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RESEARCH ARTICLE

Characterization of Self-Microemulsifying Dosage Form: Special Emphasis on Zeta Potential Measurement

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ABSTRACT

The emulsion is a disperse system which is thermodynamically unstable. To improve the stability of the disperse system microemulsion or nanoemulsion was prepared to improve thermodynamic stability. Zeta potential is a physical property which is exhibited by any particle in suspension/emulsion, i.e., in colloidal dispersion. It can be used to optimize the formulations of suspensions and emulsions. Zeta potential is the measure of overall charges acquired by particles in a particular medium and is considered as one of the benchmarks of stability of the colloidal system. As a rule of thumb, suspensions/dispersed system with zeta potential above 30 mV (absolute value) are physically stable. Suspensions with a potential above 60 mV show excellent stability. Suspensions below 20 mV are of limited stability; below 5 mV they undergo pronounced aggregation if the system is stabilized by the electrostatic mechanism. If the values are low for visually stable emulsions, it could be attributed to steric repulsion between approaching molecules, i.e., system is sterically stabilized. Such sterically stabilized colloidal systems though they have low zeta potential values are found to be stable during storage. Tween is well accepted steric stabilizer for colloidal systems. Stability of such a visually stable emulsion or microemulsions should be carried out under accelerated or long-term stability conditions to confirm the globule size and zeta potential on aging.

Keywords: SMEDDS, surfactants, zeta potential

INTRODUCTION

The emulsion is a disperse system which is thermodynamically unstable. To improve the stability of the disperse system microemulsion or nanoemulsion was prepared to improve thermodynamic stability.

FORMULATION OF SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)

SMEDDS is defined as mixtures of oils (natural/synthetic), surfactants (solid/liquid) or alternatively, and cosolvents/cosurfactants that have a capacity to form fine oil-in-water (o/w) microemulsions on dilution followed by agitation in gastrointestinal fluid (*in vivo*) or when added to the dissolution medium (*in vitro*). The appearance of SMEDDS formulations is transparent or bluish tinge, with particle size in the range of 1–200 nm on dilution. As emulsions are metastable and thermodynamically unstable dispersed forms, SMEDDS is physically and thermodynamically stable formulations that are easy to manufacture.[1-3]

ORAL ABSORPTION AND BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUG BY SMEDDS

Bioavailability enhancing property has been associated with a number of *in vivo* properties of lipid formulation including:

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- The formation of fine dispersions and micellar structure to prevent precipitation of the drug compound.
- The ability of lipids and their metabolite to initiate changes to the gastrointestinal luminal pH to favor improved drug absorption.
- The inhibition of cellular efflux mechanisms which keep the drug out of circulation.
- Certain lipid excipients are associated with selective drug absorption into the lymphatic transport system; there by avoids first-pass metabolism.

Thus, SMEDDS may be a promising technology to orally administered emulsions due to their relatively high physical stability and ability to be delivered in standard soft/hard gelatin capsules.[4,5]

Advantages of SMEDDS

a) Dissolution rate is directly correlated with the absorption of the drug. The SMEDDS has the ability to present the drug in the solubilized form with a globule size in between 1 and 200 nm results in an increase in the effective surface area leads to rapid absorption.[3,6-8]
b) Ease of manufacturing and scale-up is advantages that make SMEDDS unique as compared to other drug delivery systems.
c) SMEDDS minimizes the intersubject and intrasubject variation in absorption, which leads to variability in the bioavailability of most of the drugs. Presence or absence of food does not alter the effect of on absorption of SMEDDS.
d) SMEDDS is digested after the drug is absorbed. The drug is in solubilized and micron size, which easily crosses the mucin as well as aqueous unstirred layer diffusion layer of luminal fluid.[9-11]
e) SMEDDS formulation can be sterilized; therefore, they can be given parenterally with i.v. fluids.
f) Other advantages are low viscosity, thermodynamically stable, optically isotropic, ultralow interfacial tension, spontaneously formed, and self-preserving.[12-14]

Disadvantages of SMEDDS

a) Capsule leakage
b) Compatibility with capsule shell
c) Liquid dosage form
d) High production cost
e) Few choices of dosage form
f) Irreversible drug precipitation
g) High surfactant concentration leads to GI irritation.

EXCIPIENTS USED IN FORMULATION OF SMEDDS

The self-emulsification process is dependent on the nature of the oil-surfactant, the oil and surfactant concentration and oil to surfactant/cosurfactant ratio and also depends on the temperature at which self-emulsification has to occur. Literature survey significantly demonstrated that specific pharmaceutical excipient combination could lead to the efficient self-emulsifying mechanism.[15-17]

Oil phase

The oil is one of the important excipients in the development of self-emulsifying formulation. As it has the capacity to solubilize marked amounts of lipophilic drugs, as well as it facilitates the self-emulsification process [Table 1]. Oils facilitate the transport of drugs through the intestinal lymphatic

Table 1: List of oils that can be used in self-microemulsifying drug delivery system

Triglycerides	Oils
Medium chain triglycerides	Caprylic/capric triglyceride derived from coconut oil, palm seed oil
Semi-synthetic MCT	Miglyol 812
	Solutol HS 15
	Captex 300, 355, 500, 200
Long chain triglycerides	Corn oil
	Olive oil
	Peanut oil
	Rapeseed oil
	Sesame oil
	Hydrogenated soybean oil
	Hydrogenated vegetable oil
	Castor oil
	Soybean oil

system as it improves absorption. Long and medium chain TG oils with different degrees of saturation were used for the development of self-micro/nanoemulsifying formulations. Sometimes edible oils are also preferred. Modified or hydrolyzable vegetable oils have been widely used as they possess good emulsification properties, better compatibility with most of surfactants, accepted for oral administration, and proven better drug solubilization capacity.

Surfactant

The most widely used surfactants being the non-ionic surfactant with high hydrophilic-lipophilic balance (HLB). The most commonly used surfactants are ethoxylated polyglycolyzed glycerides and Polysorbate 80 (Tween 80). Surfactants of natural origin are preferred as they are considered to be safer as compared to synthetic surfactants, but their capacity of self-emulsification is limited. Non-ionic surfactants are less toxic as compared to ionic surfactants. The excess proportion of surfactant concentration will lead to irritation to the gastrointestinal mucosa. The surfactants used in the development of SMEDDS should have HLB value between 10 and 16. Surfactants with high HLB value immediately form o/w droplets as well as there is the rapid spreading of the formulation within dissolution medium or in gastrointestinal luminal fluid. For effective absorption, the precipitation of the drug at the GI luminal pH should be avoided, and the drug should be kept in solubilized form for a prolonged period of time at the site of absorption [Table 2].

Cosurfactants/cosolvents

Organic solvents such as ethanol, propylene glycol, and polyethylene glycol are a suitable vehicle for oral delivery for most of the drugs. Cosurfactants/cosolvents have the capacity to dissolves large quantities of the hydrophilic surfactants as well as drugs. Cosolvents have the capacity to increases the solvent capacity to solubilize the drugs. This may lead to greater chances of occurrence of drug precipitation. A third reason for the inclusion of cosolvents is to provide rapid dispersion of systems, when it contain a greater proportion of water-soluble surfactants [Table 3].

ZETA POTENTIAL MEASUREMENT OF SELF-MICROEMULSIFYING DOSAGE FORM

A dispersed system remains stable as long as the repulsive forces are sufficiently strong to outweigh other attractive forces. The repulsive forces are generally acquired through one or combination of both of the following mechanism.[18]

1. Electrostatic repulsion which arises from the presence of ionic charges on the surface of the dispersed system.
2. Steric repulsion, presence of uncharged molecules on the surface of particles.

Table 2: List of surfactants that can be used in self-microemulsifying drug delivery system

Generic name	Brand name	Hydrophilic-lipophilic balance value
Glyceryl monooleate	Capmul GMO	3–4
PEG 300 linoleic glycerides	Labrafil M 2155 CS	4
PEG 300 oleic glycerides	Labrafil M 1944 CS	4
Sorbitan monooleate	Span 40	4.3
Sorbitan monolaurate	Span 20	8.6
Polyoxyl 35 castor oil	Cremophor EL	12–14
PEG 1500 lauric glycerides	Gelucire 44/14	14
PEG 400 capric/caprylic glycerides	Labrasol	14
Polysorbate 80	Tween 80	15
Polyoxyl 40 hydrogenated castor oil	Cremophor RH 40	14–16
Polysorbate 20	Tween 20	16.7
Polyoxyl 60 hydrogenated castor oil	Cremophor RH 60	14–18

Zeta potential is a physical property which is exhibited by any particle in suspension/emulsion, i.e., in colloidal dispersion. It can be used to optimize the formulations of suspensions and emulsions. Zeta potential is the measure of overall charges acquired by particles in a particular medium and is considered as one of the benchmarks of stability of the colloidal system[19]. High positive or high negative value of zeta potential will repel particles from each other and a system having zeta potential value ±30 mV is considered as stable formulation is dispersed in a liquid as colloidal dispersion. In case of development of SMEDDS formulations surfactants and cosurfactant were required along with the oil phase. The most preferred surfactant and cosurfactant are nonionic. As a rule of thumb, suspensions/dispersed system with zeta potential above 30 mV (absolute value) are physically stable. Suspensions with a potential above 60 mV show excellent stability. Suspensions below 20 mV are of limited stability; below 5 mV they undergo pronounced aggregation if the system is stabilized by the electrostatic mechanism.[20]

The zeta potential value of such a formulation approaches near to zero, or it may be up to −20 mV. The absolute value of zeta potential was lower and found in incipient instability for colloidal dispersion. Such colloidal systems are considered to be unstable, and on storage, it may lead to separation of two phases. As in the development of microemulsion, Tween 20/80 is frequently used as surfactant or cosurfactant. They come under the class of non-ionic surfactants. The use of tween as a surfactant produces a microemulsion with less zeta potential value (changeless). Small zeta potential value attributes to the use of tween as a surfactant. However, an investigation by Roland *et al.* [21] revealed that the zeta potential values sometimes do not fit with stable emulsions, where the most visually stable emulsions [Figure 1] exhibits the lowest zeta potential values. This means that electrostatic stabilization is not the main mechanism for the stability of such emulsions with low zeta potential values.

The excellent ability of nonionic emulsifiers to solubilize and disperse hydrophobic oils such as fats and mineral oil in water leads to extensive use of this type of emulsifier. Non-ionic emulsifier adsorbs only marginally to make hydrophilic surfaces hydrophobic or hydrophobic surfaces hydrophilic and differ from the results obtained with most ionic emulsifiers.

Table 3: List of cosurfactants that can be used in self-microemulsifying drug delivery system

S. No.	Name
1	PEG 200,400,600
2	Propylene glycol
3	Ethanol
4	Transcutol P
5	Lauroglycol FCC
6	Tetraglycol

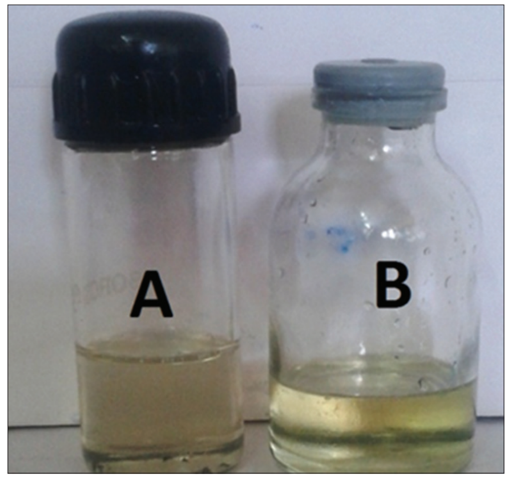

Figure 1: Visually stable microemulsions containing tween 20 as surfactant

In the sterically stabilized dispersions, the colloidal stability of polymer particles is provided by steric repulsion between approaching particles. The thick surface layer formed by non-ionic emulsifier makes a barrier for particles approaching one another. Nonionic surfactants form a coat around the particles which avoid agglomeration and sterically stabilize the system. Such sterically stabilized colloidal systems though they have low zeta potential values are found to be stable during storage. Tween 20/80 is well accepted steric stabilizer for colloidal systems.

LITERATURE REVIEW OF SOLID SMEDDS [TABLE 4]

Pouton published about SMEDDS. They highlighted the criteria for excipient selection, assessment of the efficiency of emulsification, and phase diagram.

Table 4: Literature examples of active pharmaceutical ingredients formulated as self- microemulsifying/nanoemulsifying drug delivery systems using as a surfactant (non-ionic) where zeta potential values found to be below ± 30 mV

Drug	Oil	Suractant: cosurfactatnt	Conclusion
Valsartan	Capmul MCM	Tween 80:PEG 400 non-ionic mixture	Better bioavailability as compared to suspension.[28]
Acyclovir	Sunflower oil	Tween 60 and glycerol non-ionic mixture	Zeta potential of the optimal system was neutral (−2.3 mV) and based on the study. The system is found to be stable.[29]
Lovastatin	Peceol	Cremophor RH 40 and Transcutol-P non-ionic mixture	Optimized SMEDDS formulation comprises of 12% Peceol, 44% cremophor RH 40 and 44% transcutol P, which showed spontaneous emulsification properties and good thermodynamic stability.[30]
Valsartan	Capmul MCM C8	Tween 80 and PEG 400 non-ionic mixture	Better *in-vitro* as well as *in-vivo* performance of liquid as well as solid SMEDDS as compared to the plain drug.[31]
Telmisartan	Oleic acid	Tween 80 and PEG 400	*In-vitro* drug release of S-SMEDDS was much higher than that of plain telmisartan.[32]
Chloramphenicol		Poloxamer 188 non-ionic	Low zeta value is attributed to a non-ionic surfactant, which decreases the electrostatic repulsion between the particles and sterically reduction in surface tension between the aqueous phase and organic phase. Surfactant helps to stabilize the newly generated surfaces and prevents particle aggregation.[33]
Repaglinide	Olive oil	Tween 80, PEG 400 non-ionic	A result of stability studies confirms the stability of the developed formulation.[34]
Rifampin	Cetyl palmitate	Tween 80/Poloxamer 188 non-ionic mixture	SLN formulation of the drug was found to be satisfactory with respect to particle size range and drug release profile.[35]
Valsartan	Castor oil	Tween 80 and PEG 600 non-ionic mixture	Valsartan SEDDS formulation was superior to marketed formulation with respect to *in-vitro* dissolution profile.[36]
Tretinoin	Capryol 90	Tween 80 and propylene glycol	The developed formulations are stable.[37]
Cephalosporin antibiotic	Capryol 90	Labrasol AND Lutrol E 400 non-ionic mixture	The prepared SMEDDS formulations, consisting of Labrasol and Lutrol E400 as surfactant components and Capryol 90 as oil are stable.[38]
Functional compounds	n-heptane n-hexane	Tweens (20, 40, 60) and n-butanol non-ionic	The developed formulations are stable.[39]
Hexanitrohexaazaisowurtzitane	n-butyl acetate	Tween 80 non-ionic: 2-propanol (w/w)	Average particle size increases from 8 nm to 70 nm.[40]
Mirtazapine	Capmul	Tween 80: PEG 400 (non-ionic)	Better absorption through the nasal mucosa.[41]
Myricetin	Oleic acid	Tween 80 non-ionic	Improved bioavailability of drug due to the microemulsion system.[42]
Nebivolol hydrochloride	Capmul	Tween 60-PEG 400 non-ionic mixture	During stability study no-phase separation, precipitation, and physical appearance at accelerated stability study.[43]
Ibuprofen	Palm	Tween 80 non-ionic	Stability study carried out. Formulations were found to be stable.[44]
Griseofulvin	Olive oil	Glyceryl Mono state, Tween 40, 80 non-ionic	Stability study carried out and formulations were found to be stable.[45]
Clopidogrel	Capmul MCM	Tween 80:PEG 400 non-ionic	A stability study confirms the stability of the developed formulation.[46]
Celecoxib	LAS	Tween 20	Improved bioavailability.[47]
Rosuvastatin calcium	PEG 8-caprylic glyceride/Capryol 90 with Maisine 35-1	Tween 20: Lutrol E 400	The developed formulations showed better *in-vivo* release profile as compared to plain rosuvastatin calcium and found to be stable during storage.[48]

SMEDDS: Self-microemulsifying drug delivery systems

They also highlighted the biological consideration for selection of drug candidate to develop SMEDDS.[22] Ying formulated SMEDDS for vinpocetine to enhance the oral bioavailability. The formulations developed using ethyl oleate, solutol HS and transcutol P as oil, surfactant, and cosurfactant, respectively. The dissolution rate of SMEDDS formulation containing vinpocetine was significantly higher than that of the commercial tablet. The bioavailability of vinpocetine is significantly enhanced using SMEDDS approach.[23]

Bachhav and Patravale developed SMEDDS of glyburide a BCS Class II antidiabetic drug. The developed microemulsion exhibited globule diameter size of 133.5 nm with a polydispersity index of 0.94. The stability studies were carried out as per the ICH guidelines, and the developed formulation was found to be stable.[24]

Dixit and Nagarsenker developed self-nanoemulsifying granules for enhancement in the bioavailability of the ezetimibe. *In vitro* dissolution studies showed an increase in dissolution as compared to pure ezetimibe. *In vivo* studies in rats revealed that significant reduction in the total cholesterol levels as compared to plain ezetimibe.[25]

Setthacheewakul *et al*. studied the improvement in solubility, dissolution, and *in vivo* performance of curcumin when formulated as SMEDDS. *In vitro* dissolution and *in-vivo* pharmacokinetic study showed enhancement in solubility and bioavailability for curcumin.[26]

Ghosh *et al*. developed micro-emulsion drug delivery system for acyclovir to improve its oral bioavailability. A Labrafac-based microemulsion formulation was developed for oral delivery of acyclovir. The *in vitro* intra duodenal diffusion and *in-vivo* study showed 12.78 times improvement in bioavailability.[27]

CONCLUSION

Zeta potential is a measure of the stability of formed microemulsion. The value of zeta potential is dependent on the selection of surfactant and cosurfactant. For the development of SMEDDS/SNEDDS, surfactants are used which are non-ionic in nature. It may result in a low value of zeta potential, i.e., −20 mV or sometimes <−5 mV. The values are found to be in incipient stability range, i.e., agglomerates will form on storage. If the values are low for visually stable emulsions, it could be attributed to steric repulsion between approaching molecules, i.e., system is sterically stabilized. Such sterically stabilized colloidal systems though they have low zeta potential values are found to be stable during storage. Tween 80 is well accepted steric stabilizer for colloidal systems. Stability of such a visually stable emulsion or microemulsions should be carried out under accelerated or long-term stability conditions to confirm the globule size and zeta potential on aging.

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