDS: Sesame oil, cremophor RH40, and peceol. Upon dilution with water, both SMEDDS resulted in clear to bluish transparent microemulsions with a narrow droplet size of 30 nm. The industrial usefulness of the developed SMEDDS was evaluated with regard to bioavailability and chemical stability using the vitamin D analog, seocalcitol, as model compound. The absorption and bioavailability of seocalcitol in rats were approximately 45% and 18%, respectively, from both the MC-SMEDDS and LC-SMEDDS, indicating similar *in vivo* behavior of the two formulations, despite the difference in nature of lipid component. There was no improvement in bioavailability by the use of SMEDDS, compared to the bioavailability achieved from simple medium-chain triglycerides (MCT) and long-chain triglycerides (LCT) solutions (22–24%). After 3 months' storage at accelerated conditions (40°C/75% RH), a decrease in the concentration of seocalcitol of 10–11% was found in MC-SMEDDS lipid solutions of MCT and LCT. In this study, the simple lipid solutions seem to be a better choice compared with the developed SMEDDS due to slightly higher bioavailability and better chemical stability of seocalcitol.[25]

Wei *et al*. (2006) enhanced the bioavailability of silymarin by SMEDDS. The SMEDDS consisting of silymarin, Tween 80, ethyl alcohol, and ethyl linoleate. Particle size changes of the microemulsion were evaluated upon dilution with aqueous media and loading with the incremental amount of silymarin (100 mg/1 g) pharmacokinetics and bioavailability of silymarin suspension, solution and SMEDDS were evaluated and compared in rabbits. Plasma silybin, which was treated as the representing component of silymarin, was determined by high-performance liquid chromatography (HPLC) after the average administration of silymarin suspension, plasma silybin level was very low and fell below the limit of detection 4 h. As for silymarin solution and SMEDDS, a double peak of maximum concentration was observed. Relative bioavailability of SMEDDS was dramatically enhanced in an average of 1.88 and 48.82 fold that of

silymarin polyethylene glycol 400 (PEG 400) solution and suspension, respectively. Hence, bioavailability of silymarin was greatly enhance by SMEDDS formulation, this is due to improved lymphatic transport pathway other than improved release may contribute to enhancement of bioavailability of silymarin.[26]

Patel *et al*. (2007) prepared and *in vivo* evaluated SMEDDS containing fenofibrate. The optimized formulation was composed of Labrafac CM10 (31.5%), Tween 80 (47.3%), PEG 400 (12.7%), and fenofibrate (8.5%). Accurately weighed fenofibrate was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then, the components were mixed by gentle stirring and vortex mixing and were heated at 40°C on a magnetic stirrer until fenofibrate was completely dissolved and the mixture was stored at room temperature for further use. Pseudoternary phase diagrams were used to evaluate the microemulsification area, and the release rate of fenofibrate was investigated using and *in vitro* dissolution test comparative pharmacodynamics evaluation was investigated in terms of lipid-lowering efficacy, using a triton-induced hypercholesterolemia models in rats. The SMEDDS formulation significantly reduced serum lipid levels in phases I and II of the triton test, as compared with plane fenofibrate. The SMEDDS formulation showed complete release in 15 min as compared with a plain drug, which shows a limited dissolution rate.[27]

Juan *et al*. (2008) improve the anticancer effect of oral 9-nitrocamptothecin (9-NC) on human cancer xenografts in nude mice by SMEDDS. 9-NC is an orally administered topoisomerase-I inhibitor for the treatment of pancreatic carcinoma, but its oral absorption and bioavailability are poor. The main objective of this study was to develop optimal 9-NC microemulsion prepared by SMEDDS. Two SMEDDS formulations of 9-NC prepared from a mixture of ethyl oleate, Tween-80 (T-form) or Cremophor EL (C-form), and PEG-400/ethanol were formed as microemulsions. Under dilution with aqueous phase 1:10 of optimal 9-NC SMEDDS, the droplet sizes of resulting microemulsions were (30.8 ± 4.6) nm and (39.8 ± 8.2) nm for SMEDDS T-form and C-form, respectively, and the zeta potential values were (4.3 ± 0.5) mV and (5.7 ± 0.5) mV, respectively. In SKOV-3 cells, the growth inhibition of various 9-NC formulations was greatest with SMEDDS T-form as compared to 9-NC suspension. It was indicated that the area under the plasma concentration-time curve (area under curve [AUC]) values of various formulations of 9-NC after oral administration ranked as the following sequence: SMEDDS T-form (360.12 ± 19.44 ng h/ml), SMEDDS C-form (351.71 ± 33.66 ng h/ml), > 9-NC solution (241.21 ± 24.67 ng h/ml), and > 9-NC suspension (161.24 ± 24.31 ng h/ml). The 9-NC SMEDDS formulations also produced significantly more tumor shrinkage when compared to 9-NC suspension in nude mice bearing human ovarian cancer xenografts. The results suggest that SMEDDS is a promising drug delivery system to increase the oral bioavailability and antitumor effects of 9-NC and may be applied to other lipophilic drugs. 9-NC SMEDDS represents a novel 9-NC therapy for cancer patients.[27]

Zhang *et al*. (2008) developed SMEDDS to enhance the oral bioavailability of the poorly water-soluble drug, oridonin. The influence of the oil, surfactant, and cosurfactant types on the drug solubility and their ratios on forming efficient and stable SMEDDS were investigated. The SMEDDS was characterized by morphological observation, droplet size and zeta potential determination, cloud point measurement, and *in- vitro* release study. The optimum formulation consisted of 30% mixture of Maisine 35-1 and Labrafac CC (1:1), 46.7% Cremophor EL, and 23.3% Transcutol P. *In-vitro* release test showed a complete release of oridonin from SMEDDS in an approximately 12 m. The absorption of oridonin from SMEDDS showed a 2.2-fold increase in relative bioavailability compared with that of the suspension. Our studies demonstrated the promising use of SMEDDS for the delivery of oridonin by the oral route.[28]

Jing *et al*. (2009) enhanced the oral absorption of curcumin by SMEDDS. SMEDDS has been successfully developed to improve the solubility and oral absorption of curcumin. Suitable compositions of SMEDDS formulation were screened through solubility studies of curcumin and compatibility tests. The optimal formulation of SMEDDS was comprised of 57.5% surfactant (emulsifier OP:Cremorphor EL = 1:1), 30.0% cosurfactant (PEG 400), and 12.5% oil (ethyl oleate). The solubility of curcumin (21 mg/g) significantly increased in SMEDDS. The average particle size of SMEDDS-containing curcumin was about 21 nm when diluted in water. The spherical shape of the microemulsion droplet was observed under transmission electron microscopy (TEM). The dissolution study *in vitro* showed that more than 95% of curcumin in SMEDDS could be dissolved in pH 1.2 or pH 6.8 buffer solutions in 20 min, however, less than 2% for crude curcumin in 60 min. The *in situ* absorption property of curcumin-loaded SMEDDS was evaluated in the intestines of rats. The results showed that the absorption of curcumin in SMEDDS was through passive transfer by diffusion across the lipid membranes. The results of oral absorption experiment in mice showed that SMEDDS could significantly increase the oral absorption of curcumin compared with its suspension.[29]

Bachhav *et al*. (2009) developed SMEDDS of glyburide (antidiabetic agent of BCS class II) and studied *in vitro* evaluation. The SMEDDS was developed to enhance the dissolution rate (solubility) of glyburide. The solubility of glyburide in various oils, surfactants, and cosurfactant s was determined using the shake flask method. The optimized SMEDDS formulation consisted of glyburide, Capryol 90 (oily phase), Transcutol P (cosurfactant), Tween 80 (surfactant), and hydroxypropyl cellulose (viscosity enhancer) (0.075:15.1:53.30:3.0:0.075) in w/w. All the components were mixed by vortexing. The ternary phase diagram was plotted to identify the area of microemulsion existence. *In vitro* studies were done using USP XXIII apparatus I at 37.5°C at 100 rpm at pH 1.2 and 7.4 using SMEDDS of glyburide, pure glyburide powder, and glyburide tablet (marketed formulation). The results show that glyburide SMEDDS showed more than 90% glyburide release in 5 min in both the dissolution media. This indicates that SMEEDS formulation increases the dissolution rate as compared to tablets and powder.[30]

Adhvait *et al*. (2010) prepared SMEDDS of valsartan (angiotensin II antagonist) for improving dissolution rate bioavailability. The valsartan SMEDDS were prepared using Capmul MCM (oil), Tween 80 (surfactants), and PEG 400 (cosurfactants). The particle size distribution, zeta potential, and polydispersity index (PDI) were

determined and were found to be 12.3nm, -0.746, and 0.138, respectively. Ternary phase diagram was constructed to evaluate the microemulsion domain. Dissolution rate of valsartan was measured by *in vitro* dialysis bag method using phosphate buffer 6.8 pH. HPLC method was used to determine the drug content. Oral availability of valsartan SMEDDS was checked using the rabbit model. Result of diffusion rate and oral bioavailability of valsartan SMEDDS were compared with those of pure drug solution and of marketed formulation indicates that valsartan SMEDDS showed maximum drug release as compared to pure drug solution and marketed formulation. The AUC and time showed significant improvement as a value obtained was 607 ng h/mL and 1 h for SMEDDS in comparison to 445.36 and 1.36 h for marketed formulation suggesting significant increase ($P < 0.001$) in the oral bioavailability of valsartan SMEDDS.[31]

Zhuang *et al*. (2011) prepared SMEDDS of penfluridol (drug for chronic schizophrenia) for solubility enhancement. The optimal formulation of penfluridol loaded self-microemulsion consists of penfluridol 5.0%, oil (MCT) 15.8%, surfactant (cremophor EL) 52.8%, and cosurfactant (PEG-400) 26.4%. SMEDDS has the average particle size at approximately (53.5 ± 4.3) nm. TEM revealed the spherical nature and size homogeneity of the microemulsion droplets. No significant variations (droplet sizes and penfluridol contents) in microemulsion were observed over a period of 30 days at 4 °C and 25 °C, respectively. The developed SMEDDS proved to be a potential approach to enhance the solubility of penfluridol.[32]

Guo *et al*. (2011) prepared and evaluated SMEDDS of dipyridamole (coronary vasodilator and antiplatelet agent) for improving oral bioavailability. It shows poor and variable bioavailability after oral administration due to pH-dependent solubility, low biomembrane permeability, as well as being a substrate of P-glycoprotein. The optimized formulation contains 18% oleic acid, 12% Labrafac lipophile WL 1349, 42% Solutol HS, and 28% isopropyl alcohol. It was found that the performance of SMEDDS with the combination of oleic acid and % Labrafac lipophile WL 1349 increased compared with just oil. The average droplet size of microemulsion was 89 nm and the morphology of microemulsion was determined by TEM. Ternary phase diagrams of oils, surfactants/cosurfactants, and water were developed using the water titration method. The weight ratio of surfactant to cosurfactant (km) was varied from 9:1, 8:2, 7:3, 6:4, 5:5, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. Moreover, using the ternary phase diagram microemulsifying area was determined the *in vitro* dissolution studies indicated that dipyridamole in SMEDDS dissolved rapidly and completely as compared to tablets. The *in vivo* studies in rats showed that dipyridamole in SMEDDS formulation had a 2.06 fold increased absorption compared with a simple drug suspension.[33]

Goyal *et al*. (2012) were studied to develop, optimize, and evaluate a SMEDDS of the poorly water-soluble drug and lovastatin (cholesterol-lowering agent). Solubility of lovastatin was determined in various vehicles (oils, surfactants, and cosurfactants). Ternary phase diagrams were constructed to identify the efficient self-emulsification region using oils, surfactants, and cosurfactants in an aqueous environment. The optimized SMEDDS of lovastatin was prepare using Capryol 90 (20%) as oil, cremophor RH40 (40%) as surfactants, and Transcutol P (40%) as cosurfactant. Infrared spectroscopy, differential scanning calorimetric, and X-ray diffraction studies indicated no incompatibility between drug, oil, and surfactants. The *in vitro* drug release shows that SMEDDS of lovastatin has 94% more drug release than that of drug solution. The results of this study indicate that the SMEDDS of lovastatin, owing to nanosize, has the potential to enhance its absorption and without interaction or incompatibility between the ingredients.[34]

Yan *et al*. (2020), SMEDDS is a uniform and transparent solution consisting of oil phase, surfactant, cosurfactant, and a small amount of water. It could be orally administered under GI peristalsis and spontaneously dispersed to form an o/w microemulsion with typical particle sizes lower than 100 nm. The microemulsion forms a hydration layer that easily passes through the GI wall, which increases the permeability to intestinal epithelial cells, thereby increasing the solubility of poorly soluble drugs and significantly improving bioavailability. This paper mainly introduces the main factors of improving the bioavailability of microemulsion delivery system, the application of SMEDDS, and the characteristics of SMEDDS *in vivo* and *in vitro*. Finally, it summarizes the current prospects of SMEDDS in this field and the challenges ahead.[35]

Wang *et al*. (2020), the composition of the SMEDDS was preliminary screened by the pseudoternary phase diagram. Subsequently, the central composite design method was employed to optimize the prescription of the SMEDDS loaded with phillygenin. The prepared SMEDDS of phillygenin was characterized in terms of morphology, droplet size distribution, PDI, and stability. Then, the *in vitro* dissolution and oral bioavailability were analyzed. The optimized SMEDDS of phillygenin consisted of 27.8% Labrafil M1944CS, 33.6% Cremophor EL, 38.6% PEG-400, and 10.2 mg/g phillygenin loading. The prepared SMEDDS of phillygenin exhibited spherical and uniform droplets with small size (40.11 ± 0.74 nm) and satisfactory stability. The *in vitro* dissolution experiment indicated that the cumulative dissolution rate of the SMEDDS of phillygenin was significantly better than that of free phillygenin. Furthermore, after oral administration in rats, the bioavailability of phillygenin was significantly enhanced by the SMEDDS. The relative bioavailability of the SMEDDS of phillygenin was 588.7% compared to the phillygenin suspension. These findings suggest that the SMEDDS of phillygenin can be a promising oral drug delivery system to improve the absorption of phillygenin.[36]

Rasoanirina *et al*. (2020) to develop SNEDDS to improve the transcorneal permeability of voriconazole. A "mixture design around a reference mixture" approach was applied. This latter included four components, namely, isopropyl myristate, PEG 400, Tween® 80, and Span® 80 as oil, cosolvent, surfactant, and cosurfactant, respectively. Droplet size was selected as a response. The effect of mixture components on droplet size was analyzed by means of response trace method. The optimal formulation was subjected to stability studies and characterized for droplet size, PDI, pH, osmolarity, viscosity, and percentage of transmittance. *Ex-vivo* transcorneal permeation of the optimal and the marketed formulations was carried out on excised bovine cornea using Franz cell diffusion apparatus.[37]

SMEDDS

Recently, due to good and reliable results, there is a great emphasis on SMEDDSs to improve the oral bioavailability of lipophilic drugs. Self-emulsification is a phenomenon, which has been exploited commercially for many years in formulations of emulsifiable concentrates of herbicides and pesticides. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles, surfactant dispersions self-emulsifying formulations, emulsions, and liposomes having advantages and limitations. SMEDDS or self-emulsifying oil formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or, alternatively, one or more hydrophilic solvents and cosolvents/surfactants. There has been growing interest in the use of lipidic excipients in formulations and in self-microemulsifying lipid formulations (SMEDDS) because of their ability to solubilize poorly water-soluble "lipophilic" drugs and overcome the problem of poor drug absorption and bioavailability.[38] It is significant to note that the approach for producing fine emulsion by SMEDDS/SNEDDS is analogous to the low-energy emulsification technique for nanoemulsions. The concentration of the surfactants and cosurfactant within SMEDDS system influence diffusion of the drug from oil globule to dissolution media; therefore, diffusion fundamentally limits the rate of dissolution.[39,40] The major difference between SEDDS, SMEDDS, and SNEDDS are listed in [Table 1].

Advantages of SMEDDS

Potential advantages of SMEDDS systems include:

- They are able to self-emulsify rapidly in gastrointestinal fluids and under the influence of gentle agitation provided by peristaltic and other movements of GIT, they form a fine o/w emulsion.[41]
- They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.
- They can be used for liquid as well as solid dosage forms.[42]
- They require lower dose of drug with respect to conventional dosage forms.
- Fine oil droplets of SMEDDS would pass rapidly, facilitating wide distribution of the drug throughout the stomach and promote the wide distribution of the drug throughout the GIT, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.

Table 1: Major difference between SEDDS, SMEDDS, and SNEDDS

Property	SEDDS	SMEDDS	SNEDDS
Size	>300 nm	<250 nm	<100 nm
Appearance	Turbid	Optically clear	Optically clear
Hydrophilic lipophilic balance (HLB)	<12	>12	>12
Classification as per LFCS	Type II	Type III B	Type III B
Concentration of oil	40–80%	>20	>20
Concentration of surfactant	30–40%	40–80%	40–80%

- Emulsions are sensitive and metastable dispersed forms, while SMEDDS are physically stable formulations.
- As compared with oily solutions, they provide a large interfacial area for the partitioning of the drug between oil and water.[43]
- Ease of manufacture and scale-up is one of the most important advantages that make SMEDDS unique when compared to other drug delivery systems such as solid dispersions, liposome, and nanoparticles, as they require very simple and economical manufacturing facilities such as simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of the pharmaceutical industry in the SMEDDS.[42,43]

Disadvantages of SEDDS

- One of the obstacles for the development of SMEDDS and other lipid-based formulations is the lack of good predictive *in vitro* models for assessment of the formulations.
- Traditional dissolution methods do not work because these formulations potentially are dependent on digestion before the release of the drug.[43]
- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.
- Volatile cosolvents in the conventional SMEDDS formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- Formulations containing several components become more challenging to validate.[42]
- High production costs.
- Low drug incompatibility.
- Drug leakage. Hence, it may allow less drug loading.[43]

Formulation/Composition of SMEDDS

The formulation generally consists of drug, oily vehicle, surfactant, co-surfactant, and even cosolvents. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions under gentle agitation following dilution by aqueous phases (i.e., the digestive motility of the stomach and intestine provide the agitation required for self-emulsification *in vivo* in the lumen of the gut). This spontaneous formation of an emulsion in the GIT presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption. Selection of a suitable self-emulsifying formulation depends upon the assessment of (1) physicochemical properties of the drug, such as pKa, polarity, and solubility in various components (2) physicochemical nature of oily phase, surfactant, and cosurfactant (3) the area of the self-emulsifying region as obtained in the phase diagram, (4) the ratio of the components, especially oil to surfactant ratio, and (5) the droplet size distribution of the resultant emulsion following self-emulsification.[41,42]

Rationale for Selection of SMEDDS Components

Characteristically SMEDDS formulation includes drug, oil, surfactant, and cosurfactant.

- Drug
  For the development of SMEDDS formulation, the lipophilicity along with the dose of the active should be thoroughly scrutinized. Preferably, the drug should possess a low dose; log $P \geq 2$, moreover, should not be susceptible to the first-pass metabolism. The drug inherently should exhibit significant solubility in pharmaceutically acknowledged lipids, surfactants, and cosolvents.[41]
- Oils
  MCT possessing carbon atoms ranging from 6 and 12 are fundamentally transported by the portal blood to the systemic circulation. However, long-chain triglycerides possessing carbon atoms higher than 12 are transported through intestinal lymphatics. Since MCT prominently have high solvent capacity moreover not susceptible to oxidation, they are potentially employed in lipid-based formulation systems.[42]
- Surfactants
  Surfactants contribute the interfacial film besides the interfacial tension being greatly reduced to a low value which enables the dispersion process. Hydrophilic lipophilic balance (HLB) value and concentration of surfactant are significant in the selection of surfactant. For efficient performance, the emulsifier employed in the system should possess HLB value higher than 12, which promotes the formation of small o/w droplets with expeditious dispersion in aqueous media. Basically, non-ionic surfactant with greater HLB value is preferred for the formulation system as they are less toxic than ionic surfactants. HLB value and concentration of surfactant are significant in the selection of surfactant. For efficient performance, the emulsifier employed in the system should possess.[42,43]
- Cosurfactants
  Flexibility to the interfacial layer is imparted by cosurfactants, where the interfacial tension is greatly reduced to an almost negative value. The flexibility induces various curvatures essential to form microemulsion across a wide range. As a cosurfactant mostly, medium chain length alcohols are employed.[43]

Mechanism of Self-emulsification

According to Reiss (19), self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation:

$$DG = SN_i pr_i 2s$$

Where, DG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r, and s represents the interfacial energy. The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence [Figure 1].

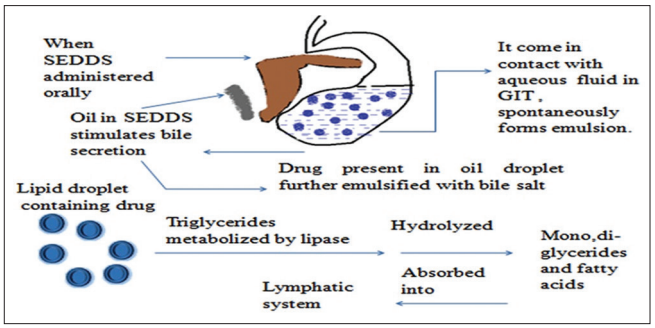

Figure 1: Mechanism of SMEDDS

In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive or negative (then, the emulsification process occurs spontaneously). Emulsification requiring very little input energy.[44]

Application of SMEDDS

SMEDDS formulation is composed of lipids, surfactants, and cosolvents. The system has the ability to form an o/w emulsion when dispersed by an aqueous phase under gentle agitation. SMEDDSs present drugs in small droplet size and well-proportioned distribution and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SMEDDS protect drugs against hydrolysis by enzymes in the GIT and reduce the pre-systemic clearance in the GI mucosa and hepatic first-pass metabolism.[45]

Solubility Enhancement of Acyclovir Using SMEDDS

Acyclovir, an antiviral drug, is a poorly water-soluble drug with a pKa, 2.27 having a pH-dependent solubility and dissolution rate. Acyclovir showed a good absorption from GIT, but due to poor solubility or dissolution rate in GIT it shows low and erratic bioavailability (absorption rate)

To get a better dissolution rate, the solubility of acyclovir is enhance by SMEDDS and an immediate release formulation will be developed to get a quick pharmacological response.

Conclusion

Lipid-based drug delivery systems, especially SMEDDS, are a promising approach for improving the bioavailability of the poorly soluble drug. Bioavailability enhancement has been attributed to a number of factors, including delivery of the drug in solution to the GIT, increased bile secretion, easier partition of the drug into

the mixed micelles that are believed to facilitate drug absorption, stimulation of gastric lymphatic transport, and increased intestinal permeability. The effect of lipids on the bioavailability of orally administered drugs is highly complex due to numerous mechanisms by which the lipids can alter the biopharmaceutical characteristics of the drug. A better understanding of the role of individual lipids, surfactants, and cosurfactants in the formation of SMEDDS, with regard to the dispersion process, the structure of the formed emulsion particle, and drug solubilization is very important in successful designing of these formulations. Therefore, this review focused on the physic-chemical and biopharmaceutical aspects of the SMEDDS which may be helpful for the advancement of this technology to obtain safer, more stable, and efficacious SMEDDS formulations.

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