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A REVIEW ON SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM OF POORLY WATER SOLUBLE

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Abstract:
Lipid-based drug delivery systems are extensively reported in the literature for enhancing drug solubility, permeability, and bioavailability. These systems include simple oil solutions, coarse, multiple, and dry emulsions, complex self-emulsifying, micro emulsifying, or nano emulsifying drug delivery systems. Self-emulsifying systems, further classified as self-micro emulsifying drug delivery systems (SMEDDS) and self-nano emulsifying drug delivery systems (SNEDDS), are the most prevailing and commercially viable oil-based approach for drugs that exhibit low dissolution rate and inadequate absorption. Ever since the progress of SNEDDS, they drew the interest of researchers in order to deal with the challenges of poorly water-soluble drugs. SNEDDS is a proven method for enhancing the solubility and bioavailability of lipophilic compounds. Considering the ease of large-scale production and the robustness of SNEDDS, several formulations techniques are commercially available. The stability of SNEDDS can be further enhanced by solidifying liquid SNEDDS. Controlled release and supersaturated SNEDDS received patient compliance with larger drug loading. The presence of biodegradable ingredients and "drug-targeting opportunities" facilitate SNEDDS' clear merit and distinction amongst available solubility enhancement techniques. In this article, an attempt was made to present an overview of SNEDDS, their mechanism, formulation excipients, and potentials of SNEDDS, recent advancements, advantages, and disadvantages of SNEDDS formulations. The article also focuses on reviewing the application of SNEDDS in enhancing the bioavailability of antihypertensive drug.

KEYWORDS*: Self nanoemulsifying drug delivery system; SNEDDS; Rosuvastatin calcium; solubility study, Ternary Phase Diagram.*

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INTRODUCTION:

Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drug having the problem of low bioavailability, high intra and inter subject variability and lack of dose proportionality. To overcome these problems various formulation strategies are reported in the literature including the use of surfactants, cyclodextrins, nanoparticles, solid dispersions, micronization, lipids and permeation enhancers. [1,2] However, these approaches cannot guarantee the physicochemical stability of the drug compounds. An additional emphasis has been placed on presenting and maintaining the drug at a molecular level in the solution form throughout its period in the GI tract. Thus the use of lipid andsurfactant based formulation is among several approaches found to be capable of improving the bioavailability of poorly water soluble drugs. In recent years, self-nanoemulsifying drug delivery systems (SNEDDS) as lipid and surfactant-based formulations showing a practical achievement in improving the oral bioavailability of poorly soluble drug compounds by presenting and maintaining the drug in a dissolved state, at the molecular level, in small droplets of oil, throughout its transit through the GI tract. SNEDDS is an isotropic mixture of oil, surfactant and co-surfactant, and they are capable of forming thermodynamically stable o/w nanoemulsions upon moderate stirring provided by the stomach and the upper small intestine. Rosuvastatin calcium (ROS) is a synthetic lipid Lowering agent, chemically known as (3R,5S,6E)-7-{4-(4-fiuorophenyl)-6(1-methylethyl)-2-[methyl(methylsulphonyl)amino] pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid calcium salt(2:1).[3]It is also used in the treatment of osteophoresis, benign prostatic hyperplasia and Alzheimers disease.[4] The oral bioavailability of ROS is 20% because of low aqueous solubility due to its crystalline nature and is extensively metabolized by liver via oxidation, lactonization and glucoronidation.[5,6] After oral administration of ROS, the peak plasma concentration was attained within 35hrs, the volume of distribution was 1.1-1.4 liter/kg, and plasma protein binding was 90%.

ADVANTAGES OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS)

Nanoemulsion (SNEDDS) have a much large surface area and free Energy than micro emulsions (SMEDDS)19.The self-Nanoemulsifying drug delivery system is important to improve the Bioavailability20.The ability of nanoemulsion (SNEDDS) to dissolve large quantities of lipophilic Drug, along with their ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal vehicles for the purpose of parenteral transport21.The SNEDDS is important to provide ultra-low interfacial tension and provide a large o/w interfacialareas22.Nanoemulsion (SNEDDS) was formulated in a variety of formulations Such as liquids, sprays, foams, creams, ointments and gels and it is Used nanoemulsion in pharmaceutical field as well as used in drug delivery system such as oral, topical and parenteral nutrition23.In Self Nanoemulsifying Drug Delivery System(SNEDDS) is Essential For oils and their main components have the number of applications in medicine, food, beverages, preservation, cosmetics and it is also used for the fragrance and pharmaceutical industries24.It is used as Ayurvedic system and unnani system25.The Self Nanoemulsifying drug Delivery System(SNEDDS) having site specific as well as targeted drug delivery system.

DIS ADVANTAGES OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS)

The preparations of Nanoemulsion (SNEDDS) are difficult to prepare because the high-pressure homogenizer as well as ultrasonic equipment was available in recent year and the nanoemulsion preparation was expensive27.The Stability of Self Nanoemulsifying drug delivery
system was affected by Temperature and Ph.

PREPARATION METHODS FOR SNEDDS

Method of preparation for SNEDDS includes active pharmaceutical ingredient, excipient, polymers and emulsifier. Different methods for the preparation of Self Nano-emulsifying drug delivery system but, mainly divided into 2 methods:

A. *High-energy-emulsification.*

B. *Low-energy-emulsification*

The high-energy-emulsification method includes higher pressurized-homogenization (HPH), Ultra sonication and Micro-fluidization. The low-energy method includes Phase-inversion, Spontaneous emulsification. Using combination of both technique, such as high-energy emulsification and low-energy emulsification, for prepared reverse Self Nano-emulsifying drug delivery system are highly viscous system.

High Energy Emulsification Method:

1. High pressure homogenization (HPH):

The preparing of Self Nano-emulsifying drug release system want important compel homogenization. This style above all old as higher-pressurized-homogenizer/locate-homogenizer gives Nano-emulsion particularly muffled particle extent (up to

1nm). This scattering in 2 phases (oil-mixture & aqueous-phase) is attained speeding mixed substance through a trivial cove chop at exact excessive load (500-5000 psi), addresses invention in higher disorder and hydraulic-shear develops an awfully charge particles of emulsion

2. Ultrasonication:
It is the more convenient method lowering drops sized in this method; the energy-range is given through sonotrodes known to be Sonicator-probe. It bottles hold back piezo-electric quartz precious stone that preserves spread out & tighten the comeback of broken exciting volt. End point in Sonicator contacts the liquid medium; its container produces mechanical throb and captives enrolled. Formation of captives shut down vapour cavities in liquid. Thus, ultrasounds canister straight produces an emulsion. In this mode is above all old for laboratories purpose, everywhere blend drop dimension is soothing as 0.2mm canister is obtained.

3 Micro-fluidizations:
Micro-fluidization original addition methodology, that employees the custom of a manoeuvre said micro-fluidizer. manoeuvre was second-hand in above what is usual hassle affirmative disarticulation pump (500-20000psi), which break open the produce through the interaction chamber, consequential incredibly fair particles in the submicron range. This deal with is constant a number of an era to get hold of a beloved range to shaped even or homogenous Nano-emulsion system.

Low Energy Emulsification:
1. Phase inversion emulsification method:
Here is a method employed a transition of phase by applying very increased temperature route in emulsification.

2. Continuous emulsification:
In this system of emulsification is always formed. In which, the groundwork of consistent and standardized organic resolution consisting of grease & lipophilic-surfactant infill with tears miscible surfactant and hydrophilic-surfactant phase. The organic point was injected-in-aqueous stage below unbroken alluring stirring; string Oil-in-Water was prepared. Aqueous-stage was unconcerned as fading below concentrated pressurized.

Different dosage form of Solid SNEDDS (s-SNEDDS):
- Self-emulsifying sustained release microspheres
- Self-emulsifying beads
- Self-emulsifying solid dispersions
- Self-emulsifying sustained/controlled release pellets
- Self-emulsifying sustained/controlled release tablets
- Dry emulsions
- Self-emulsifying capsules
- Self-emulsifying nanoparticles
- Self-emulsifying suppositories
- Self-emulsifying implants

Surfactants:
The surfactant from natural origin is suitable as compared to synthetic surfactants. The natural surfactants include extract of *Sapindusmukorossi*, *Verbascumdensiflorum*, *Equisetum arvense*, *Betulapendula*and *Bellisperennis*soapwort. Surfactant has pronounced impact on the process of emulsification, droplet size and nano-emulsifying region. The properties which are considered are affinity to oil phase, HLB in oil and viscosity. The screening of surfactants are done on the basis of emulsifying ability and this is achieved by mingling oil and surfactants under warm conditions and then dilute with deionized water to prepare isotropic mixtures.
***Anionic surfactants*:** Potassium laurate, sodium lauryl sulphate
Cationic surfactants: Quaternary ammonium halide
Nonionic surfactants: Polysorbate (tweens), Sorbitan esters (Spans)
Co-surfactants/Co stabilizers: Co-surfactants are employed to enhance the emulsification of the surfactant. The screening is done by mixing several co-surfactants with certain surfactant and oily phase under heating conditions and then diluted with water to prepare the isotropic mixtures. Examples include Glycofurol, Phospholipids, Propylene glycol, PEG, monoethyl ether, ethanol, triacetin**.**

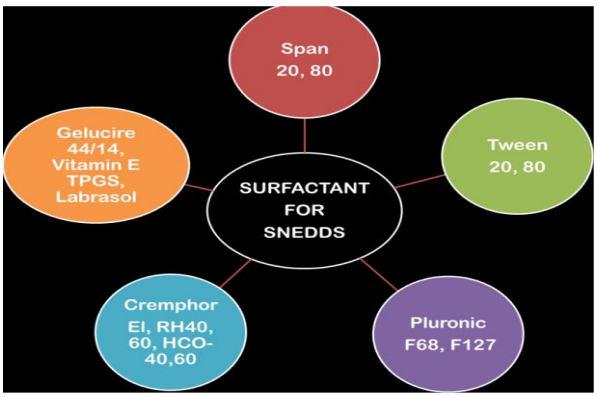

Figure 2: Commonly used surfactants in SNEDDS

SNEDDS Characterization

1. Thermodynamic stability of emulsion

The physical stability of lipid based formulation is also crucial to it performance, which can be adversely affected by precipitation the drug in the excipients matrix. In addition poor formulation physical stability can lead phase separation of the excipients affecting not only formulation performance but visual performance as well.

a) Centrifugation study

The formulations were centrifuged using laboratory centrifuge (REMI R-8C) at 5000 rpm for 30 min. The resultant formulations were then checked for any instability problem, such as phase separation, creaming or cracking. Formulation which is stable selected for further studies.

b) **Heating and cooling cycle**

Three heating/cooling cycles between 4◦C and 40◦C with storage at each temperature for not less than 24 h. The resultant formulations were assessed for their physical instability like phase separation and precipitation. Formulation which passes this test subjected for further test .

c) Freeze thaw cycle

Freeze thawing was employed to evaluate the stability of ROS Calcium loaded SNEEDS. Formulations were subjected to 3 freeze-thaw cycles, which included freezing at −4◦C for 24 h followed by thawing at 40◦C for 24 h. Centrifugation was performed at 3000 rpm for 5 min. The formulations were then observed for phase separation. Formulation which passes all these three test & those having least Smix concentration were optimized formulation .

2.self emulsification time

The efficiency of self-emulsification is assessed using dissolution apparatus. 1ml SEDDS was dissolved in 250ml of water at 37±0.5◦C. Gentle agitation was provided by paddle rotating at 60RPM. SEDDS was assessed visually according the rate of emulsification and the final appearance of the emulsion. Also any precipitation was observed visually.

3.Dispersibility Test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed by standard USP II dissolution apparatus. One ml of each formulation was dissolved in 500 ml of water at 37 ± 1◦C. A standard stainless steel dissolution paddle is used with rotating speed of 50 rpm to provide gentle agitation. The in vitro performance of the formulations is visually assessed by following grading system.

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

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

c. Grade C: Fine milky emulsion that formed within 2 min.

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

e. 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 nano emulsion when dispersed in GIT.

4. Percent Transmittance

The Rosuvastatin calcium SNEDDS were reconstituted with distilled water and the resulting nanoemulsion was observed visually for any turbidity. Thereafter, its % transmittance was measured at 638.2 nm using UV–VIS spectrophotometer (Shimadzu UV 1800) against distilled water as the blank.

5. Droplet size measurement

SNEDDS formulation (10 µl) was diluted with 10 ml deionized water in a beaker with constant stirring using a glass rod. The resultant emulsion was then subjected to particle size analysis. The droplet size so formed determined by Dynamic light scattering (DLS) technique using a zetasizer (Nano ZS, Malvern Instruments, UK). He-Ne red laser, 4.0 mW, 633 nm; temperature 250c.

6.Polydispersibility Index

Polydispersity index (PDI) is measure of droplet size homogeneity and it varies from 0.0 to 1.0. Polydispersity is the ratio of standard deviation to mean droplet size in the formulation. The higher the Polydispersity, the lower the uniformity of the droplet size in the formulation. The closer to zero the Polydispersity value the more homogenous are the droplets.

7. Cloud point measurement

The optimized SNEDDS formulations were diluted with distilled water in the ratio of 1:250. The diluted samples were placed in a water bath and its temperature was increased gradually. Cloud point was spectrophotmetrically determined as the

temperature at which there was a sudden appearance of cloudiness.

8. Drug content determination

ROS Calcium SNEDDS (100 mg) was dissolved in 10 ml of methanol in 10 ml volumetric flask separately, 0.1 ml of stock solution measured accurately and transferred to 10 ml volumetric flask to which 10 ml methanol was added and filtered through whatman filter paper. The above solutions were analyzed by UV Spectrophotometer (Shimadzu UV 1800) at λmax. 244nm. the amount of ROS Calcium present in the formulation was determined using the prepared standard calibration curves of ROS calcium in methanol.

9. Preparation of Solid-SNEDDS of formulation

The SNEDDS formulations were mixed with solid carrier, Neusilin US2. Briefly, the SNEDDS was added drop wise over the solid adsorbent in a broad porcelain dish. After each addition, the mixture was mixed thoroughly using glass rod to ensure uniform distribution. Neuclilin is extremely safe with no reports of adverse reaction. Based on the usage of excipient neucilin up to 1.05 g can be used for oral uptake per day.

10. Scanning Electron Microscope study

Morphological examination of surface of Neusilin US2 and formulation adsorbed on Neusilin US2 was carried out using a scanning electron microscope. Particles were vacuum dried and coated with thin gold-palladium layer and observed microscopically at an accelerating voltage of 5.0 kV.

11.*In vitro* dissolution test

The solid SNEDDS containing 40 mg equivalent of ROS calcium were filled in to hard gelatin capsule (Capsule no. 00). ROS Calcium release from Solid-SNEDDS formulations were performed using dissolution apparatus of USP Type I Basket method with 500 ml of distilled water as dissolution medium at 37 ± 50C with basket speed at 80 rpm. Solid-SNEDDS formulation equivalent to 10 mg of ROS Calcium was introduced into dissolution apparatus Type USP I Basket method (Electro lab TDT-08L, India). 5mL samples were collected for up to 40 min at 10 min interval. The dissolution medium was replaced with 5mL fresh dissolution fluid to maintain the sink condition. The withdrawn samples were filtered and analyzed by UV spectrophotometer.

12. Morphology of SNEDDS

It is done by SEM study to check crystalline structures characteristic of rosuvastatin calcium are not seen in solid SNEDDS micrographs suggesting that the drug is present in a completely dissolved state in the solid SNEDDS.

CONCLUSION:

Low water solubility of BCS class II and IV drugs is responsible for poor oral absorption and hasbeen fixed through a “key strategy” called lipid-based drug delivery system. LBDDS areversatile carriers assuming different forms including emulsions. Nanoemulsions and microemulsions are thermodynamically different systems having droplets in almost same nanometric range. With the arrival of low energy and self-emulsification methods, nanoemulsions have regained their importance as SNEDDS. SNEDDS have shown high drugloading capacity, improve bioavailability and therapeutic efficiency of hydrophobic drugs. Theyhave been further modified as supersaturated, solid and even controlled release SNEDDS. Theirpotential for carrying and delivering biomolecules such as insulin, leuprorelin etc. for improvedpermeability and reduced enzymatic degradation is well established. SNEDDS are now well-known for their mucus permeating capacity as well as their capability of enhancing lymphaticuptake. As SNEDDS are suitable for surface functionalization, they can be designed for activetargeting to desired organs. Gap between SNEDDS and their commercial products is due to lackof complete understanding of their *in-vivo* behavior and so far has been filled by development ofreflective *in-vitro* test. In recent times, some new SNEDDS development methods like HLBresponse surface methodology have been adopted to surpass the drawbacks of old methodologiesSand thus making SNEDDS an eminent and favorable drug delivery technique.

REFERENCES:

1. Akiladevi D, Prakash H, Biju G, Madumitha N. Nano-novel approach: Self Nano Emulsifying Drug Delivery System (SNEDDS)-Review Article. Research Journal of Pharmacy and Technology. 2020;13(2):983-90.
2. Makadia HA, Bhatt AY, Parmar RB, Paun JS, Tank H. Self-nano emulsifying drug delivery system (SNEDDS): future aspects. Asian Journal of Pharmaceutical Research. 2013;3(1):21-7.
3. Maruti TS, KisanBobe D, Potnis V, Dhamane S, Suresh PV. A REVIEW-SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS). 2020.
4. Reddy SM, Baskarla S. A Review on Formulation and Development of Solid Self-Nano Emulsifying Drug Delivery Systems.International Journal of Pharmaceutical

Sciences and Nanotechnology. 2021;14(4):5519-228.
5. Fritz Blatter, Crystalline forms of Rosuvastatin Calcium salt Us Patent No. 20080194604A1, (2008)
6. ShloitWizel, Crystalline Rosuvastatin Calcium, US Patent No. 20080176878A1. (2008)
7.Kommuru TR, Gurley B, Khan MA, Reddy IK. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. Int J Pharm 2001; 212:233–46.
8. Yogeshwar G. Bachhav and Vandana B. Patravale,SMEDDS of Glyburide : Formulation, In Vitro Evaluation, and Stability Studies, AAPS Pharm SciTech, Vol. 10, No. 2, June (2009),482-487.
9. Chiragraval et al; Enhanced oral bioavailability of olmesartan by using nove solid SEDDS, international journal of advanced pharmaceutics, vol-2, 2012, 82-92.
10. Shweta Gupta, SandipChavhan, Krutika K. Savant, "Self-nanoemulsifying drug delivery system for adefovirdipivoxil: Design, characterization, in vitro and ex vivo evaluation" Coll. & Surf. B: Physicochem. Eng. Aspects 2011; 392:145– 155
11.PannerSelvam R, Kulkarni P K. Design and Evaluation of Self Nanoemulsifying Systems forPoorly Water Soluble HIV Drug, *Journal of PharmaSciTech*, 4(1), 2014, 24-28.
12. Daniela S, Bernardi, Tatiana A, Pereira, Naira R Maciel, JosianeBortoloto, Gisely S Viera1,Gustavo C Oliveira and Pedro A Rocha-Filho.Formation and stability of oil-in-water nanoemulsions containing rice bran oil, *in vitro* and *in vivo* assessments, Bernardi*et al*. *Journalof Nanobiotechnology*, 9(2), 2011, 44, 2-9
13. KanokpornBurapapadh, Mont Kumpugdee-Vollrath. DoungdawChantasart, PornsakSriamornsak. Fabrication of pectin-based nanoemulsions loaded with itraconazole for pharmaceutical application, *CarbohydratePolymers*, 82(1), 2010, 384-393
14. Srilatha R, Aparna C, PrathimaSrinivas, Sadanandam M. Formulation, Evaluation and Characterization of GlipizideNanoemulsion, *Asian J Pharm Clin Res*, 6(2), 2013, 66-71.
15. GautamSeema, Singh Arunkumar. Self Nanoemulsifying Drug Delivery System- A Naval approach for Improving Bioavailability, *Journal of Drug Delivery and Therapeutics*.4(6),2014,33-38.
16. Pouton, C.W.; Porter, C.J.H. Formulation of Lipid-Based Delivery Systems for Oral Administration: Materials, Methods and Strategies. Adv. Drug Deliv. Rev. **2008**, 60, 625–637.
17. Date, A.A.; Desai, N.; Dixit, R.; Nagarsenker, M. Self-Nanoemulsifying Drug Delivery Systems: Formulation Insights, Applications and Advances. Nanomedicine**2010**, 1595–1616
18. Singh, B.; Bandopadhyay, S.; Kapil, R.; Singh, R.; Katare, O.P. Self-Emulsifying Drug Delivery Systems (SEDDS): Formulation Development, Characterization, and Applications. Crit. Rev. Ther. Drug Carrier Syst.**2009**, 26, 427–521.
19. Kollipara, S.; Gandhi, R.K. Pharmacokinetic Aspects and in Vitro–in Vivo Correlation Potential for Lipid-Based Formulations. Acta Pharm. Sin. B **2014**, 4, 333–349.]
20. Mu, H.; Holm, R.; Môllertz, A. Lipid-Based Formulations for Oral Administration of Poorly Water-Soluble Drugs. Int. J. Pharm. **2013**, 453, 215–224.
21.Shen H, Zhong M. (2006). Preparation and evaluation of selfmicroemulsifyingdrug delivery systems (SMEDDS) containing atorvastatin. J Pharm Pharmacol 58:1183–91.
22.Singh B, Bandopadhyay S, Kapil R, Singh R, et al. (2009). Selfemulsifyingdrug delivery systems (SEDDS): formulation development, characterization, and applications. Crit Rev Ther Drug Carrier Syst 26:427–521.
23.Sinha S, Ali M, Baboota S, Ahuja A, et al. (2010). Solid dispersion as an approach for bioavailability enhancement of poorly water-soluble drug ritonavir. AAPS Pharm Sci Tech 11:518–27
24.Tommasini S, Calabro` ML, Raneri D, et al. (2004). Combined effect of pH and polysorbates with cyclodextrins on solubilization ofnaringenin. J Pharm Biomed Anal 36:327–33.
25.Wang L, Dong J, Chen J, et al. (2009). Design and optimization of a new self-nanoemulsifying drug delivery system. J Colloid Interface Sci330:443–8.