Review Article

Self-Emulsifying Drug Delivery System: An Approach to Enhance Solubility

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ABSTRACT

Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are mixtures of oils, surfactants, and cosurfactants, which are emulsified in aqueous media under conditions of gentle stirring and digestive motility that are encountered in the gastrointestinal (GI) tract. We found that SEDDSs could efficiently improve oral absorption of the sparingly soluble drugs by rapid self-emulsification and, subsequently, dispersion in the absorption sites. SEDDSs possess unparalleled potential in improving oral bioavailability of poorly water soluble drugs. Following their oral administration, these systems rapidly disperse in GI fluids, yielding micro-or nanoemulsions containing the solubilized drug. Owing to its miniscule globule size, the micro/nanoemulsifed drug can easily be absorbed through lymphatic pathways, bypassing the hepatic first-pass effect.

Introduction

In recent years, the formulation of poorly soluble compounds has presented interesting challenges for formulation scientists in the pharmaceutical industry. Upto 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and intersubject variability and lack of dose proportionality. To overcome these problems, various formulation strategies are exploited including the use of surfactant, lipid permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions. Recently, much attention has been paid to lipid-based formulations, with particular emphasis on self-emulsifying drug delivery systems (SEDDSs), to improve the oral bioavailability of lipophilic drugs.[1]

However, conventional SEDDSs, which are mostly prepared in a liquid form and orally administered in soft or hard gelatin capsules, can have some disadvantages such as high production costs, low drug incompatibility and stability, drug leakage and precipitation, and capsule aging.[2] Thus, incorporation of liquid SEDDS into a solid dosage form is compelling and desirable. Recently, a new drug delivery technology called solid SEDDS, which combines the advantages of SEDDS and those of solid dosage forms, has been investigated.[2] SEDDS 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 co-solvents/surfactants.[3-5]

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Advantages of self-emulsifying drug delivery systems over conventional drug delivery systems

1. Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these systems can form fine oil in water (o/w) emulsion or microemulsion (S(M)EDDS). Fine oil droplets would pass rapidly facilitating wide distribution of the drug throughout the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.[6]
2. Emulsions are sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulations that are easy to manufacture.
3. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.

4. Potential advantages of these systems include enhanced oral bioavailability, more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut. Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.[7,8]

Composition of self-emulsifying drug delivery systems

The self-emulsifying process depends on:
1. The nature of the oil–surfactant pair
2. The surfactant concentration
3. The temperature at which self-emulsification occurs[9]

Oils

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.[10,11] Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages. Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride oils.[12]

Surfactant

Non-ionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30 and 60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen[13]

Co-solvents

Co-solvents like diehylene glycol monoethyle ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol, polyethylene glycol ether (glycofurol), 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 cosurfactant in the microemulsion systems.[14]

Formulation of self-emulsifying drug delivery systems

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants to water soluble co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions.[15] The following should be considered in the formulation of SEDDS: the solubility of the drug in different oils, surfactants and co-solvents; the selection of oil, surfactant and co-solvent based on the solubility of the drug, and the preparation of the phase diagram,[16] and the preparation of an SEDDS formulation by dissolving the drug in a mix of oil, surfactant and co-solvent. The addition of a drug to an SEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil–surfactant ratio. So, the design of an optimal SEDDS requires preformulation solubility and phase diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent.[17]

Characterization of self-emulsifying drug delivery systems

The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

Visual assessment

This may provide important information about the self-emulsifying and microemulsifying property of the mixture and the resulting dispersion.[18,19]

Turbidity measurement

This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.

Droplet size

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion.[20-22] Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size.[23-25] The reduction of the droplet size to values below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions.[26]

Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to the presence of free fattyacids.[27]

Determination of emulsification time

Self-emulsification time, dispersibility, appearance and flow ability were observed and scored.[28]

Biopharmaceutical aspects

The ability of lipids and/or food to enhance the bioavailability of poorly water soluble drugs has been comprehensively reviewed and the interested reader is directed to these references for further details. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms including the following.[29]

a) *Alterations (reduction) in gastric transit,* thereby slowing delivery to the absorption site and increasing the time available for dissolution.[30]
b) *Increases in effective lumenal drug solubility:* The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures, either directly (if sufficiently polar) or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.[31]
c) *Stimulation of intestinal lymphatic transport:* For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly, or indirectly via a reduction in first-pass metabolism.[32-35]
d) *Changes in the biochemical barrier function of the GI tract:* It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism.[36-39]
e) *Changes in the physical barrier function of the GI tract:* Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water soluble, and in particular, lipophilic drugs.[8]

Application of self-emulsifying drug delivery system

Supersaturable self-emulsifying drug delivery system

The high surfactant level typically present in SEDDS formulations can lead to GI side effects and a new class of supersaturable formulations, including supersaturable SEDDS (S-SEDDS) formulations, have been designed and developed to reduce the surfactant side effects and achieve rapid absorption of poorly soluble drugs.[40-44] The S-SEDDS approach is designed to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturation is intended to increase the thermodynamic activity of the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier,[45] e.g., an S-SEDDS of paclitaxel (PTX) was developed using hydroxypropyl methyl cellulose (HPMC) as a precipitation inhibitor with a conventional SEDDS formulation, and a poorly soluble drug, PNU-91325, was formulated as an S-SEDDS. It is worth emphasizing that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach provides a better toxicity/safety profile than the conventional SEDDS formulations.[46,47]

Solid self-emulsifying drug delivery system

SEDDS are normally prepared as liquid dosage forms that can be administrated in soft gelatine capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/spheronization to provide a good *in vitro* drug release (100% within 30 minutes, T50% at 13 minutes).[48,49]

Recent approaches in self-emulsifying drug delivery system

1. SEDDS of coenzyme Q10 was prepared and this resulted in enhanced bioavailability and reduced toxicity.[50]
2. Lipophilic compound WIN 54954 was formulated as SEDDS in triglyceride oil/non-ionic surfactant mixtures and resulted in improved reproducibility of the plasma profile in terms of *C*max and *T*max.[51]
3. Self-microemulsifying drug delivery system (SMEDDS) of simavastin was developed to enhance its oral bioavailability. This study illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds.[52]
4. A novel SEDDS of PTX (used for the treatment of solid tumors) was prepared and it was found that SEDDS was chemically stable for at least 1 year when kept as two part formulation and also the drug loading was increased by approximately fivefold. Compared to marketed i.v. formulation, the excipient presented a significantly reduced cytotoxicity and led to a stable microemulsion.[53]
5. An antimalarial drug, Halofantrine, was prepared as SEDDS and SMEDDS and resulted in an eightfold improvement in absolute oral bioavailability relative to previous data of the solid.[11]
6. Enhanced bioavailability upto 1.88 of silymarin was achieved by SMEDDS.[54]
7. Using SEDDS, self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone was prepared and the study revealed that SNEDDS overcame the drawbacks of the traditional emulsified system, such as low solubility and irreversible precipitationof the active drug in the vehicle with time.[55]
8. The two novel SMEDDSs containing Labrasol with different dilutions on tight junction were studied and found that Labrasol at a concentration of 0.1 and 1% was shown to increase the permeability of mannitol by 4.6-fold and 33.8-fold, respectively.[56]
9. The solid self-emulsifying system (SES) was used in the delivery of diclofenac and results indicated that diclofenac could be comfortably administered in the form of self-emulsifying tablets using goat fat and Tween 65 admixtures.[57]
10. SEDDS containing ketoprofen was formulated as sustained release dosage form and it was found that drug release was increased.[58]

Mechanism of self emulsification

Self emulsifying process is related to the free energy,

$$\Delta G = \sum N\pi r^2\sigma \quad (1)$$

Here, N is the number of droplets with radius r and σ is the interfacial energy. It is apparent from the equation that the spontaneous formation of interface between the oil and water phase is energetically not favorable. The systems commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense.

Mustafa and Groves developed a method of quantitatively assessing the ease of emulsification by monitoring the turbidity of the oil–surfactant system in a water stream, using phosphated nonyl phenoloxylate (PNE) and phosphated fatty alcohol ethoxylate (PFE) in *n*-hexane, and suggested that the emulsification process may be associated with the ease with which water penetrates the oil–water interface, with formation of liquid crystalline phase resulting in swelling at the interface, thereby resulting in greater to relate the phase behavior to the spontaneity of emulsification, with liquid crystals formation, tending to form emulsion more readily, as indicated by the lower equilibration times.

Pouton has argued that the emulsification properties of the surfactant may be related to phase inversion behaviour of the system. For example, if one increases the temperature of the oil in the water system stabilized by using non-ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion. The surfactant is highly mobile at the phase inversion temperature; hence the o/w interfacial energy is minimized, leading to a reduction in energy required to bring about emulsification.[59]

Excipients used in SEDDS

Polyglycolyzed glycerides (PGG) with varying fatty acid and polyethylene glycol (PEG) chain lengths giving them a varied HLB value, in combination with vegetable oils, have been used to solubilize poorly water soluble drugs and improve their bioavailability. According to the manufacturer, these products are derived from selected, high purity, food-grade vegetable oils which are reacted with pharmaceutical grade PEG and are therefore expected to be well tolerated by the body.[27]

Recently, the emulsification and solubilization properties of PGG-based oils, Labrafils, in self-emulsifying formulations have been investigated using Tween 80 and Tween 20 as surfactants. Danazol (a poorly water soluble compound with an estimated aqueous solubility of <1 mg/mL and log $P = 4.2$) and mefenamic acid (a non-steroidal anti-inflammatory drug with an aqueous solubility of 40 mg/ml and log $P = 5.3$) were selected as the model drugs.[27] The more hydrophilic oil–surfactant mixtures showed greater emulsification ability and a smaller particle size. A linear relationship was observed between the HLB of the mix and the solubility of both danazol and mefenamic acid, with more hydrophilic mixtures producing greater drug solubility.

These results should serve as a useful guide to the proper selection of PGG for SEDDS. Galactolipids, which are polar lipids commonly found in the chloroplast membranes of green plants and a natural part of the human diet, are the main surfactants in formulations of cyclosporine. Similar to PLs, galactolipids have good emulsifying properties, but one major difference is that PLs are charged, while galactolipids are non-ionic and regarded as being safe for long-term use. However, surfactants of natural origin usually have a limited self-emulsification capacity.[60]

The commonly used emulsifiers are various solid or liquid ethoxylated PGGs and polyoxyethylene 20 oleate (Tween 80). Excipients in the formulation are usually selected from the Generally Recognized As Safe (GRAS) list of ingredients as published by the Food and Drug Administration (FDA). If compounds are not listed in GRAS, their potential toxicity is of utmost importance.

An S-SEDDS of PTX was developed using HPMC as a precipitation inhibitor with a conventional SEDDS formulation. *In vitro* dilution of the S-SEDDS formulation results in formation of a microemulsion, followed by slow crystallization of PTX on standing. This result indicates that the system is supersaturated with respect to crystalline PTX and the supersaturated state is prolonged by HPMC in the formulation. In the absence of HPMC, the SEDDS formulation undergoes rapid precipitation, yielding a low PTX solution concentration. A pharmacokinetic study showed that the PTX S-SEDDS formulation produces approximately a 10-fold higher maximum concentration (*C*max) and a 5-fold higher oral bioavailability compared with that of the orally administered Taxol formulation (F 2.0%) and the SEDDS formulation without HPMC.

A poorly soluble drug, PNU-91325, was formulated as an S-SEDDS. The comparative *in vitro* studies indicated that the presence of a small amount of HPMC in the formulation was critical to achieve a stabilized supersaturated state of PNU-91325 upon mixing with water. An S-SEDDS formulation composed of 30% w/w Cremophor (surfactant), 9% PEG 400, 5% Dimethyl amine, 18% Pluronic L44, 20% HPMC, and other minor components had an oral bioavailability of ~76%, comparable with that of a neat Tween formulation (bioavailability 68%). Note that the weight ratio of drug to cremophor EL is 1:7.5 in the S-SEDDS formulation, while the weight ratio of drug to Tween is 1:39 in the neat Tween formulation.

Applying the S-SEDDS approach, a reduced amount of surfactant is deliberately used with HPMC in order to produce a temporarily supersaturated state with reduced solubilization. This is to obtain a high free drug concentration through generating and maintaining a supersaturated state *in vivo* and to increase the driving force for absorption. It is worth emphasizing that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach provides a better toxicity/safety profile than the conventional SEDDS formulations. However, the underlying mechanism of the inhibited crystal growth and stabilized supersaturation by means of these polymers is poorly understood even although several studies have been carried out to investigate this.[28]

Technique of solid self-emulsifying drug delivery system development

Solid SEDDS were developed mainly by adsorption of solid carriers, spray drying, melt extrusion, dry emulsion, solid dispersion, etc. These solid SEDDS can be converted into pellets, tablets and capsules.

Solid carriers

These solid carriers have the property to absorb liquid/semisolid formulation as SES. It is a simple procedure, where SES is incorporated into a free-flowing powder material which has adsorption quality. The mixture is uniformly adsorbed by mixing in a blender. This solid mixture is filled into capsule or added to more excipient before compression into tablets. The above mixture

is solidified to powder forms using three kinds of adsorbents: microporous calcium silicate (Florite™ RE), magnesium aluminum silicate (Neusilin™ US2) and silicon dioxide (Sylysia™ 320).[61]

Spray drying

In this technique, first the prepared formulation containing oil, surfactant, drug, solid carrier, etc., is sprayed into a drying chamber through a nozzle. The volatile vehicles first evaporate leaving behind small solid particles. These particles are then filled into capsules or compressed into tablets.

Melt extrusion

This formulation technique depends on the property of the plastic mass material which can be easily extruded with pressure. Here, there is no need for addition of liquid form of excipient but a constant temperature and pressure needs to be maintained.

Dry emulsion

It is mainly o/w emulsion, which is then converted into solid form by spray drying/solid carrier/freeze drying.[62]

Dosage forms from self-emulsifying system

Self-emulsifying capsule

It is a capsule containing liquid or semisolid form of SES. In the GIT, the capsules get dispersed to SES uniformly in the fluid to micron size, enhancing the bioavailability. Second type of self-emulsifying capsule is solid SES filled into capsule.

Self-emulsifying tablets

Nazzal *et al*. developed self-nanoemulsified tablet dosage form of ubiquinone. The main objectives of this study were to study the effect of formulation ingredients on the release rate of ubiquinone and to evaluate an optimized self-nanoemulsified tablet formulation. The first self-nanoemulsion system containing ubiquinone was prepared as a nanoemulsion. This nanoemulsion was adsorbed by granular materials and then compressed to form tablets. The optimized formulation of coenzyme Q10 self-nanoemulsified tablet dissolution profile showed that 80–90% drug release took place in 45 minutes.

Attama *et al*. formulated the solid SESs in the delivery of diclofenac. This solid SES was developed using goat fat and Tween. The fatty material and surfactant were heated together and melted. This was added to weighed quantity of drug and the drug was dissolved in the molten mass. This molten mass was then poured into plastic mould and cooled. These tablets liquify at body temperature without agitation, and under the gastrointestinal conditions, agitation due to peristaltic movement will lower the liquification time, resulting in faster emulsification with increased plasma concentration. Different formulation ratios show varying dissolution profile at constant speed/agitation. These tablets showed good release profiles with acceptable tablet properties.[63]

Self-emulsifying pellets

Tuleu *et al*. conducted comparative bioavailability study in dogs by comparing a self-emulsifying formulation of progesterone presented as pellets and in the liquid form with an aqueous suspension of progesterone. The *in vitro* dissolution tests showed that nearly 100% of progesterone dissolved within 30 minutes and within 5 minutes from capsules containing progesterone dissolved in SES. From the aqueous suspension, 50% of the dose was released within 60 minutes. They also tested pellets administered orally to dogs versus the same dose of progesterone dissolved in liquid SES in capsules or a suspension of micronized progesterone.[64] Figure 1 shows the processing of lipid and coadministered drug. In their study, it was found that SES pellets and SES solution had higher plasma levels of progesterone at each time point as compared to the aqueous suspension of progesterone.

Franceschinis *et al*. developed a method of producing self-emulsifying pellets (SEPs) by wet granulation. They first developed a binder solution containing an oil (mono and diglycerides), polysorbate 80 and model drug nimesulide in different proportions. This oil–surfactant mixture was stirred, then added to water to form SES. The second step was to prepare granules from microcrystalline cellulose (MCC) and lactose in a granulator. These binder solutions were sprayed onto the granules and pellets were formed by increasing the speed of the granulator. Pellets were able to generate significantly smaller droplets with respect to the corresponding emulsions. Serratoni *et al*. presented controlled drug release from SEPs.

SESs were formed by mixing oil–surfactant within solublized drug in appropriate concentrations because higher quantity of drug incorporated into SES could be precipitated when diluted with water. This SES was added into damp mass of MCC and lactose monohydrate, water was then added to the prepared wet mass for extrusion–spheronization to form pellets. These pellets were coated by hydrophilic polymers, namely ethyl cellulose, and then coated by aqueous solution of HPMC in a fluid bed coater. The ability of this formulation is to enhance dissolution of the model drug, where dissolution results for the uncoated pellets containing methyl or propyl parabens, with and without the addition of SES was compared.

Ahmed abdalla and Karsten Mader investigated preparation and characterization of SEPs formulation. They formulated three SESs separately by melting Cithrol Glecerides mono sterates (mono

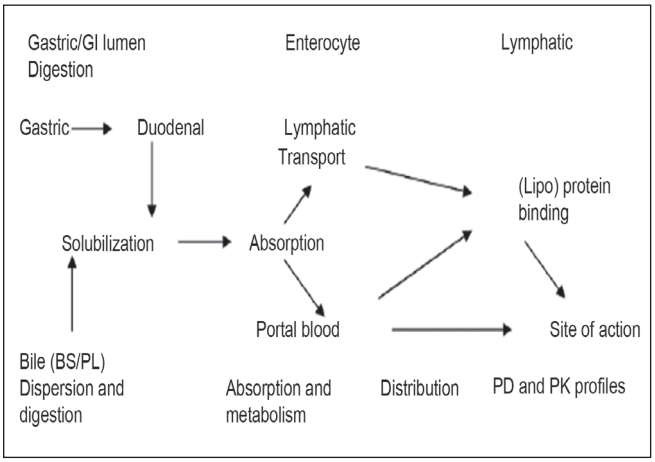

Figure 1: Processing of lipid and coadm*inistered* drug

and diglycerides) and solutol HS. To this was added drug, dye and spin probe. Then water was added to the molten lipid blend until a creamy mass was formed, and then dry MCC was added to it to form a suitable mass for extrusion.

The dye was added for assessment of self-emulsification and spin probe was added for the release kinetics and microenvironment of pellets, during release process, which were assessed using electron spin resonance spectroscopy. The dissolution profile showed complete release of drug as diazepam from the non–self-emulsifying GMS/MCC pellets. It had a threefold duration of action. Nearly 90% of the drug was released after an hour, while only 55% was released from the GMS/MCC pellets. Pellets composed of MCC/GMS were only capable of releasing diazepam until the saturation solubility was reached.[60]

Tosio *et al*. prepared bilayered SEPs. SEP was formed by coextrusion–speronization with two cohesive layers. In that, type 1 pellets had formulation A (a matrix made of lactose and MCC loaded with an SES dispersion) in the inner part and formulation B (an inert matrix containing lactose, MCC, and water) in the outer part, and type 2 pellets had formulation B in the inner core and formulation A externally. SEPs were formulated in two steps: first, oil–surfactant mixture was prepared and then added to water to form SES and this mixture was then loaded into MCC and lactose to form suitable extrusion–speronization mass for pellets. Pellets of type I plus 2% of croscarmellose sodium released 90% of vinpocetine as a model drug within 30 minutes; pellets of type II were released in 20 minutes and from the physical mixture only 25% of drug was released after 60 minutes.

Self-emulsifying beads

SES can be formulated as a solid dosage form by using less excipient. Patil and Paradkar discovered that deposition of SES into microporous polystyrene beads was done by solvent evaporation. Porous polystyrene beads (PPB) with complex internal void structures were typically produced by copolymerizing styrene and divinyl benzene. It is inert and stable over a wide range of pH, temperature and humidity. Geometrical features such as bead size and pore architecture of PPB, were found to govern the loading efficiency and *in vitro* drug release from SES loaded PPB.[41]

Self-emulsifying microsphere

You *et al*. formulated solid SE sustained release microspheres using the quasi-emulsion solvent diffusion method for the spherical crystallization technique. Zedoary turmeric oil release behavior could be controlled by the ratio of HPMC acetate succinate to Aerosil 200 in the formulation. The plasma concentration time profiles were achieved after oral administration of such microspheres to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS.

Self-emulsifying nanoparticle

Nanoparticle technology can be applied to the formulation of self-emulsifying nanoparticle. One of the solvents is an injection. In this method, the prepared molten lipid mass contains lipid, surfactant and drug. This lipid molten mass is injected dropwise into a non-solvent system. This is filtered and dried to get nanoparticles. By this method, 100 nm size particle with 70–75% drug loading efficiency is obtained. The second technique is sonication emulsion diffusion evaporation. By this method are coloaded 5-flurouracil and antisense epidermal growth factor receptor (EGFR) plasmids into biodegradable polylactidecoglycolide (PLGA)/carboxmethylchitosan (CMC) nanoparticles. The mixture of PLGA and CMC had an SE effect, with no additional surfactant required. Trickler *et al*. developed a novel nanoparticle drug delivery system consisting of chitosan and glycerylmonooleate (GMO) for the delivery of PTX. These chitosan/GMO nanoparticles with bioadhesive properties increased cellular association and were prepared by multiple emulsion (o/w/o) solvent evaporation methods.[27]

Conclusion

SEDDS in solid dosage form has improved solubility/dissolution, absorption and bioavailability for poorly water soluble drug.

This is the method suited for lipophilic drugs where resulting emulsification gives faster dissolution rates and absorption. Solid SEDDS is superior to SEDDS in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Solid SEDDS has the flexibility to develop into different solid dosage forms for oral and parenteral administrations. SEDDSs are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

References

1. Burcham DL, Maurin MB, Hausner EA, Huang SM. Improved oral bioavailability of the hypocholesterolemic DMP 565 in dogs following oral dosing in oil and glycol solutions. Biopharm Drug Dispos 1997;18:737-42.
2. Serajuddin AT, Sheen PC, Mufson D, Bernstein DF, Augustine MA. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersion. J Pharm Sci 1988;77:414-7.
3. Myers RA, Stella VJ. Systemic bioavailability of penclomedine (NSC-338720) from oil-in-water emulsions administered intraduodenally to rats. Int J Pharm 1992;78:217-26.
4. Schwendener RA, Schott H. Lipophilic arabinofuranosyl cytosine derivatives in liposomal formulations for oral and parenteral antileukemic therapy in the murine L1210 leukemia model. J Cancer Res Clin Oncol 1996;122:723-6.
5. Shah NH. Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving *in vitro* dissolution and oral absorption of lipophilic drugs. Int J Pharm 2006;106:15-23.
6. Gursoy RN, Benita S. Self-emulsifying drug delivery systems for improved oral delivery of lipophilic drugs. Biomed Pharmacother 2006;8:173-82.
7. Constantinides PP. Lipid microemulsions for improving drugs dissolution and oral absorption: Physical and biopharmaceutical aspects. Pharm Res 1995;12:1561-72.
8. Khoo SM, Humberstone AJ, Porter CJ, Edward GA, Charman WN. Formulation design and bioavailability assessment of lipidicsilf-emulsifying formulation of halofanitrine. International Journal of Pharmaceutics 1998;167:155-64.
9. Sugimoto M, Okagaki T, Narisawa S, Koida Y, Nakajima K. Improvement of dissolution characteristics and bioavailability of poorly water soluble drugs by novel cogrinding methodusing water soluble polymer. Int J Pharma 1998;160:11-9.

10. Farah N, Laforet JP, Denis J. Self micro emulsifying drug delivery systems for improving dissolution of drugs: *In vitro* evaluations. AAPS PharmSciTech 1998;161:15-23.
11. Nazzal S, Khan MA. Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. Int J Pharm 2006;315:110-21.
12. Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: Physical and biopharmaceutical aspects. Pharm Res 2009;12:1561-72.
13. Craig DQM, Barker SA, Banning D, Booth SW. An investigation into the mechanism of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. Int J Pharm. 1995; 114:103-10.
14. Gursoy N, Garrigue JS, Razafindratsita A, Lambert G, Benita S. Excipient effects on *in vitro* cytotoxicity of a novel paclitaxel selfemulsifying drug delivery system. J Pharm Sci 2003;92:2420-7.
15. Gershanik T, Benita S. Positively-charged self-emulsifying oil formulation for improving oral bioavailability of progesterone. Pharm Dev Technol 2009;1:147-57.
16. Tarr BD, Yalkowsky SH. Enhanced intestinal absorption of cyclosporine in rats through the reduction of emulsion droplet size. Pharm Res 2003;6:40-3.
17. Charman SA, Charman WN, Rogge MC, Wilson TD, Dutko FJ, Pouton CW. Self-emulsifying drug delivery system: Formulation and biopharmaceutic evaluation of an investigational lipophilic compound. Pharma Res 2002;9:87-93.
18. Holm R, Jensen IH, Sonnergaard J. Optimization of self-microemulsifying drug delivery system using D-optimal design and the desirability function. Drug Dev Ind Pharm 2006;32:1025-32.
19. Shen H, Zhong M. Preparation and evaluation of self-microemulsifying drug delivery system containing atorvastatin. J Pharm Pharmacol 2008;58:1183-91.
20. Patil P, Joshi P, Paradkar A. Effect of formulation variables on preparation and evaluation of gelled self emulsifying drug delivery systems of ketoprofen. AAPS PharmSciTech 2004;5:1-8.
21. Shen HR, Zhong MK. Preparation and evaluation of self micro emulsifying drug delivery systems containing atorvastatin. J Pharm Pharmacol 2006;58:1183-91.
22. Wei L, Sun P, Nie S, Pan W. Preparation and evaluation of SEDDS and SMEDDS containing Carvedilol. Drug Dev Ind Pharm 2005;31:785-94.
23. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, *et al*. Development of self-microemulsifying drug delivery systems for oral bioavailability enhancement of simvastatin in beagle dog. Int J Pharm 2004;274:65-73.
24. Hong JY, Kim JK, Song YK, Park JS, Kim CK. A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption. J Control Release 2006;110:332-8.
25. Chae GS, Lee JS, Kim SH, Seo KS, Kim MS, Lee HB, *et al*. Enhancement of the stability of BCNU using self-emulsifying drug delivery systems (SEDDS) and *in vitro* antitumor activity of self-emulsified BCNU-loaded PLGA wafer. Int J Pharm 2008;301:6-14.
26. Kommuru TR, Gurley B, Khan MA, Reddy IK. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: Formulation development and bioavailability assessment. Int J Pharm 2005;212:233-46.
27. Attama AA, Nzekwe IT, Nnamani PO, Adikwu MU, Onugu CO. The use of solid self-emulsifying systems in the delivery of diclofenac. Int J Pharm 2003;262:23-8.
28. Serratoni M, Newton M, Booth S, Clarke A. Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. Eur J Pharm Biopharm 2007;65:94-8.
29. Grove M, Müllertz A, Nielsen JL, Pedersen GP. Bioavailability of seocalcitol II: Development and characterisation of self-microemulsifying drug delivery systems (SMEDDS) for oral administration containing medium and long chain triglycerides. Eur J Pharm Sci 2006;28:233-42.
30. Yang WW, Wang LQ. Enhanced bioavailability of silymarin by self-microemulsifying drug delivery system. Eur J Pharm Biopharm 2006;63:288-94.
31. Date AA, Nagarsenker MS. Design and evaluation of selfnanoemulsifying drug delivery systems (SNEDDS) for cefpodoximeproxetil. Int J Pharm 2007;329:166-72.
32. Taha EI, Al-Saidan S, Samy AM, Khan MA. Preparation and *in vitro* characterization of self nanoemulsified drug delivery system (SNEDDS) of all-trans-retinol acetate. Int J Pharm 2004;285:109-19.
33. Perng CH, Kearney AS, Patel K, Palepu NR, Zuber G. Investigation of formulation approaches to improve the dissolution, a poorly water soluble lipooxygenase inhibitor. Int J Pharma 1998;176:31-8.
34. Nazzal S, Guven N, Reddy IK, Khan MA. Preparation and characterization of Coenzyme Q10 Eudragit solid dispersation. Drug Dev Ind Pharm 2002;28:49-57.
35. Pouton CW. Self-emulsifying drug delivery system; assessment of the efficiency of emulsification. Int J Pharm 1985;27:335-48.
36. Patravale VB, Date AA, Kale AA. Oral self micro emulsifying system: Potential in drug delivery system. Pharm Technol 2003;29:44-8.
37. O'Driscoll CM. Lipid based formulation for intestinal lymphatic delivery. Eur J Pharm Sci 2002;15:405-15.
38. Charman SA, Charman WN, Rogge MC, Wilson TD, Dutko FJ, Pouton CW. Self-emulsifying drug delivery system: formulation and biopharmaceutical evaluation of an investigational lipophilic compound. Pharm Res 1992;9:87-93.
39. Kossena GA, Boyd BJ, Porter CJ, Charman WN. Separation and characterization of the colloidal phases produced on digestion of common formulation lipids and assessment of their impact on the apparent solubility of selected poorly water soluble drugs. J Pharm Sci 2003;92:634-48.
40. Amidon GL, Lennernas H, Shah VP, Crison JR. Therotical basis for a biopharmaceutical classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995;12:413-20.
41. Franceschinis E, Voinovich D, Grassi M, Perissutti B, Filipovic-Grcic J, Martinac A, *et al*. Self-emulsifying pellets prepared by wet granulation in high shear mixer: Influence of formulation variables and preliminary study on the *in vitro* absorption. Int J Pharm 2005;291:87-97.
42. Newton M, Petersson J, Podczeck F, Clarke A, Booth S. The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture. J Pharm Sci 2000;90:987-95.
43. Reiss H. Entropy induced dispersion of bulk liquid. J Colloid Interface Sci 1975;53:61-70.
44. Groves MJ, Mustafa RM. Measurement of "spontaneity" of self emulsifiable oils. J Pharm Pharmacol 1974;26:671-88.
45. Groves MJ, Mustafa RM, Carless JE. Phase studies of mixed surfactants n-hexane and water. J Pharm Pharmacol 1974;26:616-23.
46. Friedman D. Non-aqueous compositions for oral delivery of insoluble bioactive agents. US Patent.
47. Ockner RK, Manning JM. Fatty acid binding protein in the small intestine; indentification, isolation and evidence for its role in cellular fatty acid transport. J Clin Invest 1974;54:326-38.
48. Greenberger NJ, Rodgers JB, Isselbacher KJ. Absorption of medium and long chain triglycerides: Factors influencing their hydrolysis and transport. J Clin Invest 1966;45:217-27.
49. Porter CJ, Charman WN. Uptake of drug into the intestinal lymphatic after oral administration. Adv Drug Deliv Rev 1997;25:71-89.
50. Cheema M, Palin K, Davis SS. Lipid Vehicles for intestinal lymphatic drug transport. J Pharm Pharmacol 1987;39:55-6.
51. Embleton JK, Pouton CW. Structure and function of gastro intestinal lipase. Adv Drug Deliv Rev 1997;25:15-32.
52. Wakerley MG, Pouton CW, Meakin BJ, Morton FS. Self-emulsification of vegetable surfactant mixtures: A proposed mechanism of action. American Chem Soc Symp Ser 1986;311:242-55..
53. Ishida M, Tawa R, Shibata N, Takada K. Oral solid gentamicin preparation using emulsifier and adsorbent. J Control Release 2005;105:23-31.
54. Verreck G, Brewster ME. Melt extrusion based dosage forms: Excipients and processing conditions for pharmaceutical formulations. J. melt extrusion 2004;97:85-95.
55. Bamba J, Cave G, Bensouda Y, Tchoreloff P, Pulsieux F, Couarrraze G. Cryoprotection of emulsions in freeze drying: Freezing process analysis. Drug Dev Ind Pharm 1995;21:1749-60.
56. Christensen KL, Pedersen GP, Kristensen HG. Technical optimization of redispersible dry emulsions. Int J Pharm 2001;212:195-202.
57. Hansen T, Holm P, Schultz K. Process characteristics and compaction of spraydriedemulsions containing a drug dissolved in lipid. Int J Pharm 2004;287:55-66.
58. Jang DJ, Jeong EJ, Lee HM, Kim BC, Lim SJ, Kim CK. Improvement of

bioavailability and photostability of amlodipine using redispersible dry emulsion. Eur J Pharm Sci 2006;28:405-11.
59. Nazzal S, Nutan M, Palamakula Shah AR, Zaghloul AA, Khan MA,. Optimiztion of a self-nanoemulsified tablets dosage form of Ubiquinone using response surface methodology: Effect of formulation ingredients. Int J Pharm 2002;240:103-14.
60. Tuleu C, Newton M, Rose J, Euler D, Saklatvala R, Clarke A, *et al*. Comparative bioavailability study in Dogs of a self-emulsifying formulation of progesterone presented in a pellets and liquid form compared with an aque*ous* suspension of progesterone. J Pharm Sci 2004;93:1495-502.
61. Abdalla A, Mader K. Preparation and characterization of a self-emulsifying pellets formulation. Eur J Pharm Biopharm 2007;66:220-6.
62. Raghavan SL, Kiepfer B, Davis AF, Kazarian SG, Hadgraft J. Membrane transport of hydrocortisone acetate from supersaturated solutions: The role of polymers. Int J Pharm 2001;19:95-105.
63. Pellet MA, Castellamo S, Hadgraft J, Davis AF. The penetration of supersaturated solutions of piroxicam across silicone membranes and huamn skin *in vitro*. J Control Release 1997;46:205-14.
64. Hasegawa A, Taguchi M, Suzuki R, Miyata T, Nakagawa H, Sugimoto I. Supersaturation mechanism of drugs from solid dispersions with enteric coating agents. Chem Pharm Bull 1988;36:4941-50.

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