SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): A REVIEW

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Self-emulsifying drug delivery system is mixture of oils, surfactant, cosurfactant, which are emulsified in aqueous media under condition of gentle stirring and digestive motility that would be encountered in the gastrointestinal tract. SEDDS is one of the approaches to improve the oral bioavailability of the hydrophobic drugs. The liquid SEDDS can be converted into solid dosage form without affecting drug release property. Due to its small size the micro/nano emulsified drug can easily be absorbed through lymphatic pathways thereby bypassing the hepatic first-pass effect. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. Self-emulsification occurs when entropy changes that favor dispersion is greater than the energy required to increase the surface area of the dispersion.

Keywords: SEDDS, oil, surfactant, cosurfactant

INTRODUCTION

In recent years, the formulation of poor water soluble compounds present interesting challenges for formulation scientists in the pharmaceutical industry. Up to 45% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability, high intra- and inter-subject variability, and lack of dose proportionality. In the oral formulation of such compounds, a number of attempts - such as decreasing particle size, use of wetting agents, co-precipitation, and preparation of solid dispersions have been made to modify the dissolution profile and thereby improve the absorption rate. Recently, more attention is focused on lipid-based formulations to improve the bioavailability of poorly water soluble drugs. Among many such delivery options, like incorporation of drugs in oils, surfactant dispersion, emulsions and liposomes, one of the most popular approaches is the self-emulsifying drug delivery systems (SEDDSs)[1]. There are several techniques by which the rate & extent of drug absorption can be increased as, by increasing the rate or extent of dissolution, facilitating the absorption process etc. So, to formulate a self emulsifying formulation these approaches are generally used.

SEDDS are described as mixtures of oil, surfactant, co-surfactant and drug. Traditional preparation of SMEDDS involves dissolution of drugs in oils and blending with suitable solubilizing agents[2]. It can be used to improve oral absorption of highly lipophilic compounds[3]. SEDDS typically produce emulsions with a droplet size range 100 and 300 nm while SMEDDS are transparent micro emulsion with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS and these are physically stable formulation that are easy to manufacture upon mild agitation followed by dilution in aqueous media such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions (SMEDDS)[4]. They form fine oil-in-water emulsions, when introduce into an aqueous phase under gentle agitation. Such mixtures are expected to self-emulsify quickly in the aqueous media of stomach, the digestive motility providing the agitation required for emulsification[5]. Oral absorption of several drugs has been reported to be enhanced by SEDDS by one of the several mechanisms which include increasing membrane fluidity to facilitate transcellular absorption, opening tight junction to allow paracellular transport, inhibiting Cytochrome P450 (CYP450) enzymes to increase intracellular concentration and residence time by surfactants, and stimulating lipoprotein/chylomicron production by lipid[6].

SEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent and filling the formulation into capsules. The oral drug delivery of hydrophobic drugs may be made possible by SEDDS. The

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main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favour the drug remaining in the lipid droplets[8]. There are two types of self-emulsifying lipid formulations (SELFs) systems[10].

-Self-emulsifying drug delivery systems (SEDDSs).

-Self-micro-emulsifying drug delivery systems (SMEDDSs).

Both SEDDSs and SMEDDSs have different characteristics associated with improved drug release properties. SEDDS formulations will be having the simple binary systems which include lipophilic phase and drug, or lipophilic phase, surfactant and drug. And they have the droplet size in the range of 200nm-300nm and the dispersion has a turbid appearance. And also the concentration of oil is 40-80% in SEDDS. The formulation of a SMEDDS requires the use of a co-surfactant to make a microemulsion and they are characterized by having droplet size below 50nm, and the dispersion has an optically clear-to-translucent appearance. The concentration of oil in SMEDDS is less than 20 %. The potential advantages of these systems (SEDDS) include enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, protection of drug(s) from the hostile environment in gut, control of delivery profiles, reduced variability including food effects, protection of sensitive drug substances, high drug payloads, liquid or solid dosage formulation, physically stable formulations that are manufacture easily etc[7-11]. However these systems also suffer from certain disadvantages as traditional dissolution method does not work, because these formulations potentially dependent on digestion prior to release of the drug. This *in vitro* model needs further development and validation before its strength evaluated. Difficulty in establishing *in vitro - in vivo* correlations and hence prototype lipid based formulations needs to be developed and tested *in vivo* in a suitable animal model.[12] The drawback of this system also include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which may cause potential damage to the GIT.

Composition of SEDDS

SEDDS are composed of oil, surfactant & their formulation depends upon basically three factors which include; the nature of oil–surfactant pair, surfactant concentration and the temperature at which self emulsification occurs.

Oils

Oils are most important constituents as these can solubilize the lipophilic drugs in a specific amount and can facilitate self-emulsifying and increase the fraction of lipophilic drug transported via the intestinal lymphatic system & increasing absorption from GI tract. Both long chains triglycerides and medium-chain triglycerides oils with different degree of saturation have been used for the formulation of SEDDS. Examples include corn oil, mono, di, tri-glycerides, olive oil, oleic acid, sesame oil, beeswax etc. [13-16]

Surfactants

Nonionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.)[17]. The surfactant strength ranges is 30–60% w/w of the formulation in order to form a stable SEDDS[15]. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and 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. It can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules. [18-22]

Co-solvents

Relatively high surfactant concentration (usually more than 30 % w/w) is needed to produce an effective SEDDS[23]. Cosolvents like diethylene glycol monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, polyethylene glycol ether (Glycofurol)[19] may be help to dissolve more amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the important role of the co-surfactant in the microemulsion systems.

Mechanism of self-emulsification

According to Reiss, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion[15]. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between oil and water phases and can be described by the equation:

$$DG = S\, N_i\, p\, r_i\, 2\, S$$

Where, DG- The free energy associated with the process (ignoring the free energy of mixing), N- 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, subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer on the surface of emulsion droplets, and hence reduce the interfacial energy, as well as providing a barrier to prevent coalescence[9].

Formulations of SEDDS

The following points should be considered in the formulations of SEDDS

1. The solubility of drugs in different oil, surfactant and cosolvents.
2. The selection of oils, surfactant & cosolvent based on the drug solubility and preparation of phase diagram.
3. Mixing of oil, surfactants and co-surfactant at 50^0C with a magnetic stirrer.
4. Then, dissolve drug in the blank SEDDS with stirring to form an isotropic mixture, the addition of drug to SEDDS in critical because the drug interferes with self emulsifying process to certain extent, which leads to changes in optimal oil surfactant ratio, so, design of optimal SEDDS require preformulation solubility and phase diagram study[3].
5. Cooling to room temperature and equilibrating for 24 h before use [4].

Preparation of the solid SEDDS[6]

Solid SEDDS can be 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 capsule

1. **Solid carriers**

These solid carriers have property to absorb liquid/semisolid formulation as self emulsifying system (SES). It is a simple procedure, where SES is incorporated into a free flowing powder material which has adsorption quality[23]. 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[18]. The above mixture can then be solidified to powder forms using various adsorbents: microporous calcium silicate (FloriteTM RE); magnesium aluminum silicate (NeusilinTMUS2) and silicon dioxide (SylysiaTM 320).

2. **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[22]. The volatile vehicles evaporate leaving behind small solid particles. These particles are then filled into capsules or compressed into tablets.

3. **Melt extrusion**

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

4. **Dry emulsion**

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

5. **Melt extrusion/extrusion spheronization**

Melt extrusion is a solvent-free process that allows high drug loading (65%), and content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform size, shape and density, by forcing it through a die under controlled temperature, flow rate, and pressure conditions[25]. The size of the extruder aperture will determined the approximate size of the resulting spheroids. The extrusion–spheronization process is commonly used in the pharmaceutical industry to make uniformly sized pellets. The extrusion–spheronization process requires first the dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder followed by extrusion into a spaghetti-like extrudate to get spheroids of uniform size. Then, these are dry sifted to achieve the desired size distribution, coating (optional) [7].

Capsule filling with liquid and semisolids self emulsifying system[3]

Capsule filling is the simple and most common technology for encapsulation of liquid or semi solid SE formulation for the oral routes. If it is used for semi solids the heating of semisolid excipients to at least at 208^0C (above its melting points) is done and actice substances are incorporated with stirring and this molten mixture is filled in capsules and cooled to room temperature.

Dosage forms for self emulsifying system

1. **Self emulsifying capsule**

After administration of capsules containing conventional liquids SE formulations, microemulsion droplets form and disperse in the GIT to reach site of absorption[15]. If irreversible phase separation of microemulsion occur an improvement of drugs absorption can't be expected[24]. This problem can be overcome by sodium dodecyl sulfate may be added into the SE formulation. The super saturatable SEDDS can be designed using small quantity of HPMC to prevent precipitation of drug by generating and maintaining a super saturatable state *in vivo*. Liquid SE ingredients can be filled into capsules in solid or semi solid state obtains by adding solid carriers (absorbents polymers). As an example, a solid PEG matrix can be chosen[3].

2. **Self--emulsifying sustained / controlled release tablets**

Combination of lipids and surfactant has presented great potential preparing SE tablets. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDSs into solid dosage form a gelled SEDDS may be prepared[20]. Colloidal silicon dioxide (aerosol 200) may be used as gelling agent for the oil based systems, which serves the dual purpose & reduced the amount of required solidifying excipients and aiding in slowing down of the drug release[14]. SE tablets are of great utility in obviating adverse effect. Inclusion of indomethacin (or other hydrophobic NSAID) for example, into SE tablets may increase its penetration efficacy through GI mucosal membrane, potentially reducing GI bleeding. The SES usually is composed of glycerol monolaurate and tyloxapol.

3. **Self emulsifying microspheres**

Solid SE sustained release microspheres can be prepared using the quasi emulsion solvent diffusion method for the spherical crystallization technique[26]. Zedoary turmeric oil release behavior may be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to aerosil 200 in the formulation[29]. The plasma concentration time profiles can be achieved after oral administration of such microspheres into rabbits, with a bioavailability of 133.6% with respect to the conventional liquid SEDDS[4].

4. **Self emulsifying sustained / controlled release pellets**

Pellets, as a multiple dosage form, possess many advantages over conventional solid dosages form, such as flexibility of manufacture, reducing intra subject and inter subject variability of plasma profile and minimizing GI irritation without affecting lowering drug bioavailability. SE controlled release pellets incorporating drugs in SES enhanced their rate of release and then by coating pellet with a water insoluble polymer may reduce the rate of drug release. Pellets can be prepared by extrusion / spheronization and contain to water insoluble model drugs (methyl and propyl paraben). SES may contain mono diglycerides and polysorbate 80[3].

5. **Self emulsifying bead**

Self emulsifying system can be formulated as a solid dosage form by using less excipient. Porous polystyrene beads (PPB) with complex internal void structures can be typically produced by copolymerising styrene and divinyl benzene. It is inert and stable over a wide range of pH, temperature and humidity. Features, such as bead size and pore architecture of PPB, can be found to govern the loading efficiency and in vitro drug release from SES-loaded PPB[6].

6. **Self emulsifying nanoparticles (SENs)**

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 sized particles with 70-75% drug loading efficiency is obtained. The second technique is sonication emulsion diffusion evaporation. By this method coloaded 5-flurouracil and antisense epidermal growth factor receptor

(EGFR) plasmids into biodegradable PLGA/carboxy methyl-chitosan (CMC) nanoparticles were prepared. The mixture of PLGA and CMC had an SE effect, with no additional surfactant required.

7. Self emulsifying solid dispersion

Solid dispersions could increase the dissolution rate and bioavailability of poor water soluble drugs. These excipients have the potential to increase further the absorption of poor water soluble drugs[30]. Relative to previously used PEG solid dispersions and filled directly into hard gelatin capsule in molten state thus obviating the former requirement for milling and blending before filling. SE excipients like gelucire 44114, labrasol, transcutol and TPGS (tocopherol / polyethylene glycol 1000 succinate) have been widely used in this field[3].

8. Self emulsifying suppositories

S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption of the drug[24]. Glycyrrhizin, which, by the oral route, achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. These formulations included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester[7].

9. Self emulsifying implants

Research into SE implants has greatly enhanced the utility of S-SEDDS. Example, 1, 3-bis (2-chloroethyl)-1-nitrosourea (carmustine) a chemotherapeutic agent is use to treat malignant brain tumors. However, its effectiveness is hindered by its short half-life. Loomis invented those copolymers having a bioresorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses.

Table1. Methods of preparation of SEDDS

Formulation type	Composition	Characteristics
Type I	Oils without Surfactant	Non-dispersible poor solvent capacity except for high lipophilic drugs, requires digestion to releases drug
Type II	Oils and water-insoluble surfactant	SEDDS, turbid o/w dispersion (particle size 0.25-2 µm), unlike to lose solvent capacity on dispersion, possible loss of solvent capacity on digestion
Type III	Oils, water-soluble surfactants and co-solvents	SEDDS/SMEDDS, slightly bluish to clear dispersion, possible loss of solvent capacity on dispersion, less easily digested, possible loss of solvent capacity on digestion
Type IV	Water-soluble surfactant and co-solvents (oil free)	Forms a clear micellar solution on dispersion, likely loss of solvent capacity on dispersion, unlikely to be digested

Characterization of SEDDS

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

Visual assessment

This may provide important information about the self-emulsifying and microemulsifying property of the mixture and about the resulting dispersion[9].

Droplet size analysis and particle size measurements

The droplet size of the emulsions is determined by photon correlation spectroscopy, using a Zetasizer able to measure sizes between 10 and 4000 nm[16]. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system compatibility with excess water.

Assessment of self emulsification

The USP 24 rotating paddle apparatus is used to evaluate the efficiency of self-emulsification of different mixtures. One gram of mixture is added to 200 ml of distilled water with gentle agitation condition provided by a rotating paddle at 70 rpm and at a temperature of 37°C. The process of self emulsification is visually monitored for the rate of emulsification and for the appearance of the produced emulsions [4].

Viscosity determination

The rheological properties of microemulsion are evaluated by Brook Field viscometer if it is o/w types and if it is w/o types then high viscous.

Droplet size analysis

The droplets size of the emulsion is determined by photon correlation spectroscopy using Zeta sizer, enables to measure the sizes between 10 and 5000 nm[3].

Thermodynamic stability studies

The stability of a lipid –based formulation is also important for its performance, which can produce adverse effect in the form of precipitation of the drug in the excipient matrix solution[28]. In addition, the poor physical stability of the formulation can lead to phase separation of the excipient, which affects not only formulation performance, as well as visual appearance of formulation. In addition, incompatibilities between the formulations and the gelatin capsules shell can lead to brittleness, delayed disintegration, or incomplete release of drug. For thermodynamic stability studies three main steps, are preformed-

1. **Heating cooling cycle:** Six cycles between the refrigerator temperature (5^0C) and 45^0C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.
2. **Centrifugation:** Passed formulations are centrifuge at thaw cycles between 20^0C and $+25^0$C with storage at each temperature for not less than 48 h at 3600 rpm for 20 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.
3. **Freeze thaw cycle:** Those formulations that pass this test show good stability with no phase separation, creaming or cracking.

Dispersibility test

The efficiency of self-emulsification of oral emulsion is assessed by using a standard USP XXII dissolution apparatus 2 for dispersibility test. One millilitre of each formulation is added in 500 mL of water at 37 ± 1 ^{0}C. A standard stainless steel dissolution paddle is used with rotating speed of 50 rpm to provide gentle agitation. *In vitro* performance of the formulations is visually assessed by using the following grading system:

Grade A: Rapidly forming (within 1 min) emulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that forming within 2 min.

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and B formulations will remain as emulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation[8].

Refractive index and percent transmittance

Refractive index and percent transmittance prove the transparency of formulations. The refractive index of the system is measured by refractometer by putting a drop of solution on slide and it comparing with water (1.222)**.** The percent transmittance of the system is measured at particular wavelength using UV spectrophotometer against distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 98 percent, then formulation have transparent nature[8].

In vitro diffusion study

In vitro diffusion studies are carried out to study the drug release behaviors of formulations from liquid crystalline phase around the droplets using dialysis technique[3].

APPLICATIONS

(1) Improvement of solubility and bioavailability.
(2) Protection against biodegradations.
(3) Oral delivery of hydrophobic drugs can be made possible by SEDDS.
(4) SEDDS solved problems associated with the delivery of poorly soluble drugs.

Examples – Bioavailability enhancement of poorly soluble drugs after administrations of SEDDS.

a. Halofantrine shows higher bioavailability from SMEDDS.
b. Vitamin EBA 3- folds higher from SEDDS[27].
c. Coenzyme Q10 BA 2- folds higher from SEDDS.
d. Progesterone BA-9 folds higher from SEDDS.
e. Nimodipine showed improved the *in vitro* and *in vivo* performance from SMEDDS[3].

RECENT APPROACHES IN SELF EMULSIFYING DRUG DELIVERY SYSTEMS

1. Surfactant mixtures resulted in improved reproducibility of the plasma profile in terms of *C*max and *T*max.
2. SEDDS of coenzyme Q10 ware prepared and this resulted in enhanced bioavailability and reduced toxicity. Lipophilic compound WIN 54954 was formulated as SEDDS in triglyceride oil/nonionic.
3. Self-microemulsifying drug delivery system (SMEDDS) of Simavastin have been developed to enhance its oral bioavailability. This study illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds[10].
4. A novel SEDDS of PTX (used for the treatment of solid tumors) was prepared and was found that SEDDS was chemically stable for at least 1 year when kept as two part formulation and also the drug loading could be increased by approximately fivefold. Compared to marketed I.V. formulation, the excipient presented a significantly reduced cytotoxicity and led to a stable microemulsion[15].
5. An antimalarial drug, Halofantrine, was prepared as SEDDS and SMEDDS and resulted in an eight fold improvement in absolute oral bioavailability relative to previous data of the solid.
6. Enhanced bioavailability upto 1.88 of silymarin was achieved by SMEDDS[7].
7. Using SEDDS, self-nano emulsified 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 precipitation of the active drug in the vehicle with time[1].

FUTURE PROSPECTS

In relation to formulation development of poorly soluble drugs in the future, there are now techniques being used to convert liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules, which can then be further processed into conventional 'powder-fill' capsules or even compressed into tablets. Hot melt granulation is a technique for producing granules or pellets, and by using a waxy solubilising agent as a binding agent, up to 25% solubilising agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents, such as the Neusilin (Fuji Chemicals) and Zeopharm (Huber) products for converting liquids into powders – which can then be processed into powder fill capsules or tablets. But to obtain solids with suitable processing properties, the ratio of SEDDS to solidifying excipients must be very high, which seems to be practically non-feasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of SEDDS in solid dosage forms will be significantly reduced if SEDDS is gelled. Colloidal silicon dioxide (Aerosil 200) is selected as a gelling agent for the oil based systems, which may serve the dual purpose of reducing the amount of solidifying excipients required and aiding in slowing drug release.

Table No. 2. Some marketed SEDDS products

Drug	Trade Name
Cyclosporine	Neoral
Ritonavir	Norvir
Amphenavir	Agenerase
Sequinavir	Fortovase
Cyclosporine	Gengrafi
Cyclosporine	Sandimmune

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