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A REVIEW ON SELF EMULSIFYING DRUG DELIVERY SYSTEM

SHASHANK KHUGSHAL[1], ASHUTOSH BADOLA[1], PREETI KOTHIYAL[1], SHWETA BALUNI[2]

1. Department of Pharmaceutics, Shri Guru Ram Rai Institute of Technology & Sciences, Dehradun, (248001) Uttrakhand, India.
2. Department of Medical sciences, Shri Guru Ram Rai Institute of medical and health Sciences, Dehradun, (248001) Uttrakhand, India.

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Abstract: Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. For lipophilic drugs, which have dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption. Due to low bioavailability, many drugs are not suitable for oral delivery or dose is increased. SEDDS provide a possible way to deliver the drug with increased bioavailability. SEDDS are liquid to semi-solid in nature, but it has certain drawbacks like formulation development, storage, stability, etc. It can be orally administered in soft or hard gelatin capsules. These systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility. The improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. In the present study we formulate self-emulsified drug delivery systems (SEDDS) through the nano emulsion for the effective delivery of Atorvastatin which is a HMG-COA Inhibiter. The following evaluations were carried out on the formulations: visual isotropicity, emulsification time, drug content, in vitro drug release, infinite aqueous dilution, post dilution drug precipitation and in vivo anti inflammatory tests respectively. This review article explains how self-emulsifying drug delivery systems can increase the solubility and bioavailability of poorly soluble drug.

Keywords: Self emulsifying drug delivery system (SEDDS), Oil, Co-surfactant, Surfactant, Self-micro-emulsifying drug delivery systems (SMEDDS).

Corresponding Author: MR. SHASHANK KHUGSHAL

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INTRODUCTION

Self micro emulsifying drug delivery system (SMEDDS) 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 that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids.[2] SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SEDDS requires the use of a co-surfactant to generate a micro emulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm–5 mm and the dispersion has a turbid appearance. A large number of drugs being discovered today are highly lipophilic and poorly water soluble. They show poor and erratic bioavailability [3]. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation [4-8]. SMEDDS formulation is in theory, comparatively simple. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils, surfactants and if required an antioxidants. Often co-surfactants and co-solvents are added to improve the formulation characteristics. In the present topic, focus will be on lipid based drug delivery systems (e.g. Self-Emulsifying Drug Delivery systems (SEDDS)). Emulsion particles can be of either micro- or nano-size, depending on the composition of the system. These formulations circumvent the dissolution step in the gastro-intestinal tract, but are still dependent on digestion.

NEED OF SEDDS:

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. 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. 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 favor the drug remaining in the lipid droplets.47 Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical

stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of case SEDD system is a good option.

Advantages: [9, 10]

- Enhanced oral bioavailability
- Reduction in dose
- Protection of drugs from hostile environment in the gut.
- targeting of drugs
- Controlled drug delivery
- Reduced variability including food effects.
- Reproducibility can be achieved.
- Patient compliance.

Disadvantages: [11, 12]

- No accurate predictive in vitro models for assessment of the formulations.
- Low stability and portability.
- Large quantity of surfactants in the formulations can induce GI irritation.

LIMITATIONS

One of the obstacles for the development of self emulsifying drug delivery systems (SEEDS) and other lipid-based formulations is the lack of good predicative in vitro models for assessment of the formulations [13, 14]. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, an in vitro model simulating the digestive processes of the duodenum has been developed. This in vitro model needs further development and validation before its strength can be evaluated. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model. Future studies will address the development of the in vitro model [15, 16].

Mechanism of Self- Micron Emulsification:

According to Reiss, the energy required to increase the surface area of the dispersion for self-emulsification process bear less importance when compared to the entropy change that favors dispersion. Self- micron emulsifying process is related to the free energy. That is free energy of the conventional emulsion is a direct function of the energy essential to create a new surface between the oil and water phases and can be described by the equation:

$$DG = S\ N\ p\ r\ 2s$$

Where, DG is the free energy related to the process, N is the number of droplets of radius r and s represents the interfacial energy. The emulsion is stabilized by emulsifying agents only after the two phases of emulsion is separated with respect to time to reduce the interfacial area. The emulsifying agent forms a monolayer of emulsion droplets, and hence reduces the interfacial energy, and providing a barrier to avoid coalescence. In the case of self micron emulsifying systems, the free energy required to form the emulsion is either very low or positive, or negative [17].Emulsification requires very little input energy involves destabilization through contraction of local interfacial regions.

Composition of SEDDSs

The self-emulsifying process depends on:

• The nature of the oil–surfactant pair

• The surfactant concentration

• The temperature at which self-emulsification occurs.

A. Oils [18, 19, 20]

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. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride. [21, 22] Both long and medium chain

triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations.

B. Surfactants [23, 24]**:** Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) [25]. Safety is a major determining factor in choosing a surfactant The four main groups of surfactants are defined as following-

a) **Anionic Surfactants**:- where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3 -). Examples: Potassium laurate, sodium lauryl sulphate.

b) **Cationic surfactants: -** where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

c) **Ampholytic surfactants: -** (also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

d) **Nonionic surfactants: -** where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene. Examples: Sorbitan esters (Spans), poly -sorbates (Tweens).

C. Co-Solvents [26]**:-** The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value [27].

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 [28, 29]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including:

1. Alterations (reduction) in gastric transit: thereby slowing delivery to the absorption site and increasing the time available for dissolution [30].

2. Increase in effective luminal 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 phospholipids (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.

3. 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 [31, 32].

4. 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 glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism [33, 34].

5. 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 [35, 36]. 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.

6. Effect of oils on the absorption: Such formulations form a fine oil-in-water emulsion with gentile agitation, which may be provided by gastrointestinal motility. A SES also improves the reproducibility of the plasma level–time profile. Various physiological mechanisms have been proposed to explain the effect of oils on the absorption of water-insoluble compounds, including altered gastrointestinal motility, increased bile flow and drug solubilization, increased mucosal permeability, enhanced mesenteric lymph flow, and increased lymphatic absorption of water insoluble drugs and bioavailability also increased of hydrophobic compound.

Characterization of SEDDSs

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.

1. **Visual assessment:** This may provide important information about the self emulsifying and micro emulsifying property of the mixture and about the resulting dispersion.

2. **Turbidity measurement:** This is to identify efficient self emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.

3. **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. Photon correlation spectroscopy, microscopic techniques or a coulter nano size are mainly used for the determination of the emulsion droplet size. The reduction of the droplet size below 50 µm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions.

4. **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 presence of free fatty acids.

5. **Determination of emulsification time:** Self-emulsification time, dispersibility, appearance and flow ability was observed and scored according to techniques described in H. Shen et al. used for the grading of formulations. **OTECHNIQUES OF SOLID SEDDS**

EVALUATION [37, 38, 39]

1. Thermodynamic stability studies

The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipients matrix. In addition, poor formulation physical stability can lead to phase separation of the excipients, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

a) **Heating cooling cycle:** Six cycles between refrigerator temperature (40C) and 450C 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.

b) **Centrifugation:** Passed formulations are centrifuged thaw cycles between 210C and +25 0C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those

c) Formulations that does not show any phase separation are taken for the freeze thaw stress test.

d) **Freeze thaw cycle**: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

2. Dispersibility test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 mL of water at 37 ± 0.5 0C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system.

Grade A: Rapidly forming (within 1 min) nanoemulsion, 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 formed within 2 min.

Grade D: Dull, grayish 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 Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

3. Turbidimetric Evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification)

4. Viscosity Determination

The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. so, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosities then it are w/o type of the system.

5. Droplet Size Analysis Particle Size

Measurements

The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. 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's compatibility with excess water.

6. Refractive Index and Percent

Transmittance

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333)**.** The percent transmittance of the system is measured at particular wavelength using UVspectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

7. Techniques for Solid Formulations [40-51]

Techniques are chosen on the basis of properties of lipid excipients. The techniques reviewed hereunder facilitate the transformation of liquid or semi-solid formulations into solid particles (powders, granules or pellets) which could subsequently be filled into capsules, sachets or compressed into tablets.

a. Spray Cooling

The molten droplets are sprayed into cooling chamber, which will congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the

liquid mixture and to generate droplets: rotary, pressure, two-fluid or ultrasonic atomizers.

b. Spray Drying

Spray drying is defined as a process by which a liquid solution is sprayed into a hot air chamber to evaporate the volatile fraction. Polyoxylglycerides (lauroyl or stearoyl) have been used alone or in combination with a solid carrier (silicon dioxide) to form microparticles of etoricoxib and

glibenclamide. Dry emulsion technology solves the stability problems associated with classic emulsions (phase separation, contamination by microorganism, etc.) during storage and helps also avoid using harmful or toxic organic solvents. Dry emulsions may be redispersed into water before use. Medium chain triglycerides are commonly used as oil phase for these emulsions.

c. Adsorption on Solid Carriers

Solid carriers are used for the adsorption of liquid formulation to get final solid product and it will be free flowing so that it can be compressed or directly filled in hard gelatin capsules. A significant benefit of the adsorption technique is good content uniformity as well as the possibility for high lipid exposure. The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproylpolyoxylgly or spheronized pellets .The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can, by further mixing under controlled conditions transform to spheronized pellets. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder during melt granulation. Nucleation (onset of granule formation) is largely affected by binder viscosity at high impeller speed and binder particle size at low speed. Depending on the combination of process parameters, two distinct mechanisms namely “distribution” and “immersion” may be at play in the development of granules. Fine or atomized excipients with low viscosity at high impeller speed

Favor a homogenous “distribution” of the binder onto the surface of the powder.

d. Melt Extrusion/ Spheronisaton

Extrusion is a process of converting a raw material with plastic properties into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow and pressure conditions. This approach has been successfully tried for 17β- estradiol and two model drugs with surfactants such as sucrose monopalmitate, lauroylpolyoxylglycerides and polysorbate80 (Tween® 80). Gelucire 44/14 to be used directly in the core of the formulation matrix. An innovative “systemincylinder” molding technique was recently employed to develop a dual purpose (enhanced bioavailability and controlled release) formulation with propranolol hydrochloride. Melt extrusion is a solvent free process that allows high drug loading as well as content uniformity for low dose high potency actives.

e. Supercritical Fluid Based Method

Lipids may be used in supercritical fluid based methods either for coating of drug particles, or for producing solid dispersions. For environmental reasons, the preferred supercritical fluid of

choice is supercritical carbon dioxide. Examples include controlled release applications using glyceryltrimyristate (Dynasan™ 114) and stearoyl polyoxyl glycerides (Gelucire®50/02).

f. Solid Lipid Nanoparticles and Nanostructure Lipid Carriers

SLN and NLC are two types of submicron size particles (50– 1000 nm) composed of Physiologically tolerated lipid components. SLN are produced by high-pressure homogenization of the solid matrix and drug with an aqueous solution of the glyceryldibehenate as solid lipid matrix and poloxamers 188 or polysorbates 80 as surfactants. They typically contain liquid lipid excipients such as medium chain triglycerides in addition to classic components of SLN. They have been mainly used for controlled-release applications in oral 86, intravenous 87 or topical route.

Pharmaceutical applications of Multiple Emulsions:

a. They can mask the bitter taste and order of drug, e.g. chlorpromazine [52].

b. Multiple emulsions are used in food [53].

c. They can be used to prolong the release of drug thereby providing sustained release action [54, 55].

d. Essential nutrients like carbohydrates, fats and vitamins can all be emulsified and can be administered to bed ridden patient as sterile intravenous injection.

e. Emulsion provides protection to drugs which are susceptible to oxidation or hydrolysis [56, 57].

f. Intravenous emulsions of contrast media have been developing to assist in diagnosis.

g. Increase in dosing interval.

h. Hydrophilic as well as hydrophobic drug can be entrapped.

Future Trend:

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 products for converting liquids into powders – which can

then be processed into powder fill capsules or tablet. Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. 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. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract.

CONCLUSION

SEDDS formulation can be optimized for the delivery of hydrophobic compounds with drug loading; minimum surfactant concentration and proper infinite dilution can be achieved without drug precipitation. Self-emulsifying drug delivery system can be use for the formulations of drugs compounds with poor aqueous stability. Development of this technology SEDDS will continue to enable novel applications in drug delivery system. SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and Traditional preparation of SEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents.

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