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Review Article

SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEED) O/W MICROEMULSION FOR BCS CLASS II DRUGS: AN APPROACH TO ENHANCE AN ORAL BIOAVAILABILITY

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ABSTRACT

Most of the drugs are being discovered are lipophillic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Due to their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophillic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs one of them is Self-Micro Emulsifying Drug Delivery Systems (SMEDDS).

Keywords: Novel SEDDS, SMEDDS, Lipid/ oil based system, Self emulsifying system

INTRODUCTION

Recently synthesized drug that are being discovered are lipophillic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Because of their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophillic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs.

The Self-Dispersing Lipid Formulations (SDLFs) is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/lipophillic drugs and to improve the oral bioavailability of poorly absorbed drugs. The SDLFs contain oil and a surfactant mixture into which the drug is incorporated. They emulsify when mixed with aqueous environment. The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs [1, 2, 3]. After self-dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. Bioavailability enhancement results from the finely dispersed state of the drug containing lipid globules. The large surface area enhances the dissolution. The emulsion globules are further solubilized in the gastrointestinal tract by bile fluids. The presence of surfactant causes enhanced absorption due to membrane induced permeation changes. The droplets formed are either positively charged or negatively charged. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the ileum [31]. A cationic emulsion has greater bioavailability than an anionic emulsion [29, 30]. The SDLFs are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion. Therefore, they are not dependent on bile secretion for absorption. The emulsified form itself is readily absorbable. This ensures a rapid transport of poorly soluble drugs into the blood. Many researchers have reported applications of SEDDS for delivering and targeting lipophilic drugs eg, coenzyme Q10 [4], vitamin E [5], halofantrine [6] and cyclosporin A [7].

Potential advantages

Includes

1. Enhanced oral bioavailability (enabling dose reduction)

2. More consistent temporal profiles of drug absorption

3. Selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut [8, 9].

Drawbacks of SEDDS

Includes

1. Chemical instabilities of drugs and high surfactant concentrations.

2. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.

3. Moreover, volatile co solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

Various major components of SMEDDS

Drugs

Mainly dugs from BCS II class are used in formulation of the SEDDS includes

Ontazolast [26]	Vitamin E [27]
Simvastatin [23]	Tocotrienols [28]
Danazol [25]	Itraconazole [24]

Oils

Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SMEDDS. Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-micro emulsification markedly reduces their use in SMEDDS. Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as GELUCIRE ,Other suitable oil phases are digestible or non-digestible oils and fats such as olive oil, corn oil, soya bean oil, palm oil and animal fats [12] etc

Surfactant

Nonionic surfactants with high Hydrophilic Lipophilic Balance (HLB) values are used in formulation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively

high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules [22].

Co-surfactant

In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion [12, 14].

Co-solvent

Organic solvents are suitable for oral administration. Examples are ethanol, propylene glycol, and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base [13]. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents.

Consistency builder

Additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and /or beeswax [15] etc

Polymers

Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of forming matrix are used. Examples are hydroxy propyl methyl cellulose, ethyl cellulose, [11] etc

Recent advancements in SEDDS

Includes

1. Self-emulsifying sustained/controlled-release tablets

2. Self-emulsifying capsules

3. Self-emulsifying suppositories

4. Micro emulsion Drug Delivery

5. Self-emulsifying Nanoparticles

6. Self-emulsifying sustained/controlled-release pellets

Mechanism of SMEDDS

No single theory explains all aspects of micro emulsion formation. Schulman et al. [16] considered that the spontaneous formation of micro emulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. Thermodynamic theory of formation of micro emulsion explains that emulsification occurs, when the entropy change that favour dispersion is greater than the energy required to increase the surface area of the dispersion [17] and the free energy (ÄG) is negative. The free energy in the micro emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation:

ÄG = S N a r 2 óð

Where, ÄG is the free energy associated with the process (ignoring the free energy of the mixing), N is the number of droplets of radius r and ó are presents the interfacial energy. With time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. Therefore, the emulsion resulting from aqueous dilution are stabilized by conventional emulsifying agents, which forms a mono layer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to prevent coalescence.

Evaluation of SMEDDS

1. Visual assessment may provide important information about the self-emulsifying property of the SMEDDS and about the resulting dispersion [10, 18, and 19]. Estimation of the increased drug dissolution and absorption from large surface area afforded by the emulsion. Inhibit gastric motility by oil / lipid phase of emulsion allows more time for dissolution and absorption of drug from lipid phase. Fatty acids are distributed between other aqueous solution emulsion droplets and the micelles (formed by bile salt) Monoglycerides along with water insoluble components such as vitamins, lipophillic drugs are moved into the micelles, which diffuse through gut content to intestinal mucosa. Short chain fatty acids along with hydrophilic drug are diffused directly to portal supply, while longer fatty acids are utilized in chylomicron formation. Once monoglycerides along with lipophillic drugs are transported into intestinal mucosa, chylomicron synthesis takes place and are released into lymphatic's efficiency of the self-emulsification can be done by evaluating the rate of emulsification and particle size distribution [20]. Turbidity measurement to identify efficient self-emulsifying can be done to establish whether the dispersion has reached equilibrium rapidly and in reproducible time [10].

2. Droplet polarity and droplet size are important emulsion characteristics. Polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion and concentration of the emulsifier. A combination of small droplets and their appropriate polarity (lower partition coefficient o/w of the drug) permit acceptable rate of release of the drug. Polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophillic drug [10, 11].

3. Size of the emulsion droplet is very important factor in self-emulsification / dispersion performance, since it determine the rate and extent of drug release and absorption [10, 19]. The Coulter nano-sizer, which automatically performs photon correlation analysis on scattered light, can be used to provide comparative measure of mean particle size for such system. This instrument detects dynamic changes in laser light scattering intensity, which occurs when particle oscillates due to Brownian movement. This technique is used when particle size range is less than 3µm; a size range for a SMEDDS is 10 to 200 nm [10].

4. For sustained release characteristic, dissolution study is carried out for SEMDDS. Drugs known to be insoluble at acidic pH can be made fully available when it is incorporated in SMEDDS [11].

CONCLUSION

Self-Micro Emulsifying Drug Delivery Systems appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophillic drugs. As there is increase in oral drug absorption of BCS II class drugs, so we can say it is one of the method for enhancing oral bioavailability of drug

REFERENCES

1. Wakerly, M.G., et al., Self-emulsification of veg: oil-non-ionic surfactant mixtures, ACS symp. Ser. 311, 1986, 242-255.
2. Wakerly M.G., Pouton C.W and Maekin B.J, Evaluation of the self emulsifying performance of a non-ionic surfactant-vegetable-oil mixture, J.Pharma. Pharmacol. 1987, 39, 6P.
3. Pouton C.W, Effects of the inclusion of a model drug on the performance of self-emulsifying formulations, J. Pharma. Pharmacol. 1985, 37,1P.
4. Kommuru T. R., Gurley B., Khan M. A. and Reddy I. K., Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment, Int. J. Pharm. 200, 212, 233.246.
5. Julianto T., Yuen K. H. and Noor A. M., Improved bioavailability of vitamin E with a self-emulsifying formulation, Int. J. Pharm. 2000, 200, 53.57.
6. Khoo S. M., Humberstone A. J., Porter C. J. H., Edwards G. A. and Charman W. N., Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine, Int. J. Pharm.,1998, 167, 155.164.
7. Gao Z.G., Choi H.G., Shin H. J., Park K. M., Lim S.J., Hwang K. J. and Kim C.K., Physicochemical characterization and evaluation of a micro emulsion system for oral delivery of cyclosporine A, Int. J. Pharm.,1998, 161, 75.86.

8. Pouton C. W., Formulation of self-emulsifying drug delivery systems, Adv. Drug Deliv. Rev., 1997, 25, 47.58.
9. Pouton C. W. and Charman W. N., The potential of oily formulations for drug delivery to the gastrointestinal tract, Adv. Drug Deliv. Rev, 1997, 25, 1.2.
10. Pouton C. W., Self-emulsifying drug delivery system: Assessment of the efficiency of emulsification, Int. J. Pharm., 1985, 27, 335.348.
11. Barthelemy et al., Composition with sustained release of active principle capable of forming microemulsion, US Patent 6309665, Oct.30, 2001.
12. Methods and formulation for increasing the bioavailability of poorly water-soluble drugs. US Patent 5993858, Nov.30, 1999.
13. Constaantinides, P.P, Lipid micro emulsion for improving drug dissolution and oral absorption: physical and biopharmaceutical aspect, Pharm, Res., 1995, 12(11), 1561-1572.
14. Bose S, and Kulkarni P.K., Self emulsifying drug delivery systems: A review, Ind. J.Phar. Edu. 2002, 36(4), 184-190.
15. Arthur Osol., Ed., Remington s pharmaceutical sciences: Emulsifying and suspending agents, 15th Ed., Pennsylvania: Mack Publishing, 1975, 1246.
16. Schulman J.H., Stoeckenius W. and Prince L.M., Mechanism of Formation and Structure of Micro Emulsions by Electron Microscopy, J. Phys. Chem., 1959, 63(10), 1677-1680.
17. Muranishi, N., Kinugava, M., Nakajima, Y., Muranishi, S., and Sezakki, H., Mechanism for the inducement of the intestinal absorption of poorly absorbed drugs by mixed micelles, I: Effect of various lipid-bile salt mixed micelles on the intestinal absorption of streptomycin in the rat, Int. J. Pharm., 1980, 4, 271-279.
18. Gershanik,T. and Benita,S, Positively charged self emulsifying bioavailability of progesterone, Pharm Dev. Tech., 1996, 1, 147-157.
19. Craig D.Q.M., Barker S. A., Banning D. and Booth S.W., An investigation into mechanism of size analysis and low frequency dielectric spectroscopy, Int. J. Pharm., 1995, 114, 103-110.
20. Craig, D.Q.M., et al., An investigation into the physico-chemical properties of self emulsifying systems using low frequency dielectric spectroscopy, surface tension measurement, and particle size analysis, Int. J. Pharm., 1993, 96, 147-155.
21. Kovarik JM, Mueller EA, Van Bree JB, Tetzloff W, Kutz K, Reduced inter- and intra individual variability in cyclosporine pharmacokinetics from a micro emulsion formulation, J Pharm Sci, 1994, 83, 444– 446.
22. Crison JR, Amidon GL, US Patent No. 5,993,858, issued November 30, 1999.
23. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB, and Pharm, 238, 2002, 153–160. Cho SH, Development of self micro emulsifying drug delivery sys51. Gao P, Morozowich W, Development of supersaturable self emulsifying systems (SMEDDS) for oral bioavailability enhancement of simvastatinin drug delivery system formulations for improving the oral absorbing beagle dogs, Int J Pharm, 2004, 274, 65-73.
24. Hong JY, Kim JK, Song YK, Park JS, Kim CK, A new self-emulsifying 2003, 2386–2398. Formulation of itroconazole with improved dissolution and oral ab53. Christopher JHP, Susan AC, Rachel DW, Evaluation of emulsifiable sorption, J Control Release, 110, 2006, 332 -338.
25. Cosine GA, Boyd BJ, Porter CJH, Charman WN, Separation and sulfonphthalein in human, J Pharm Sci, 64, 1975, 991-994. Characterization of the colloidal phases produced on digestion of 58. Osborne DW, Ward AJI, Neill KJ, Micro emulsions as topical drug common formulation lipids and assessment of their impact on the delivery vehicles: in vitro transdermal studies of a model hydrophilic apparent solubility of selected poorly water soluble drugs, J Pharm drug, J Pharm Pharmacol, 43, 1991, 451-454. Sci, 92, 2003, 634-648.
26. Hauss DJ, Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor, J Pharm Sci, 87, 1998, 164-169.
27. Julianto T, Yuen KH, Noor AM, Improved bioavailability of vitamin E with a self emulsifying formulation, Int J Pharm, 200, 2000, 53-57.
28. Yap SP, Yuen KH, Influence of lipolysis and droplet size on tocotrienol absorption from self-emulsifying formulations, Int J Pharm, 281, 2004, 67–78.
29. McClintic JR, Physiology of the Human Body, 2nd Edition, Wiley, New York, 1976, 189.
30. Lin JH, Chen W, King J, The effect of dosage form on oral absorption of L-365, 260, a potent CCK receptor antagonist, in dogs, Pharm Res, 8, 1991, 272.
31. Groves MJ, Degalindez DA, The self-emulsifying action of mixed surfactants in oil, Acta Pharm Suec, 13, 1976, 361- 372.