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SCIENTIFIC REVIEW

Self-Emulsifying Drug Delivery Systems

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Self-Emulsifying Drug Delivery Systems

SUMMARY

The oral route is one of the most preferred ways for chronic drug therapy; but the drug dissolution is usually a rate determining step of the absorption processes for poorly water soluble drugs. Approximately 40% of marketing products are poorly soluble or lipophilic compound that lead to restricted oral bioavailability. To solve this problem, numerous methods such as solid dispersions, liposomes, use of cyclodextrins, nanoparticles, salt formation are utilized. Lipid based formulation is a useful route for enhancing oral bioavailability of biopharmaceutics classification system, Class-2 drugs. Various types of lipid based formulation exist such as emulsion, self-emulsifying drug delivery systems, self-microemulsifying drug delivery systems, and solutions of the drug in lipid medium. Self-emulsifying drug delivery system is one type of lipid based formulation that is defined as isotropic mixtures of natural or synthetic oils, non-ionic surfactants or one/more hydrophilic solvent and co-solvents/surfactant. Self-emulsifying drug delivery systems are stable systems that increase the drug dissolution, provided by a large interfacial area of dispersion in oral administration. These systems form fine emulsions in the gastrointestinal tract with mild agitation, provided by gastric mobility and provide a large interfacial area for drug partitioning between oil and water phases, which increases in solubility and expand absorption. Potential advantages of these systems include the increased oral bioavailability, reduced in needed dose, controlled drug delivery, selective drug targeting, and advanced intestinal lymphatic transport of drugs that would be useful in reducing first pass of the drugs.

Key Words: *Self-emulsifying systems, drug delivery system.*

Kendiliğinden Emülsifiye Olan İlaç Taşıyıcı Sistemler

ÖZET

Oral yol kronik ilaç tedavisi için en çok tercih edilen yollardan biridir; ancak ilacın çözünürlüğü genelde suda çözünürlüğü zayıf olan ilaçlar için emilim süreçlerin hız sınırlayıcı basamaktır. Pazarlanan ürünlerin yaklaşık %40'ı sınırlı oral biyoyararlanıma neden olan az çözünen ya da lipofilik bileşiklerdir. Bu sorunu çözmek için katı dispersiyonlar, lipozomlar, siklodekstrinler, nanopartiküller, tuz oluşumu gibi çeşitli yöntemler kullanılır. Lipid temelli formülasyonlar, biyofarmasötik sınıflandırma sisteminde, Sınıf-2 ilaçların oral biyoyararlanımının artırılması için kullanılan bir yöntemdir. Lipid temelli formülasyonların emülsiyon, kendiliğinden emülsiyon oluşturan ilaç taşıyıcı sistemler, kendiliğinden mikroemülsiyon oluşturan ilaç taşıyıcı sistemler ve yağ ortamındaki ilaç çözeltileri gibi birçok çeşidi vardır. Kendiliğinden emülsiyon oluşturan ilaç taşıyıcı sistemler, doğal ya da sentetik yağların, iyonik olmayan yüzey etkin maddelerin ya da tek/birden çok hidrofilik çözücü ve yardımcı çözücü/yüzey etkin maddenin izotropik karışımları olarak tanımlanan bir lipid temelli formülasyon tipidir. Kendiliğinden emülsiyon oluşturan ilaç taşıyıcı sistemler, dispersiyonun büyük ara yüzey alanı sağlaması ile oral uygulamada ilaç çözünmesini artıran stabil sistemlerdir. Bu sistemler, gastrik hareketliliğin sağladığı hafif bir çalkalama ile mide-bağırsak sisteminde emülsiyon meydana getirmektedir. Böylelikle yağ ve su fazları arasında ilacın partisyonu için büyük bir yüzey alanı sağlayarak çözünürlük ve emilimin artışına neden olurlar. Bu sistemlerin avantajları, oral biyoyararlanımın artması, gereken dozda azalma sağlanması, kontrollü ilaç salımının sağlanması, seçici ilaç salımına olanak sağlaması ve ilk geçiş etkisinin azaltılması için ilaçların intestinal lenfatik geçişinde ilerleme sağlamasıdır.

Anahtar kelimeler: *Kendiliğinden emülsifiye olan sistemler, ilaç taşıyıcı sistem.*

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INTRODUCTION

Patients regard the oral route as the most convenient way for drug administration. However, the pharmaceutical industry is facing an increasing number of poorly soluble drug candidates with low, variable and food dependent bioavailability (1). More than 40% of the new chemical entities exhibit poor solubility. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties (2). A poorly soluble drug could be defined as; its dissolution rate is so slow that dissolution takes longer than the transit time past its absorptive sites, resulting in incomplete bioavailability (3). For such compounds the absorption rate from the gastrointestinal (GI) lumen is controlled by dissolution, and dissolution in the environmental lumen is the rate-controlling step in the absorption process (2,4).

The aqueous solubility of a drug is a prime determinant of its dissolution rate and in case of poorly soluble drugs; the aqueous solubility is usually less than 100 μg/mL. A further parameter that is useful for identifying poorly soluble drugs is the dose/solubility ratio of the drug. This ratio can be defined as the volume of GI fluids necessary to dissolve the administered dose (3).

Modification of the physicochemical properties such as salt formation, use of wetting agents, co-precipitation, and preparation of solid dispersions and particle size reduction of the compound may be one approach to improve the dissolution rate of the drug and improve the absorption rate. However these methods have their own limitations. For instance, salt formation of neutral compounds is not feasible and the synthesis of weak acid and weak base salts may not always be practical (4,5). The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles; such as oils, surfactant dispersions, self-emulsifying formulations, emulsions, and liposomes, with every formulation approach having its specific advantages and limitations or oral solid drugs were improved such as multiparticulates in capsule, matrix tablet, osmotic tablets (2,5).

Lipid based dosage forms, which encompass a wide variety of compositional and functional characteristics, could be advantageously utilized for the formulation of lipophilic drugs (6). Lipid formulations can reduce the inherent limitations of slow and incomplete dissolution of poorly water soluble drugs, and facilitate the formation of solubilized phases from which absorption may occur (7). The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizate within a colloidal dispersion. Lipid formulations allow the drug to remain in a dissolved state throughout its transit through the GI tract (8).

Lipid based oral dosage forms could be classified as lipid solutions, lipid suspensions, emulsions, microemulsions, nanoemulsions, solid dispersions, self-emulsifying drug delivery systems (SEDDSs), self-microemulsifying drug delivery systems (SMEDDSs), self-nanoemulsifying drug delivery systems (SNEDDSs) and self-emulsifying pellets (7,9).

SEDDSs are ideally isotropic/homogenous mixtures of natural or synthetic oils, solid or liquid surfactants and sometimes containing one or more hydrophilic solvents/co-solvents, which emulsify spontaneously under conditions of gentle agitation in the presence of water, similar to those which would be encountered in the GI tract and form fine oil-in-water emulsions or microemulsions (2,10,11). Upon contact with water, the SEDDS formulation spontaneously generates an oil-in-water drug microemulsion with a particle size<150 nm and preferably as low as 10-20 nm (12). When such a formulation is released into the lumen of the gut, it disperses to form a fine emulsion, so that the drug remains in solution in the gut, avoiding the dissolution step which frequently limits the rate of absorption of hydrophobic drug from the crystalline state. Generally this can lead to improved bioavailability, and/or a more consistent temporal profile of absorption from the gut (10). Self-emulsifying formulations usually provide the advantage of increased drug loading capacity when compared with lipid solutions as the solubility of poorly water soluble drugs with intermediate partition coefficients (2<log P<4) are typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents (8). By use of SEDDS which was containing digestible lipids and non-ionic surfactants, drug could maintain in solution in the GI tract, thus surpassing a dissolution step[1]. Self-emulsification process is specific to the nature of the oil and surfactant pair, the surfactant concentration, oil/water surfactant ratio and the temperature at which self-emulsification occurs (2).

Due to the large number of possible excipient combinations that may be used to assemble lipid based formulations and self-emulsifying systems in particular, a classification system (Lipid Formulation Classification System-LFCS) was established by Pouton in 2000 and extra type of formulation was added in 2006 (8,13-15). The main purpose of LFCS is to enable in vivo studies to be interpreted more readily and subsequently to facilitate the identification of the most appropriate formulations for specific drugs with reference to their physicochemical properties (15). LFCS provides a simple framework which can be used in combination with appropriate in vitro tests, to predict how the

fate of a drug is likely to be affected by formulation, and to optimize the choice of lipid formulation for a particular drug (13). These systems can help in solving the under mentioned problems of all the categories of the Biopharmaceutics Classification System (BCS) class drugs. For BCS Class-2 drugs, the problems are solubility and bioavailability. For BCS Class-3 drugs, the problems are enzymatic degradation, gut wall efflux and bioavailability. For BCS Class-4 drugs, the problems are solubilization, enzymatic degradation, gut wall efflux and bioavailability (14).

The LFCS briefly classifies lipid based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation (8,16). Formulations with comprise drug in solution in triglycerides and/or mixed glycerides and simple surfactant-free lipid solution formulations are classified as LFCS Type-1 (8,17). Type-1 lipid formulations represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required dose (16). The simplest lipid products are those in which the drug is dissolved in digestible oil, usually a vegetable oil or medium chain triglyceride. These oil solutions have been the standard way of administering oil soluble vitamins. When an appropriate dose of the drug can be dissolved, LFCS Type-1 formulation may be the system of choice, in view of its simplicity and biocompatibility (8).

More highly dispersed, surfactant containing systems classified as Type-2 or Type-3. Type-2 formulations which have relatively high (digestible) lipid loads contain blends of glycerides and surfactants with hydrophilic-lipophilic balances (HLBs) generally less than 12 and provide efficient initial dispersion to give a particle size in the region of 100-250 nm (17). The distinguishing features of Type-2 systems, typically referred to as SEDDS, are efficient self-emulsification and absence of water soluble components. Type-2 systems are best formulated with medium chain triglycerides and/or mono or diglycerides, blended with ethoxylated oleate esters with HLB values approximately 11 (8). Type-2 lipid based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms (16).

SEDDS are good candidates for the oral delivery of hydrophobic drugs with adequate solubility in oil or oil/surfactant blends (2). This formulations can improve the oral bioavailability of poorly soluble drugs by improving the presentation of the drug in the microemulsion to the intestinal mucosal surface glycocalyx, by a process of either simulating the behavior of or equilibrating with the intestinal bile acid mixed micellar system or the bile acid micellar system in the fed and fasted states respectively within the intestine (12). SEDDS may be a promising alternative to orally administered emulsions because of their relatively high physical stability and ability to be delivered in standard soft or hard gelatin capsules (4,5). SEDDS formulations are usually liquids (12). The rate of gastric emptying of SEDDS is similar to solutions so that they are particularly useful where rapid onset of action is desirable (10).

Many of the marketed products are LFCS Type-3 systems, but this group is particularly diverse as a result of the wide variation in the proportions of oily and water soluble materials used (15). Formulations which could include water soluble and water insoluble surfactants as well as water miscible co-solvents are referred as LBF Type-3, and have been referred to as self-microemulsifying systems, due to the optical clarity which can be achieved with these systems (8,15,16). This group has been divided into Type-3A or Type-3B, to distinguish between formulations which contain a significant proportion of oils (Type-3A) which are similar to Type-2 systems with the addition of a co-solvent or co-surfactant (often to increase drug solubility in the formulation); and those which are predominantly water soluble (Type-3B) and contain relatively little simple glycerides (15,17). Type-3B systems have low glycerides contents. Efficient design of Type-3 formulations can lead to the production of a microemulsion on dispersion in the GI tract and these systems have been described as SMEDDS (17). Such formulations lack the aqueous phase. On dilution, a SMEDDS spontaneously converts to an optically clear and thermodynamically stable microemulsion, which contains the drug in molecular dispersion. SMEDDS is a recent term construing the globule size range less than 100 nm (5,14). Besides this, SNEDDS generates microemulsion with a narrow droplet size distribution of less than 50 nm due to which these systems have also been addressed as nanoemulsions (18). When SEDDS form emulsion particles in the nanometer range, they can be referred to as SNEDDS (19). Typically Type-2 or 3 systems will undergo gastric emptying earlier and will be in a colloidal state earlier than Type-1 systems (8).

LFCS Type-4 formulations represent the recent trend towards formulations which contain predominantly hydrophilic surfactants and co-solvents. Type-4 formulations contain no oils and represent the most extremely hydrophilic formulations. The advantage of blending a surfactant with a co-solvent to give a Type-4 formulation is that the surfactant offers much greater good solvent capacity on dilution (as a micellar solution) than the co-solvent alone (13).

Here is the compositions and general feature of these four systems (Table 1).

Table 1. The compositions and general feature of the LFCS types (8,13-16).

	Increasing hydrophilic content →					
		Type-1	**Type-2**	**Type-3A**	**Type-3B**	**Type-4**
	Excipients	Oils without surfactants	Oils and water insoluble surfactants	Oils, surfactants and co-solvents (Both water insoluble and water soluble excipients)	Oils, surfactants and co-solvents (Both water insoluble and water soluble excipients)	Formulation disperses typically to form a micellar solution
Typical composition (%)	**Triglycerides or mixed glycerides**	100	40-80	40-80	<20	-
	Water insoluble surfactants (HLB<12)	-	20-60	-	-	0-20
	Water soluble surfactants (HLB>12)	-	-	20-40	20-50	30-80
	Hydrophilic co-solvents	-	-	0-40	20-50	0-50
	Particle size of dispersion (nm)	Coarse	100-250	100-250	50-100	<50
	Significance of digestibility	Crucial requirement	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required
	Characteristics	Non-dispersing, requires digestion	SEDDS without water soluble components	SEDDS or SMEDDS with water soluble components	SMEDDS with water soluble component and low oil content	Oil free formulation based on surfactants and co-solvents
	Advantages	Simple	Unlikely to lose solvent capacity on dispersion	Clear or almost clear dispersion, drug absorption without digestion	Clear dispersion, drug absorption without digestion	Good solvent capacity for many drugs, disperses to micellar solution
	Disadvantages	Formulation has poor solvent capacity unless drug is highly lipophilic	Turbid o/w dispersion	Possible loss of solvent capacity on dispersion, less easily digested	Likely loss of solvent capacity on dispersion	Loss of solvent capacity on dispersion, may not be digestible

COMPOSITION OF SEDDS/EXCIPIENT SELECTION

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract (20).

The oily/lipid component is generally a fatty acid ester or a medium/long chain saturated, partially unsaturated or unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature. Examples include mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, fatty acids, fatty alcohols, and mono-/di-/tri-glycerides (21). Unmodified edible oils provide the most `natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduce their use in SEDDS. In contrast, modified or hydrolyzed vegetable oils have contributed widely to the success of the above systems (22).

Lipophilic surfactants with HLB<10 are capable of promoting some emulsification of the oil, but the resulting emulsions are normally too crude to be useful. Hydrophilic surfactants with HLB > 10 are much superior at this providing fine, uniform emulsion droplets which are more likely to empty rapidly from the stomach (23). Furthermore, the large surface

area facilitates faster and more complete absorption. However, in most cases it is the right blend of low and high HLB surfactants that leads to the formation of a stable microemulsion upon exposure to water (24). The usual surfactant strength ranges between 30–60% of the formulation in order to form a stable SEDDS (25).

Co-solvents like diethyl glycol monoethyl ether, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether, etc. may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the microemulsion systems (26).

FORMULATION OF SEDDSs

In the formulation of SEDDS, a surfactant or a mixture of surfactants is added to the oil, so that it will emulsify spontaneously when contacted with water. The challenge is to understand the mechanism of spontaneous emulsification, so that a suitable surfactant or surfactant mixture can be chosen and its concentration in the oil is optimized. Ultra low oil-water interfacial tension and/or substantial interfacial disruption are required to achieve self-emulsification (10). Poorly water soluble molecules are solubilized only in solutions that are entirely organic and composed of either one solvent or a mixture of solvents/surfactants (27). The SEDDS formulation should instantaneously form a clear dispersion which should remain stable on dilution. The hydrophobic agent remains solubilized until the time that is relevant for its absorption (14). Disruption of the oil-water interface is caused by penetration of water into the formulation or diffusion of co-solvents away from the formulation. Both of these phenomena can be studied using equilibrium phase diagrams, which in combination with particle size measurements allow the optimization of performance of SEDDS (10).

The formulation of w/o microemulsions for use as SEDDS or SMEDDS has been investigated using blends of low and high HLB surfactants which were commercially available and pharmaceutically acceptable, typically sorbitan esters and Tween 80 (28). It was found that with the decreasing emulsifier/co-emulsifier ratio (Km) the emulsion area decreased slightly (29).

A series of SEDDS formulations are generally prepared using different surfactant/co-surfactant combinations and the oil. In all the formulations, the level of active moiety is kept constant according to the required dose. Accurately weighed drug is placed in a glass vial, and oil, surfactant, and cosurfactant are added. Then the components are mixed by gentle stirring and vortex mixing and are heated at 40-50°C on a magnetic stirrer if required, until the drug is perfectly dissolved. The mixture is stored at room temperature until further use (30).

The self-emulsifying process is depends on the nature of the oil-surfactant pair, the surfactant concentration, the temperature at which self-emulsification occurs.

The most common excipients used in a SEDDS formulation are (5);

– Lipids such as mono-/di-/tri-olein, gliseril mono linoleat, safflower oil, corn oil, medium chain triglyceride and long chain triglyceride

– Surfactants such as polysorbate 80, polyoxyl 35 castor oil, and polyoxyl hydrogenated 40 castor oil

– Solvents such as ethanol, propylene glycol and polyethylene glycol 400.

Lipids

They are the most important excipient of the SEDDS formulation because oils can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract (2,5). Unmodified edible oils provide the most 'natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduce their use in these systems. Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-dispersing formulations. MCTs were preferred in the earlier self-emulsifying formulations because of higher fluidity, better solubility properties and self-emulsification ability, but evidently they are considered less attractive compared to the novel semi-synthetic medium chain derivatives which can be defined rather as amphiphilic compounds exhibiting surfactant properties (2).

Surfactants

The two issues that govern the selection of a surfactant encompass its HLB and safety. The HLB of a surfactant provides vital information on its potential utility in formulation of SEDDS. For attaining high emulsifying performance, the emulsifier involved in formulation of SEDDS should have high HLB and high hydrophilicity for immediate formation of o/w droplets and rapid spreading of formulation in aqueous media (4,14). Non-ionic surfactants with a relatively high HLB were advocated for the design of self-dispersing systems, where the various liquid or solid ethoxylated polyglycolized glycerides and polyoxyethylene 20 oleate are the most frequently used excipients. Non-ionic surfactants are known to be less toxic compared to ionic surface active agents, but they may cause moderate reversible changes in intestinal wall permeability (2). Several surfactants

can be used to formulate these systems. The most popular surfactants have been polyoxyl 35 castor oil, polyoxyl hydrogenated 40 castor oil and polyethylene glycolylated mixed glycerides (15). SEDDS are usually formulated with triglyceride oils and ethoxylated non-ionic surfactants, usually at surfactant concentrations greater than 25% or 30%. Usually the surfactant concentration ranges between 30% and 60% in order to form stable SEDDS (2,4,10,14).

Co-solvents

Organic solvents such as ethanol, propylene glycol, polyethylene glycol are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as co-surfactants in microemulsion systems (2,4). Alcohol and other volatile co-solvents have the disadvantage of evaporating into the shell or soft/hard gelatin capsules, leading to precipitation of drug (14).

CONVERSION OF LIQUID SEDDS TO SOLID SEDDS

The primary reason to formulate SEDDS in a solid form is to consolidate the advantages of liquid SEDDS with convenience of solid oral dosage forms. Oral solid dosage forms have the following advantages: low production cost, convenience of process control, high stability and reproducibility and better patient compliance. Liquid SEDDS can be filled in soft or hard gelatin capsule or could be converted to pellets or powder (31-33). The following description elaborates various Liquid to solid SMEDDS conversion techniques.

Spray drying

Spray drying is the most widely used technique to convert liquid SEDDS into solid state. In this method the liquid SEDDS is mixed with a solid carrier in a suitable solvent. The solvent is then atomized into a spray of fine droplets. These droplets are introduced into a drying chamber, where the solvent gets evaporated forming dry particles under a controlled temperature and airflow conditions (31). The process parameters required to be controlled are inlet and outlet temperature, feed rate of solvent, and aspiration and drying air flow rate. The dry particles can then be either filled into capsules or made into tablets after addition of suitable excipients. Solid carriers that have been used commonly for this purpose are: Aerosil 200 suspended in ethanol and aqueous solution of Dextran 40 (34,35).

Adsorption to solid carriers

The liquid SEDDS can be made to adsorb onto free flowing powders that possess very large surface area and are capable of adsorbing high quantities of oil material. The adsorption can be done either by mixing liquid SEDDS and the adsorbent in a blender or by simple physical mixing. The resulting powders can be either filled into capsules or can be made into tablets after addition of appropriate excipients. The adsorbents are capable of adsorbing liquid SEDDS up to 70% of its own weight. Solid carriers used for this purpose can be microporous inorganic substances, high surface area colloidal inorganic substances or cross-linked polymers (31). Categories of solid adsorbents used are: silicates, magnesium trisilicate, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and cross-linked polymethyl methacrylate (36).

Encapsulation of liquid and semisolid SEDDS

It is one of the simplest techniques for conversion of liquid SEDDS to solid oral dosage form. Liquid SEDDS can be simply filled in capsules, sealed using a microspray or a banding process. For a semisolid SEDDS, it is a four step process: heating the semisolid excipients to at least 20°C above its melting point; adding the drug in the molten mixture while stirring; filling the drug loaded molten mixture into the capsule shell; and cooling the product to room temperature (33). The compatibility of the excipients used with the capsule shell should be well investigated. Capsule filling of SEDDS is suitable for low dose highly potent drugs and allows high drug incorporation (31).

Extrusion spheronization

This is a solvent free technique that converts liquid SEDDS into pellets using extrusion and spheronization processes. In this method the liquid SEDDS is first mixed with a binder, followed by addition of water until the mass is suitable for extrusion. The extruded mass is then spheronized to form uniform sized pellets. The pellets are then dried and size separated (33). The relative quantity of water and liquid SEDDS used in the process has an effect on size distribution, extrusion force, surface roughness of pellets, and disintegration time (37). High drug incorporation can be achieved by using this technique.

Melt granulation

Melt granulation is another solvent free technique for converting liquid SEDDS. In this method, liquid SEDDS is mixed with a binder that melts or softens at relatively low temperature. This melted mixture can be granulated. This technique is advantageous since it does not require addition of a liquid binder and subsequent drying unlike conventional wet granulation. The variables to be controlled in this process are impeller speed, mixing time, binder particle size, and the viscosity of the binder (31).

CHARACTERIZATION OF SEDDS

The ways to characterize SEDDS are; equilibrium phase diagram, determination of emulsification time, turbidity measurement, droplet size, electron microscopic studies, conductivity, photon correlation spectroscopy, zeta potential measurement, cryo-transmission electron microscopy studies, small-angle neutron scattering, rate of lipolysis and in vitro release studies (11,14,19,29,38,39). Release of drug from SEDDS cannot be evaluated using a conventional release protocol because of dissolved and emulsion-associated drugs must be separated before determination. For this purpose methods must be developed to cut off emulsion-associated drugs during sampling. So dialysis method and ultra filtration methods are developed[29]. The presence of water or another polar co-solvent in a SEDDS formulation may mean that the concentrate is itself a microemulsion. In highlighting factors that predispose efficient microemulsions it is noted that self-emulsification requires least energy close to phase inversion temperature, which is also where the capacity for water solubilization is enhanced (11).

APPLICATIONS OF SEDDS

Improvement in solubility

If a drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of BCS Class-2 drug. A SMEDDS formulation of candesartan cilexetil was prepared for directly filling in hard gelatin capsules for oral administration. The results of the study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like candesartan (40).

Enhanced bioavailability

Ketoprofen, a moderately hydrophobic nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. Ketoprofen is presented in SEDDS formulation. This formulation has enhanced bioavilability due to increase in the solubility of drug which minimizes the gastric irritation. In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SEDDS (41-44).

In another study aceclofenac loaded SNEDDS formulation was developed by Akkuş-Arslan et al[45]. The anti-inflammatory effect of aceclofenac loaded SNEDDS was investigated with carrageenan induced rat paw edema. As result of the study, it was seen that the anti-inflammatory effect increased with the use of SNEDDS, when compared with the solution and suspension forms of aceclofenac.

Protection against biodegradation

The ability of SEDDS to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, because of acidic pH in stomach, enzymatic degradation or hydrolytic degradation etc. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might act as barrier between degradating environment and the drug (30).

SEDDS AS DRUG DELIVERY CARRIERS

Self-emulsifying systems could be presented as pellets, powders, tablets, capsules, suppositories, cream form or the formulation could be presented as its liquid form (4,46-51). Self-emulsifying systems can be used in pharmaceutical field as drug delivery systems for oral, rectal and dermal applications for therapeutic needs. It could be used as pesticide formulation also. The most preferred way is oral application.

Taha et al (52) developed self-nanoemulsifying oral indomethacin formulation using Cremophor RH40 as surfactant, Capmul MCM C8 as co-surfactant and castor oil as solvent. The improved formulation was filled into hard gelatin capsules. It was seen that in the *in vivo* studies done with male Sprague dawley rats; SNEDDS filled capsules showed a significant increase in the rate and extent of drug absorption and in the bioavailability compared to the capsule filled with an oily solution of indomethacin. Marketed SEDDS, SMEDDS and SNEDDS products were generally used orally (Table 2).

Kim and Ku (50) have studied a self-emulsifying formulation with 30% of Tween 85 and 70% of ethyl oleate with indomethacin. Suppositories have done with gelatin, glycerin and distilled water. After a rectal administration of gelatin hollow type suppositories filled with the self-emulsifying system containing indomethacin, it was seen that the rectal absorption of indomethacin in the male Sprague dawley rats significantly increased by the self-emulsifying formulation, comparing with the suppository including indomethacin powder alone.

Soriano et al (51) prepared self-emulsifying cream with improved moisturizing activity. The researchers evaluated formulation's effectiveness by means of non-

Table 2. Examples of marketed products (30,55).

Active material	Trade name	Dosage form
Tretinoin	Vesanoid	Soft gelatin capsule, Roche
Cyclosporine	Neoral	Soft gelatin capsule, Novartis
Cyclosporine	Panimum bioral	Capsule, Panacea Biotec
Cyclosporine A	Sandimmunne	Soft gelatin capsule, Novartis
Cyclosporine A	Gengraf	Hard gelatin capsule, Abbott
Ibuprofen	Solufen	Hard gelatin capsule, Sanofi-Aventis
Fenofibrate	Lipirex	Hard gelatin capsule, Sanofi-Aventis
Ritonavir	Norvir	Soft gelatin capsule, Abbott
Isotretinoin	Accutane	Soft gelatin capsule, Roche
Lopinavir and Ritonavir	Kaletra	Soft gelatin capsule, Abbott
Sanquinavir	Fortovase	Soft gelatin capsule, Hoffman-La Roche
Tipranavir	Aptivus	Soft gelatin capsule, Boehringer Ingelheim

invasive assessment techniques. In another dermal study, Aydın et al (53) developed a SNEDDS formulation containing minoxidil. From the results, it was seen that SNEDDS could deliver minoxidil successfully and promote its permeation across the epidermis.

Song et al (54) have investigated stability of triazophos, which is organophosphorus insecticide, in self-nanoemulsifying pesticide delivery system. Formulations with polyoxyethylene ether surfactant and N-octyl-2-pyrrolidone were formed and investigated with dynamic light scattering and transmission electron microscopy. As a result, it was found that the effect of surfactant on the hydrolysis inhibition of triazophos in the basic condition is more prominent than that in acidic condition.

The successful marketed SEDDS preparations are given in Table 2.

CONCLUSION

SEDDSs are approach for the formulation of drug compounds with poor aqueous solubility. SEDDS is known to improve dissolution characteristics of a poorly water-soluble drug since they maintain the drug in a solubilized state in the GI tract. Lipid based formulations are still not very widespread as commercial formulations, despite their great success in bioavailability. This can be attributed to lack of proper understanding of development and manufacturing process to physical and chemical stability issues. Future focus should be on understanding of the role of lipids and surfactants in the formulation of SEDDS and SEDDS will continue to enable novel applications in drug delivery.

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