SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM:
A STRATEGY TO IMPROVE ORAL BIOAVAILABILITY

Payal Gupta1, Pramod Kumar1 Sharma, Nitin Kumar1, Yogesh Pawar1,
Jitendra Gupta2

1Department of Pharmacy, School of Medical and Allied Sciences,
Galgotias University, Greater Noida, U.P., India.
2Institute of Pharmaceutical Research, GLA University, P.O. Chaumuhan,
Mathura-281406.

ABSTRACT
Now a day oral route is the easiest and most prominent route for drug delivery. More than 40% of new chemical entities exhibit poor aqueous solubility result in unsatisfactory oral drug delivery. Self nano-emulsifying drug delivery system (SNEDDS) play important role in improvement of bioavailability, by mixture of oil, surfactant, and co-surfactant were prepared under gentle agitation and obtain by pseudo-ternary phase diagram and evaluate on the basis of Zeta size & potential, Conductivity measurement, Turbidity measurement and Transmission electron microscopy analysis.

Key Words:-Self -Nano Emulsify Drug Delivery System, Bioavailability, Surfactant, Solubility.

INTRODUCTION
Around forty percent of new chemical entities developed by the pharmaceutical industry are poorly soluble or lipophilic compounds, which result poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality1. Efforts are madewith SNEDDS to enhance the oral bioavailability of lipophilic drugs in order to increase their pharmacological efficacy2. SEDDS also called as self-emulsifying oil formulation. Because it is mixtures of oils and surfactants, ideally isotropic and sometimes containing co-solvents, when introduced into aqueous phase under gentle agitation it produce fine oil in water emulsion spontaneously3-4. Recent years Self-Nano emulsifying (SNEDDS), self-micro emulsifying (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) is used to
improve the oral bioavailability of poorly water-soluble drugs\textsuperscript{5-7}. Self-Nano emulsifying drug delivery system (SNEDDS) is isotropic mixtures of oil, surfactant, co-surfactant and drug, introduced into aqueous phases under gentle agitation. SNEDDS spread readily in the gastrointestinal tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification\textsuperscript{8}. Generally the size range of self-emulsification system varies from nanometer to micrometer, Self-Nano emulsification system have around less than 100nm size range of globule upon dispersion in water\textsuperscript{9}.

Criteria for Selection of Candidate
Self-Nano emulsification formulation enhance oral bioavailability of drug belonging to biopharmaceutical classifications II and IV, log p value should be greater than 4 and melting point should be low, size of oil droplet should be less than 100nm, upon dispersion it should be optically clear, HLB value should be greater than 12\textsuperscript{10-11}. Table 1 Biopharmaceutical Classification\textsuperscript{11}

| Class | Aqueous Solubility | Membrane Permeability |
|-------|--------------------|-----------------------|
| I     | High               | High                  |
| II    | Low                | High                  |
| III   | High               | Low                   |
| IV    | Low                | Low                   |

Limitations

- Drug should not be in high dose until they exhibit extremely good solubility in at least one of the components of SNEDDS.
- Try to maintain the solubilization of drug in such manner that it should not be precipitated\textsuperscript{12}. Due to presence of bio enhancer SNEDDS enhance bioavailability of absorbed compound by fascinating Trans cellular as well as Para cellular absorption\textsuperscript{13}.

Advantages

- Protecting reactivity of drug substances.
- Drug targeting(s) toward specific absorption site in GIT.
- Enhancement of oral bioavailability.
- Required low dose.
- Better stability.
- Fine oil droplet minimizes the gastric irritation\textsuperscript{14-16}. 
Classes of excipients used in SNEDDS

Selection of Oil
Generally selection oil used in formulation of SNEDDS, based on its solubility parameter, HLB (Hydrophilic Lipophilic balance) value, degree of esterification, melt aspect and also some physical characteristic. Oils are triglyceride lipemic formulation there are some vegetative oil formulation like hydrogenated castor oil, hydrogenated soybean oil.

Selection of Surfactant
The selection of surfactant is based on the required HLB value to form o/w Nano emulsion is greater than 10. The right blend of low and high HLB surfactants leads to the formation of a stable Nano emulsion upon dilution with water also able to lower interfacial tension to a very small value to aid dispersion process during the preparation of the Nano emulsion which provide a flexible film that can readily deform around droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region for the desired Nano emulsion type.

Selection of Co-Surfactant
Co-surfactants like medium chain alcohols (5–8 carbon units), is weakly amphiphilic molecules, assumed to concentrate in the surfactant layer of the aggregates formed by the primary surfactant. Due to their weak amphiphilic character, co-surfactants alone do not form aggregates, but they strongly support aggregation of the primary surfactant. Transient negative interfacial tension is rarely achieved by the use of single surfactant, usually making it necessary to use a combination of surfactant. Fluid interfacial film is again achieved by the addition of a co-surfactant. In the absence of co-surfactant, a highly rigid film is formed by a surfactant and thus produces nano emulsion over only a very limited range of concentration. The presence of co-surfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form Nano emulsion over a wide range of composition. Mixing long and short-chain surfactants leads to more flexible interfaces compared to usage of surfactants with a chain length intermediate between the long and the short one.

Construction of pseudo-ternary phase diagram
Ternary phase diagrams of surfactant, co-surfactant and oil were plot with varying The levels of surfactant, co-surfactant and oils were varied from 30% to 80% (v/v), 0% to 30%(v/v) and 20% to 70% (v/v), respectively. All compositions were examined for nano emulsion formation after titration each of themixtures 100 times with distilled water. Thereafter,
transmittance and globule sizes of the resulting dispersions were determined by using UV–spectrophotometer and particle size analyzer respectively. The dispersions having globule size 200 nm or below were considered acceptable.

**Evaluation**

**Droplet size determination**

In this the effect of various dispersion medium and volume on droplet size is investigated, formulations (1 ml) were diluted 50, 100 and 1000 folds with water or biorelevent media, and compared.

**Dye solubility test**

A water soluble dye (Eosin) sprinkled onto the surface of the prepare formulation and observed for spontaneous dispersion to confirm the type of nanoemulsion.

**Conductivity Measurement**

Conductivity Measurement based on the phase inversion phenomenon determines the point of aqueous phase addition where oil phase continuously changed in water continuous phase.

**Turbidity Measurement**

Hatch turbidity meter, Orbeco-Helle turbidity meter apparatus used for measurement of turbidity by reaching dispersion at equilibrium phase.

**Zeta size & Potential**

Zeta size & Potential study determine size and charge on droplet. The size affect the rate and extent of release of drug, based on mechanism carbon film supported by copper grid and blotted by filter paper to obtain thin liquid film, while the negative charge due to you free fatty acids and helps to predict flocculation effect and stability of nanoemulsion.

**Transmission Electron Microscopy (TEM):** Transmission electron microscopy study provide the information of surface morphology of the resulting nano emulsion and size by diluting the samples diluted 1000 times with water and obtain size of formulation.

**CONCLUSION**

SNEDDS is a promising approach for BCS class II or IV and drug compounds with poor aqueous solubility. The method used for lipophilic drugs where resulting emulsification gives faster dissolution rates. The oral delivery of hydrophobic drugs can be made possible by
SNEDDS which have been shown to substantially improve oral bioavailability with future development of this technology. SNEDDS will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

REFERENCES
1. Robinson JR. Introduction: Semi-solid formulations for oral drug delivery. B T Gattefosse. 1996; 89:11-3.
2. Aungst BJ. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or pre-systemic metabolism. J. Pharma. Sci. 1993; 82: 979-986.
3. Khoo SM, Humberstone AJ, Porter CJ, Edwards GA, Charman WN. Formulation design and bioavailability assessment of lipidic self-emulsifying Formulations of Halofantrine. Int J of Pharm.1998; 167: 155-164.
4. Charman SA, Charman WN, Rogge MC, Wilson TD, Pouton CW. Self-emulsifying drug delivery systems: formulation andbiopharmaceutical evaluation of an investigational lipophilic compound. Pharm Res. 1992; 9: 87-93.
5. Constantinides PP, Lipidmicroemulsions for improving drug dissolution and oral absorption: physical and biopharmaceuticalaspects. Pharm. Res. 1995; 12: 1561-1572.
6. Groves MJ, Mustafa RMA, Carless, JE. Phase studies of mixedphosphate surfactants, n-hexane and water. J. Pharm. Pharmacol.1974; 26: 616-623.
7. Wakerly MG, Pouton CW, Meakin BJ, Morton FS. Self emulsification of vegetable oil-non-ionic surfactant mixtures.ACS Symp. Ser. 1986; 311: 242-255.
8. Nazzal S, Smalyukh II, Lavrentovich OD, Khan MA. Preparation and in vitro characterization of a eutectic based semisolid self nano emulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. Int. J. Pharm. 2002; 235: 247–265
9. Chakraborty S. Shukla D, Mishra B, and Singh, Eur J Pharm Biopharm2009; 73,1-15
10. Hauss DJ, Adv Drug Deliv Rev. 2007; 59: 667-76
11. Wasan KM, Drug Devlnd Pharm. 2001;27: 267-76
12. Kim HJ, Yoon KA, Hahn M, Park ES, Chi SC. Preparation and In Vitro Evaluation of Self- Microemulsifying Drug Delivery Systems Containing Idebenone. Drug Dev. and Ind.Pharm. 2000;26(5): 523-529
13. Basalious, E.B., Shawky, N., Badr-Eldin, S.M., 2010. SNEDDS containing bioenhancers
for improvement of dissolution and oral absorption of lacidipine. I: development and optimization. Int. J. Pharm. 391, 203–211.

14. Patel J, Shah A. Self emulsifying delivery systems for poorly absorbed drugs. Int. J. Pharm. Sci. and Nano Tech. 2008; 1(2) : 123-128.

15. Patel PA, Chaulang GM. Self emulsifying drug delivery system. Research J. Pharm. and Tech. 2008; 1(4): 313-323.

16. Pouton CW. Formulation of self-emulsifying drug delivery systems. Adv Drug Delivery Rev. 1997; 25: 47-58.

17. Ramsay-Olocco K , Alexandrova L, Nellore R, Kikkion R. Li L, Coen P, Ho Q, Jung D, and Rocha C, J pharm Sci. 2004;93: 2214-21.

18. Grove M, Mullertz A, Nielsen JL, and Pedersen GP, Eur J Pharm Sci. 2006; 28: 23-42.

19. Kommuru, T.R., Gurley, B., Khan, M.A., Reddy, I.K.. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. Int. J. Pharm.2001; 212: 233–246

20. Agrawal S., Giri T K, Tripathi D K, Ajazuddin and Alexander A., A Review on Novel Therapeutic Strategies for the Enhancement of Solubility for Hydrophobic Drugs through Lipid and Surfactant Based Self MicroEmulsifying Drug Delivery System: A Novel Approach. American Journal of Drug Discovery and Development, , (2012; 2(4), 143-183.

21. D. Mou, H. Chen, D. Du, C. Mao, J. Wan, H. Xu, X. Yang, Hydrogel-thickened nano-emulsion system for topical delivery of lipophilic drugs, Int. J. Pharm. 2008;353:270–276

22. ‘M.S. Nagarsenker, A.A. Date, Design and evaluation of self-nano-emulsifyingdrug delivery (SNEDDS) for cefpodoxime proxetil, Int. J. Pharm. 2007; 329:166–172.

23. P.P. Constantinides, Lipid micro-emulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects, Pharm. Res. 1995;12: 1561–1572

24. Constantinides PP, Pharm Res. 1995;12: 1561-72.

25. Zhao Y, Wang C , Chow AH, Ren K, Cong T, Zhang Z, and Zheng Y, Int J Pharm. 38: 170-7.

26. Nazzal S, Smalyukh, ll, Lavrentovich OD, and Khan MA, Int J Pharm 2002; 235: 247-65.

27. Palamakula A and Khan MA, Int J Pharm. 2004; 273: 63-73.

28. Reimer, L and Kohl, H Transmission Electron Microscopy: Physics of Image Formation. Springer. ISBN 2008; 0-387: 34758-5.
29. Gupta J, Prabakaran L, Gupta R and Mohan G, Nanoparticles formulation using counter-ion induced gelification technique: In-vitro Chloramphenicol Release. Int. J. Pharm. Pharm. Sci. 2011; 3(3): 66-70.