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REVIEW ARTICLE

Self Micro Emulsifying Drug Delivery System (SMEDDS) - A Promising Future Aspect to Enhance the Oral Bioavailability of Poorly Water Soluble Drugs

Talath Fatima*, Syed Mohammed Abbas, Husna Banu, Asad Ahmed Khan, S. A. Azeez Basha

Deccan School of Pharmacy, Hyderabad-01, Telangana. India.

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ABSTRACT

Oral route is most preferred one as there is ease of administration and it is a painless approach. This favored route is restricted to those drug molecules that are absorbent over the gastric mucosa. Solubilization in gastrointestinal tract is the rate limiting step for absorption of these drugs. Various approaches in the formulation such as micronization, solid disbandment, and complexation with cyclodextrins have been emerging rapidly. Self Micro Emulsifying Drug Delivery Systems (SMEDDS) are the isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or instead, single or alternative hydrophilic solvents and co solvents that are having distinctive potential of forming fine oil in water micro emulsions on mild turbulence subsequently followed by dilution in the aqueous media, like in the fluids of GI tract. Self Micro Emulsifying Drug Delivery System (SMEDDS) favorably provide the dissolved drug form and also its small size of droplets imparts substantial interfacial area for the absorption of drugs. It can simply get penetrated into the gastrointestinal tract which is the major advantage over other emulsions. The major hindrance for the progress of SMEDDS is the insufficiency of better base in-vitro models for the evaluation of the formulations. Various excipients used are Tween 80, Cremophor RH 40, Polyethylene glycol 400, Labrafac Lipophile WL 1349 etc. The main aim of this is to augment the oral bioavailability of poorly water soluble drugs which may be a promising approach in future.

KEYWORDS

Cyclodextrins, Oral bioavailability, Self Micro Emulsifying Drug Delivery Systems (SMEDDS), Polyethylene glycol 400

INTRODUCTION

Oral route for administration is considered to be the paramount among all the other routes of drug administration. Nevertheless, this favored route is restricted to those drug molecules that are absorbent over the gastric mucosa. About 40% of new chemical systems show indigent aqueous solubility and give an extensive challenge to present day drug delivery system, due to their low bioavailability.

***Address for Correspondence:**
Ms. Talath Fatima,
Deccan School of Pharmacy,
Hyderabad, Telangana State, India.
E-Mail Id: talath1012@gmail.com

Solubilization in gastrointestinal tract is the rate limiting step for absorption of these drugs. These drugs are systematized as drugs of class-II by the system of biopharmaceutical classification (BCS), having deprived aqueous solubility and elevated permeability. Various approaches in the formulation such as micronization, solid disbandment, complexation with cyclodextrins have been emerging rapidly[1]. There are few commencements to upgrade the oral bioavailability of the drugs which are poorly water soluble[2]. Certainly, in few specified cases, these approaches have been very efficient. To

enhance the oral bioavailability of poorly water soluble drugs, contemporarily more surveillance is on formulations that are lipid based. Hence, particular prominence is on Self Micro Emulsifying Drug Delivery System (SMEDDS)[3].

Self Micro Emulsifying Drug Delivery Systems (SMEDDS) are the isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or instead, single or alternative hydrophilic solvents and co solvents that are having distinctive potential of forming fine oil in water micro emulsions on mild turbulence subsequently followed by dilution in the aqueous media, like in the fluids of GI tract. The turbulence required for the self emulsification is allocated by the digestive motility of the stomach and the intestine, as SMEDDS gets dispersed rapidly in the gastrointestinal tract. The fundamental variation between Self Emulsifying Drug Delivery System (SEDDS) which is also known as Self Emulsifying Oil Formulation (SEOF) and SMEDDS is that, SEDDS basically create cloudy emulsions having a droplet size ranging in between 100-300 nanometers, whereas, SMEDDS form translucent micro emulsions having a droplet size below 50 nanometers and also other major difference between these two is that when compared to SMEDDS which is having an oil concentration of 20%, SEDDS is having higher oil concentration of about 40-80%[4]. Micro emulsions, because of their water content can't be encapsulated in the soft and hard gelatin capsules. Nevertheless, the deprived acquiescence and acceptance by the patients is because of the inferior palatability which is due to the lipidic admixture[5]. A practical alternative is Self Micro Emulsifying Drug Delivery System (SMEDDS) which is system of micro emulsion that is anhydrous in form[6]. Self Micro Emulsifying Drug Delivery System (SMEDDS) favorably provide the dissolved drug form and also its small size of droplets imparts substantial interfacial area for the absorption of drugs[7,8].

Classification System of Lipid Formulation

This system was established in 2000 as a working model[9]. The foremost aim of this system is to validate in vivo analysis to elucidate more promptly and eventually, to promote the recognition of the thermo stable relevant formulations for certain drugs[8].

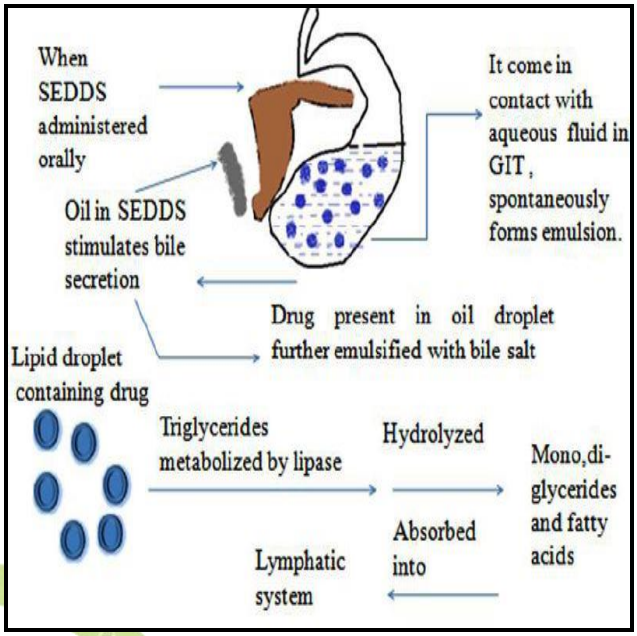

Figure 1: Self-Emulsification process[33]

TYPE-I: This system contains the formulations which include drugs in the solutions in triglycerides and glycerides that are mixed type or emulsions that are oil in water type which the emulsifiers of low concentrations stabilize[10]. This type of lipid formulation constitutes comparatively comprehensible formulation for the effective drugs or the drugs which are favorably lipophilic[1].

TYPE-II: This type of lipid formulations mainly represents the SEDDS[11]. The Self emulsification is predominantly acquired when the contents of the surfactants are over 25% (w/w)[12]. The asset of conquering the deliberate dissolution phase distinctively noticed with solid dosage forms is basically rendered by the Type-II lipid based formulations. And also initiates enormous interfacial areas which sequentially permit systematic segregation of the drug between the droplets of oil and aqueous phase where absorption eventuates[13,14].

TYPE-III: These are often denoted as Self Micro Emulsifying Drug Delivery System (SMEDDS) and can be moreover isolated into Type III A and III B formulations so as to

recognize further hydrophilic systems where hydrophilic surfactant and co solvent content raises and the content of lipid diminishes. In contrast to Type III A formulations Type III B distinctively attain substantial rate of dispersion[1].

TYPE-IV: So as to achieve the contemporary mode to formulations that mainly comprises of co solvents and surfactants that are hydrophilic, this Type-IV was currently adjoined[9].

Advantages

- SMEDDS show a greater enhancement of oral bioavailability.[15]
- There is a high proficiency in the manufacturing and also in scale-up.
- Decrease in the food effects and also the inter and intra subject instability.[16]
- The peptides that are susceptible to enzymatic hydrolysis in the gastrointestinal tract are distributed by SMEDDS.
- SMEDDS belongs to the thermodynamics stable system, and hence it is convenient to preserve it.
- SMEDDS provide various alternatives for delivery such as tablet formulation or filling of soft or hard gelatin capsules.
- SMEDDS that form micro emulsions show better stability and also optical transparency.
- It can simply get penetrated into the gastrointestinal tract which is the major advantage over other emulsions.

Disadvantages

- The major hindrance for the progress of SMEDDS is the insufficiency of better base *in vitro* models for the evaluation of the formulations.
- Usually, the conventional procedures for dissolution will not work at all, because these formulations probably are based upon the digestion precedent to the drug distribution.
- This kind of *in vitro* representation requires additional progress and also approval prior to the assessment of its potency.
- The major drawback of this system includes the precipitation of lipophilic drugs, because the co-solvents that are volatile in the standard self micro emulsifying formulations usually drift into the soft or hard gelatin capsule shells.
- Because of the dilution effect of solvents that are hydrophilic, the susceptibility of precipitation of drug on dilution may progressively get elevated.
- The other drawback is the antagonizing effects in the gastrointestinal tract, which is caused due to the chemical uncertainties of the drugs.
- It becomes more challenging to validate, as the system contains various elements in its formulation.[17]

Formulation of SMEDDS

SMEDDS mainly contains surfactants that are hydrophilic, oil and a co-solvent. To particular combinations of the pharmaceutical excipients, this approach of self emulsification is definite. It mainly rely on the oil type, pair of the surfactants and the ratios, the concentration of surfactant ad also the temperature at which this self emulsification takes place. The recognition of certain combinations of the excipients and then the interpretation of phase diagram that exhibits diverse excipient concentrations of this self emulsification is the foremost step in the formulations of SMEDDS. For the production of this system or any other lipid formulation that is stable, correlative mixing of the excipients is necessary. The surfactants that are hydrophilic and also the co-solvents are generally not compatible with that of Long Chain Triglycerides. However, the mixed glycerides which are known to be the polar oils exhibits uniformity with the hydrophilic surfactants so as to achieve the miscibility with these surfactants and it usually assist in the self-dispersion. It is necessary to carry out the physical stability tests of the formulations required, to avoid the incompatibility on storage due to the variations in the chemical nature of the lipids. The waxy excipients, if used in the formulation, should be

melted prior to weighing and then combined with the other liquid excipients[18]. The following steps must be taken into account in the formulation of SMEDDS.

- The dissolution of drugs in various co-solvents, oils and surfactants.
- The choice of these co solvents, oils, and surfactants depending upon the solubility and also the construction of a phase diagram[19].
- The development of the formulation of SMEDDS, by solubilizing the drug in oil, co solvent or surfactant.

The inclusion of a drug to this system is probably more unfavorable due to the interference with self emulsification which may cause the modification in the ideal oil-surfactant ratio. So, it mainly requires the phase-diagram and pre-formulation studies in the formulation of SMEDDS. These formulations include gelling agent or a polymer, in case of the prolonged SMEDDS[20].

Excipients Used in SMEDDS

There are various excipients used in the formulation of this drug delivery system. Some of them are as follows-

Tween 80

They may be used as emulsifiers in some oil-in-water type of emulsions. At the time of freeze-drying, this excipient obstructs the proteins from superficially persuaded contamination[21]. This excipient is FDA approved and is used as oral administration of a drug. It is widely used as a partial fatty acid ester of sorbitol and is probably applicable as a hydrophilic non-ionic surfactant (HLB-15) in many formulations containing self-dispersion technique[22].

Cremophor RH 40

For several hydrophobic Active Pharmaceutical Ingredients (APIs) and essential oils, Cremophor RH 40 acts as a solubilising agent. It also acts as an emulsifier in various emulsions[23]. Cremophor RH 40 is a polyoxyethylene derivative of castor oil and has a HLB value 14-16. It comprises of glycerol polyethylene glycol and polyethylene glycol fatty acid esters. It helps in enhancing the solubility of propellants[24].

Polyethylene glycol 400

It can be used for oral, rectal, topical, parenteral, ophthalmic delivery of drug. In case of poor water soluble drugs, Polyethylene glycols which are of liquid grade are widely employed as co-solvents that are water-miscible having acceptable properties of a solvent. Because of this, these are employed in lipid based formulations or drug delivery systems.[25]

Labrafac Lipophile WL 1349

It possesses a HLB value 1 and it is a triglyceride of medium chain basically of fractionated vegetable C8 and C10 fatty acids. It can majorly be used as a vehicle in various self-emulsifying drug delivery systems and also in creams, ointments, suspensions etc… It can also be widely used in tablets as an anti-adherent, whereas in capsules it may be used as filler. It has eminent properties such as easy penetration into the skin, spreadable property and many others.[26]

Capyrol 90

It mainly possesses 90% C8 fatty acid monoester. It is mainly used as an emulsifier in SMEDDS and is soluble in chloroform, ethanol, vegetable oils etc…and insoluble in water[27].

Transcutol P

In case of poor water soluble drugs this excipient has eminent solvent properties. It increases penetration and permeation of the drug and is majorly employed as a co solvent in self-emulsifying drug delivery systems[28].

Self Emulsification Tests

SMEDDS are either the Nano emulsions or opaque emulsions which exhibits easy phase dissociation. For the evaluation of SMEDDS, its dispersion clarity and stability, the following steps are performed.

Solubility of the Drug

To evaluate the solubility of the drug in SMEDDS, in a small quantity of excipient which

is set in micro tubes, surplus amount of drug is included in it and this amalgam is whirled. Then to enhance the solubilisation of drug, this is probably being heated in a water bath at 40^0C. To reach at an equilibrium state, the mixture is now set at room temperature for 2 days after continuous shaking. And then, at 2500-3000 rpm for 20 minutes, this is centrifuged. The supernatant obtained is diluted with alcohol and is then evaluated with UV spectroscopic method[29].

Size of the Droplet and the Zeta Potential of Nano Emulsions

Using Dynamic-Light Scattering technique, the size of the droplet and zeta potential of a nanoemulsion, which in case of SMEDDS is uniformly dispersed in water (400-500ml), is probably evaluated.

Morphological Testing of Solid SMEDDS

This is carried out with the use of Electron Microscope. With the help of double side adhesive carbon tape, the samples for testing are set on a stump of aluminum and further allowed to carry out electrical conduction after coating with palladium. To envision the samples a voltage of 5kV is applied.

Differential Scanning Calorimetry

Using Differential Scanning Calorimetry, the state of SMEDDS is identified. The samples of these are allowed to move on DSC for evaluation. The samples are scanned and the required information for evaluation is obtained using Pyris Manager Software.

Powdered X- ray Diffraction

This test is made possible using X- Ray diffractometer. With the use of monochromatic radiations, such calculations are performed. And, after the analysis the samples are encased in aluminum holder of sample with the help of a glass slide.

Mechanism of Self Emulsification

Generally, the standard emulsions are composed of two non-miscible liquids like water and oil which is further stabilized by an emulsifying agent. In between these two phases, the surface area enlargement is generated during the formation of an emulsion. The surfactant molecule that produces a kind of film throughout the internal phase droplet stabilizes the emulsion. Generally, during the formation of an emulsion, profuse surface free energy relies on the size of the droplet and the interfacial tension.

The decrease in the free energy and the interfacial tension occurs probably resulting in the dissociation of two phases, if the emulsion is not stabilized by the addition of surfactants[30]. Whereas, in case of SMEDDS, the free energy is very poor and sometimes may be positive or negative that leads to spontaneous emulsification which is thermodynamic.

Self emulsification usually takes place due to the entry of water into Liquid Crystalline phase. There is a formation of the droplet or the interface disturbance is created, after the entry of water to a definite level. This Liquid Crystalline phase is regarded as the most important phase for the prominent stability of nanoemulsion in opposition to the coalescence[31,32].

CONCLUSION

Several attempts are been made to achieve the enhancement of the oral bioavailability of poorly water soluble drugs**.** SMEDDS enhances the solubility of the drug in the GIT and can be potentially used. Regardless of substantiate potential of these systems, very few products that are lipid based are found to be profit oriented.

This is due to the deprived implementation of newer technologies. But there is a wider range of reflection through this system of drug delivery due to the fact of in vivo studies in humans.

Perhaps, due to the lack of in vitro studies, which are predictive to in vivo studies has been effectively restraining the progress of these self micro emulsifying drug delivery system.

Although, considerable efforts have already been made to improve the oral bioavailability through these systems. Furthermore, the extensive and continuous comparison of in-vitro and in-vivo studies is essential for the progress of these drug delivery systems in the foreseeable future.

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REFERENCES

1. Kyatanwar, A. U., Jadhav, K. R., & Kadam, V. J. (2010). Self-micro emulsifying drug delivery system. *Journal of Pharmacy Research*, *3*(1), 75-83.
2. Patel, N. D. (2011). An emerging technique for poorly soluble drugs: self emulsifying drug delivery system. *International Journal of Pharmaceutical & Biological Archive*, *2*(2).
3. Gursoy, R. N., & Benita, S. (2004). Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biomedicine & Pharmacotherapy*, *58*(3), 173-182.
4. Shukla, J. B., Koli, A. R., Ranch, K. M., & Parikh, R. K. (2010). Self micro emulsifying drug delivery system. *An International Journal of Pharmaceutical Sciences*, *1*(2), 13-33.
5. Patravale, V. B., Date, A. A., & Kale, A. A. (2003). Oral self micro emulsifying systems: Potential in DDS. *Pharma Technology. Express Pharma Pulse Special Feature*, *29*, 44-48.
6. Charman, S. A., Charman, W. N., Rogge, M. C., Wilson, T. D., Dutko, F. J., & Pouton, C. W. (1992). Self-emulsifying drug delivery systems: formulation and biopharmaceutic evaluation of an investigational lipophilic compound. *Pharmaceutical Research*, *9*(1), 87-93.
7. Pouton, C. W. (1985). Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. *International Journal of Pharmaceutics*, *27*(2), 335-348.
8. Shah, N. H., Carvajal, M. T., Patel, C. I., Infeld, M. H., & Malick, A. W. (1994). Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. *International Journal of Pharmaceutics*, *106*(1), 15-23.
9. Pouton, C. W. (2006). Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *European Journal of Pharmaceutical Sciences*, *29*(3), 278-287.
10. Myers, R. A., & Stella, V. J. (1992). Systemic bioavailability of penclomedine (NSC-338720) from oil-in-water emulsions administered intraduodenally to rats. *International Journal of Pharmaceutics*, *78*(1-3), 217-226.
11. Pouton, C. W. (1997). Formulation of self-emulsifying drug delivery systems. *Advanced Drug Delivery Reviews*, *25*(1), 47-58.
12. Cuine, J. F., McEvoy, C. L., Charman, W. N., Pouton, C. W., Edwards, G. A., Benameur, H., & Porter, C. J. (2008). Evaluation of the impact of surfactant digestion on the bioavailability of danazol after oral administration of lipidic self-emulsifying formulations to dogs. *Journal of Pharmaceutical Sciences*, *97*(2), 995-1012.
13. Gershanik, T., & Benita, S. (2000). Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. *European Journal of Pharmaceutics and Biopharmaceutics*, *50*(1), 179-188.
14. Constantinides, P. P. (1995). Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. *Pharmaceutical Research*, *12*(11), 1561-1572.
15. Gershanik, T., & Benita, S. (1996). Positively charged self-emulsifying oil formulation for improving oral bioavailability of progesterone.

Pharmaceutical Development and Technology, *1*(2), 147-157.

16. Charman, W. N., Porter, C. J., Mithani, S., & Dressman, J. B. (1997). Physicochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. *Journal of Pharmaceutical Sciences*, *86*(3), 269-282.
17. Khan, B. A., Bakhsh, S., Khan, H., Mahmood, T., & Rasul, A. (2012). Basics of self micro emulsifying drug delivery system. *Journal of Pharmacy and Alternative Medicine*, *1*(1), 13-19.
18. Pouton, C. W., & Porter, C. J. (2008). Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. *Advanced Drug Delivery Reviews*, *60*(6), 625-637.
19. Farah, N., Laforet, J. P., & Denis, J. (1994). Self-microemulsifying drug delivery systems for improving dissolution of drugs: in vitro/in vivo evaluation. *Pharmaceutical Research*, *11*, S202.
20. Nazzal, S., & Khan, M. A. (2006). Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. *International Journal of Pharmaceutics*, *315*(1), 110-121.
21. Chang, B. S., Kendrick, B. S., & Carpenter, J. F. (1996). Surface-induced denaturation of proteins during freezing and its inhibition by surfactants. *Journal of Pharmaceutical Sciences*, *85*(12), 1325-1330.
22. Salager, J. L., Nielloud, F., & Marti-Mestres, G. (2000). Pharmaceutical emulsions and suspensions. *Drugs Pharm. Sci*, *105*, 19-72.
23. Kibbe, A. (2000). Handbook of pharmaceutical excipients. Amer Pharmacists Assn.
24. Strickley, R. G. (2004). Solubilizing excipients in oral and injectable formulations. *Pharmaceutical Research*, *21*(2), 201-230.
25. Goodman, L., Goodman and Gilman's the pharmacological basis of therapeutics. 2006: McGraw-Hill New York.
26. Knepp, V. M., Whatley, J. L., Muchnik, A., & Calderwood, T. S. (1996). Identification of antioxidants for prevention of peroxide-mediated oxidation of recombinant human ciliary neurotrophic factor and recombinant human nerve growth factor. *PDA Journal of Pharmaceutical Science and Technology*, *50*(3), 163-171.
27. Kakuta, H., Zheng, X., Oda, H., Harada, S., Sugimoto, Y., Sasaki, K., & Tai, A. (2008). Cyclooxygenase-1-selective inhibitors are attractive candidates for analgesics that do not cause gastric damage. design and in vitro/in vivo evaluation of a benzamide-type cyclooxygenase-1 selective inhibitor. *Journal of Medicinal Chemistry*, *51*(8), 2400-2411.
28. Stuhlmeier, K. M., Li, H., & Kao, J. J. (1999). Ibuprofen: new explanation for an old phenomenon. *Biochemical Pharmacology*, *57*(3), 313-320.
29. Craig, D. Q. M., Lievens, H. S. R., Pitt, K. G., & Storey, D. E. (1993). An investigation into the physico-chemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. *International Journal of Pharmaceutics*, *96*(1-3), 147-155.
30. Craig, D. Q. M., Barker, S. A., Banning, D., & Booth, S. W. (1995). An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. *International Journal of Pharmaceutics*, *114*(1), 103-110.
31. Groves, M. J., & De Galindez, D. A. (1976). The self-emulsifying action of mixed surfactants in oil. *Acta Pharmaceutica Suecica*, *13*(4), 361.
32. Wakerly, M. G., Pouton, C. W., Meakin, B. J., & Morton, F. S. (1986). Self-emulsification of vegetable oil-nonionic surfactant mixtures: a proposed mechanism

of action. In *ACS symposium Series* (Vol. 311, pp. 242-255). Oxford University Press.

33. Khedekar, K., & Mittal, S. (2013). Self emulsifying drug delivery system: a review. *International Journal of Pharmaceutical Sciences and Research*, *4*(12), 4494.