Self-Emulsifying Drug Delivery Systems; an Overview

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Abstract: **The primary goal of research on self-emulsifying drug delivery systems (SEDDS) has been to increase the oral bioavailability of medications that fall under class II of the Biopharmaceutics Classification System. Self-emulsifying drug delivery systems (SEDDS) have the potential to significantly increase the oral bioavailability of medications that are not highly soluble in water. These systems quickly dissolve in gastrointestinal fluids after oral delivery, producing micro or nanoemulsions that contain the solubilized medication.Medium chain tri-glyceride oils and non-ionic surfactants—the latter of which is less toxic—have recently been used in the formulation of SEDDS.**

Since the addition of precipitation inhibitors (PIs) to SEDDSs aids in maintaining drug super saturation following dispersion and digestion in the gastrointestinal tract, supersaturable SEDDSs, or su-SEDDSs, have drawn attention as a means of overcoming these restrictions that limit the potential use of such systems. A pre-concentrate made up of a medication, oils, surfactants, and occasionally co-solvents and/or co-surfactants is called a SEDDS.

Additionally, we summarize various solidification techniques employed to transform liquid SEDDS to the more stable solid self-emulsifying drug delivery systems (s-SEDDS) that are associated with high patient compliance.

Keywords: **SEDDS, nanoemulsions, precipitation inhibitors, surfactants.**

INTRODUCTION

SEDDS or self-emulsifying oil formulations (SEOF) 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 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 gentleagitation. SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug Potential advantages of these systems 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.SMEDDS are the isotropic, clear mixtures of oils and surfactants and sometimes include co-solvents/co-surfactants. These are designed to form O/W microemulsions with mild agitation produced by the motility of GIT followed by solubilization and absorption of drug. SMEDDS usually produce microemulsions of droplet size below 100 nm upon dilution. Lipid-based drug delivery systems (LBDDs) have been intensively investigated to overcome various obstacles encountered in oral drug delivery including poor aqueous solubility, limited permeability, low therapeutic window, first pass metabolism as well as inter- and intra individual variability in drug response [1].Oral delivery of poor water soluble drugs using lipid as vehicle is a new and recent approach to overcome the problems. Formulation excipients like surfactants used in the lipid based formulations will aid in achieving the goal [2].

The self-emulsifying process depends on:

- The nature of the oil and surfactant
- The concentration of surfactant
- The temperature at which self-emulsification occurs.

Properties of SEDDS

1. They form o/w emulsion by gentle agitation by peristaltic movement in the G.I. tract.
2. Hydrophobic and hydrophilic drugs can be used with an oil surfactant mixture.
3. A lower dose of drugs can be used for liquid as well as a solid dosage form.
4. Clear dispersion of SEDDS should be formed instantaneously in the G.I. tract that remains stable on dilution. Such distributions are either micro (100-250nm) or nanoemulsions (less than 100 nm)

depending upon the globule size of the SEDDS formulation

Importance of SMEDDS

1. Irritation caused by prolonged contact between the drug and the wall of the GIT can be surmounted by the formulation of SMEDDS as the microscopic droplets formed help in the wide distribution of the drug along the GIT and these are transported quickly from the stomach
2. Upon dispersion in water, these formulations produce fine droplets with enormous interfacial area due to which the easy partition of the drug from the oil phase into the aqueous phase is possible which cannot be expected in case of oily solutions of lipophilic drugs
3. SMEDDS are advantageous over emulsions in terms of the stability because of the low energy consumption and the manufacturing process does not include critical steps. Simple mixing equipment is enough to formulate SMEDDS and time required for preparation is also less compared to emulsions
4. Poor water soluble drugs which have dissolution rate limited absorption can be absorbed efficiently by the formulation of SMEDDS with consequent stable plasma-time profile Constant plasma levels of drug might be due to presentation of the poorly soluble drug in dissolved form that bypasses the critical step in drug absorption, that is, dissolution
5. Along with the lipids, surfactants that are commonly used in the formulation of SMEDDS like Tween 80, Spans, Cremophors (EL and RH40), and Pluronics are reported to have inhibitory action on efflux transporters which help in improving bioavailability of the drugs which are substrates to the efflux pumps.
6. Drugs which have propensity to be degraded by the chemical and enzymatic means in GIT can be protected by the formulation of SMEDDS as the drug will be presented to the body in oil droplets
7. Microemulsion preconcentrate is advantageous over microemulsion to dispense in the form of liquid filled soft gelatin capsules
8. SMEDDS are advantageous over SEDDS as the former are less dependent on bile salts for the formation of droplets by which better absorption of the drug is expected compared to SEDDS
9. Surfactants of high HLB like Tween 80 are reported to increase the permeability of the drug when administered along with the formulation due to the loosening effect of these on tight junctions

APPLICATION:

1. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation.
2. SEDDSs present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability.
3. Selective targeting of drug(s) toward specific absorption window in GIT.
4. Protection of drug(s) from the hostile environment in gut
5. Control of delivery profiles
6. Reduced variability including food effects
7. Protective of sensitive drug substances

Disadvantage

1. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
2. This in vitro model needs further development and validation before its strength can be evaluated.
3. 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.
4. The drawbacks of this system include chemical instabilities of drugs and high surfactant
5. Concentrations in formulations (approximately 30-60%) which GIT.

Types of SEDDs:

On the basis of the water solubility of components, SEDDS can be classified as

A) Non-water soluble Component Systems

- These systems are isotropic mixtures of lipids & lipophilic surfactants having HLB value less than 12 that self emulsify to form fine oil in water emulsion in aqueous medium.
- Self emulsification is generally obtained at a surfactant level above 25% w/w. But at a surfactant

level of 50-60% w/w the emulsification process may be compromised by formation of viscous liquid crystalline gels at the oil/water interface.

- This system is also known as Type-II SEDDS according to lipid formulation classification System (LFCS). Poorly water soluble drugs can be incorporated in SEDDS & encapsulated in capsules (hard or soft gelatin) to produce convenient single unit dosage forms

B) Water soluble component system

- These systems are formulated by using hydrophilic surfactants with HLB more than 12 & co solvents such as Ethanol, Propylene Glycol & Polyethylene glycols .
- Type III SEDDS are commonly known as self micro-emulsifying drug delivery systems (SMEDDS). Type III formulations can be further divided into type III A & Type III B formulations in order to identify more hydrophilic forms. In Type IIIB, the content of hydrophilic surfactants and co solvents is increased and lipid content is reduced

Factor affecting of SEDDs

A) Nature and dose of the drug: Drugs which are administered at very high dose are not suitable for unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately are most difficult to deliver by SMEDD.

B) Polarity of the lipophilic phase: The polarity of the lipid phase is one of the factors that govern the drug release from the micro emulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of micronized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time period.

Self-emulsifying drug delivery systems

Self-emulsifying drug delivery systems (SEDDS) are lipid-based formulations that encompass isotropic mixtures of natural or synthetic oils, solid or liquid surfactants and co-surfactants. Consequently, SEDDS are usually referred to as self-nano emulsifying drug delivery systems (SNEDDS) or self micro emulsifying drug delivery systems (SMEDDS) depending on the nature of the resulting dispersions formed following their dilution.SEDDS have been reported to enhance the oral bioavailability of poorly water soluble drugs particularly those belonging to class II of the Biopharmaceutics Classification System by multiple underlying mechanisms.

Characterization of SEDDS

1. Robustness to dilution: Robustness of the resulting emulsion to dilution guarantees the absence of drug precipitation when SEDDS preconcentrates are subjected to high dilution folds in vivo [21]. Thus, SEDDS preconcentrates should be exposed to different dilution folds (e.g., 50-, 100-, and 1000-folds) with different media (e.g., 0.1 N HCl and phosphate buffer, pH 6.8) to mimic in vivo conditions [20].
2. Assessment of self-emulsification efficiency: Self-emulsification efficiency is assessed by determining self-emulsification time and the efficiency of preconcentrate dispersibility when it is exposed to aqueous dilution. The SEDDS preconcentrate is added drop wise to aqueous media with different pH values and composition in a standard USP dissolution apparatus.
3. Cloud point measurement: Cloud point could be measured after 100-fold dilution of the preconcentrate with distilled water which is then placed in a water bath with gradual increase.in temperature. Cloud point values should be sufficiently higher than 37°C (i.e., normal body temperature) to avoid phase separation in the GI tract [70].
4. Determination of zeta potential, mean droplet size and polydispersity index Mean droplet size affects the in vivo performance of SEDDS. Small mean droplet size provides large interfacial area for drug absorption and ensures the kinetic stability of the resulting emulsion. Small value of polydispersity index suggests good uniformity of droplet size distribution. High zeta potential values confirm the electrical stability of emulsion droplets and absence of aggregation [66].
5. Stability of SEDDS preconcentrates: SEDDS preconcentrates should have sufficient stability to

avoid drug precipitation as well as creaming or phase separation of the resulting nano- or microemulsions. Then, SEDDS preconcentrates are subjected to heating–cooling cycle which includes six cycles of storage at 4 and 40°C for 48 h at each temperature followed by freeze–thaw cycle which involves three cycles of storage at −21 and 25°C for 48 h at each temperature [66].

6. Droplet morphology : The morphology of emulsion droplets could be determined by transmission electron microscopy after appropriate dilution of SEDDS preconcentrate (about 1000-fold) using 2% solution of either phosphotungstic acid or uranyl acetate for negative staining.
7. In vitro lipolysis : Drugs incorporated into lipid-based formulations are already present in a dissolved form. Thus, the assessment of the applicability of these formulations should be more properly based on the rate of drug precipitation over time. In vitro lipolysis models simulate the GI environment and better predict the in vivo behaviour of lipid-based formulations .

Current and Future Aspects of Nanomedicine

During the formulation of s-SEDDS by adsorption technique, careful consideration should be given to the possible interactions between the solid carrier and the drug or other excipients in liquid SEDDS which could result in delayed or incomplete release of loaded drug [83]. Additionally, the particle size, specific surface area, tortuosity of pores as well as type and liquid SEDDS: carrier ratio should be considered [75].

PERSPECTIVES AND FUTURE TRENDS IN SEDDS DEVELOPMENT

Numerous studies have attempted to increase the disintegration rate and bioavailability of lipid formulations, such as self-emulsifying, microemulsifying, and nanoemulsifying drug formulations, in order to improve their scattering properties. Lipid-based pharmaceutical definitions have swiftly been introduced as business things into the commercial center, along with a few others in clinical improvement, thanks to the exhibition and breakthroughs in assembly. Some drugs are now commercially available, and numerous research studies have been published that use SEDDS as a solution to increase the dissolvability and, consequently, the bioavailability of lipophilic drugs.

CONCLUSION

As long as the medication is strong and has a high lipid solubility, self-microemulsifying drug delivery devices provide a new and efficient way to increase the oral bioavailability of many poorly soluble medications. The ability of SMEDDS to facilitate the lymphatic transport of highly hydrophobic medications with a high octanol:water partition coefficient and strong solubility (>50 mg/mL) in triglycerides has been established.

REFERENCE

[1]. Li F, Hu R, Wang B, Gui Y, Cheng G, Gao S, et al. Self-microemulsifying drug delivery system for improving the bioavailability of huperzine A by lymphatic uptake. Acta Pharmaceutica Sinica B. 2017;7(3):353-60.

[2]. Maulik J. Patel SSP, Natvarlal M. Patel, Madhabhai M. Patel. A Self-Microemulsifying Drug Delivery System (SMEDDS). International Journal of Pharmaceutical Sciences Review and Research 2010;4(3):29-35.

[3]. McConville C, Friend D. Development and characterisation of a self-microemulsifying drug delivery systems (SMEDDSs) for the vaginaladministration of the antiretroviral UC-781.EurJPharmBiopharm2013;83(3):322-9.

[4]. Deshmukh A, Kulkarni S. Solid self-microemulsifying drug delivery system of ritonavir. Drug Dev Ind Pharm. 2014;40:477–87

[5]. Nagarsenker MS, Date AA. Design and evaluation of self-nanoemulsifying drug delivery (SNEDDS) for cefpodoxime proxetil. Int J Pharm. 2007;329:166–72.

[6]. Zech, J.; Gold, D.; Salaymeh, N.; Sasson, N.C.; Rabinowitch, I.; Golenser, J.; Mäder, K. Oral Administration of Artemisone for the Treatment of Schistosomiasis: Formulation Challenges and In Vivo Efficacy. Pharmaceutics 2020, 12, 509.

[7]. Peng, Z.; Ji, C.; Zhou, Y.; Zhao, T.; Leblanc, R.M. Polyethylene glycol (PEG) derived carbon dots: Preparation and applications. Appl. Mater. Today 2020, 20, 100677.

[8]. Madhav KV, Kishan V. Self microemulsifying particles of loratadinefor improved oral

bioavailability: preparation, characterization and invivo evaluation. J Pharm Investig. 2018;48(4):497–508.

[9]. Rashid R, Kim DW, Yousaf AM, et al. Comparative study on solidself-nanoemulsifying drug delivery and solid dispersion system forenhanced solubility and bioavailability of ezetimibe. Int JNanomedicine. 2015;10:6147–6159.

[10]. Nisha GS, Geeta R, Vaishali P. Formulation and evaluation of SMEDDS. Int J Res Pharm Sci 2011;2(2):162-9.

[11]. ekkannti V, Kalepu S. Novel lipid based drug delivery system. IRJP2012;3(9):166-73.

[12]. Mandawgade SD, Sharma S, Pathak S, Patravale VB. Developmentof SMEDDS using natural lipophile: Application to beta-artemetherdelivery. Int J Pharm 2008;362(1-2):179-83.

[13]. Bhatt V, Rathore RP, Tanwar YS. Self miro emulsifying drug delivery system, A review. ARPB 2014;4(2):664-9.

[14]. Patel P A, et al: Self Emulsifying Drug Delivery System: A Review. Research Journal of Pharmacy and Technology 2008; 1(4): 313-323.

[15]. Kinesh V P, et al: Novel approaches for oral delivery of insulin and current status for oral insulin product. International Journal of Pharmaceutical Science and Nanotechnology 2010; 3(3): 1057- 1064.