Chapter

Self-Microemulsifying System

Mansi Shah and Anuj G. Agrawal

Abstract

Oral route is preferred for drug administration; however according to the recent scenario 40% of new drug candidates have poor water solubility and low bioavailability. One of the biggest challenges in drug delivery science is to improve low oral bioavailability problem which is associated with the hydrophobic drugs due to their unprecedented potential as a drug deliver with the broad range of application. Self-emulsifying systems have been proved as highly useful technological innovations to vanquish such bioavailability problem by virtue of their diminutive globule size, higher solubilization tendency for hydrophobic drugs, robust formulation advantages, and easy to scale up. Self-microemulsifying systems are isotropic mixers of oil, surfactant, drug and co-emulsifier or solubilizer, which spontaneously form transparent micro-emulsions with oil droplets ranging between 100 and 250 nm. Micro emulsified drug can be easily absorbed through the lymphatic pathway and it bypasses the hepatic first-pass effect. Self-microemulsifying system is a thermodynamically stable system and overcomes the drawback of layering of emulsions after sitting for a long period of time. The present literature gives exhaustive information on the formulation design and characterization of self-microemulsifying systems.

Keywords: self-micro emulsifying systems, bioavailability, lipid base formulation, surfactant

1. Introduction

An advance in in-vitro screening methods such as conjunctional chemistry is leading to publicizing of many potential chemical components with high therapeutic activity. Such rapid identification of highly potent pharmaceutical lead compounds has optimized pharmacodynamic properties but sub-optimal biopharmaceutical characteristics [1]. Most of the drugs are lipophilic in nature and has poor water solubility. Such low water solubility becomes the major challenge in successful development of their oral formulation. Also several drug compounds has low oral bioavailability which further enhances the challenge for the formulator scientist [2, 3]. More than 40% of drugs are lipophilic in nature with poor water solubility. To resolve such challenges, many approaches have been reported to improve the solubility and enhance the oral bioavailability which includes the formation of cyclodextrin complex, lipid based drug delivery system, solid dispersions, micronization, etc. [4, 5]. Among these methods, self-emulsifying systems is one of the most optimistic approaches to enhance the oral bioavailability of poorly water-soluble drugs since it maintains the drug in a solubilized state in the gastrointestinal tract [6]. A stable self-micro emulsifying system consists of mixture of drug, oil, surfactant and co-surfactant. Upon dilution with water it results into fine

oil-in-water emulsion with a droplets diameter less than 50 nm [7, 8]. The micro-emulsion droplet of self-micro emulsifying systems entraps the drug molecule completely with 100% efficacy, thus self-micro emulsifying systems shows high potential to deliver low water soluble drug [9]. Rapid emulsion formation helps to keep the drug in a dissolved form and small droplet size offers a considerably larger interfacial surface area which further accelerates the absorption rate of drug with limited solubility. Moreover, the droplets can be rapidly dispersed in blood as well as lymph and the lymphatic drug transport can avoid the first-pass effect [10]. This feature makes self-micro emulsifying systems a significant choice for oral delivery of lipophilic, low bioavailable drugs having ample of lipid solubility [11–14]. Self-emulsifying systems is a broad term which produces emulsions with a droplet size ranging from a few nanometers to several microns. A self-micro emulsifying system indicates the formulations forming transparent micro-emulsions with oil droplets ranging between 100 and 250 nm. Term self-nano emulsifying system is used to characterize the system which results into emulsion with globule size less than 100 nm [15, 16].

2. Self-micro emulsifying systems

2.1 Classification of lipidic formulations

Lipidic formulations are classified as Type I, II, III, and IV based upon excipients used. Type I formulations are non-self-emulsifying whereas Type II, III, and IV formulations are self-emulsifying. Type of emulsion formed after dilution of self-emulsifying system with water, depends upon the excipients used in formulation. Digestibility of lipidic compositions is also affected by these ingredients. Elements of lipidic systems are represented in the proceeding portion [17, 18]. Classification system of lipid formulation is shown in **Table 1**.

Type I: Drug with tri-, di- or monoglyceride in lipid based compositions is called as type I formulations. Dilution of type I formulations with aqueous media creates

Formulation	Excipients	Properties	Pros	Cons
Type I	Oils lacking of surfactants (e.g. tri-,di- and mono glycerides)	Not dispersing, it needs digestion.	Simple, Compatibility is excellent for capsule.	Formulation has poor solvent capacity unless drug is highly lipophilic.
Type II	Oils and water-insoluble surfactants.	SES formed without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particlesize0.25–2 mm)
Type III	Oils, surfactants and co solvents (both water insoluble and water-soluble excipients)	SES/SMES formed with water-soluble components	clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
Type IV	Water-soluble surfactants and Co solvents(no oils)	Formulation disperses typically to forma micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity On dispersion; might not be digestible

Table 1.
The Lipid Formulation Classification System: characteristic features, pros and cons of the four essential types of 'lipid' formulations.

coarse dispersion and is not readily dispersible. Initial digestibility by pancreatic lipase/co-lipase to engender more amphiphilic species is a pivotal necessity for their oral absorption. For potent drugs or drugs with high oil solubility, Type I formulations are preferable.

Type II: These formulation contain drug with oil and water insoluble surfactants (Hydrophilic lipophilic balance <12), and are also called as self-emulsifying systems. Self-emulsification is mainly acquired at the surfactant concentration above 25% w/w. Surfactant greater than 60% w/w that is at higher Concentration, there is formation of liquid crystalline gel phases at the o/w interface because emulsification is impeded. Such systems generate droplets size above 300 nm, when dispersed in water it developed emulsion which is opaque in nature.

Type III: Type III formulations consist of drug, oil, surfactants, and co-solvents for both water-soluble and water insoluble. Ethanol, polyethylene glycol and propylene glycols are selected as co-solvents. Such systems generate droplets size below 300 nm, when dispersed in water and are called as self-micro emulsifying systems. The obtained emulsion is either optically clear or somewhat opalescent dispersion.

Type IV: Type IV formulations consist of drug, water soluble surfactants, and co-solvents. Oil is absent in this type of formulation.

2.2 Suitable drug candidate identification for self-emulsifying systems

Drugs that belong to the Class II and Class IV of biopharmaceutical classification system offer potential platform to enhance the oral bioavailability. Log P of the drug indicates the potential utility of lipid based formulation. Maintenance of drug solubility in gastrointestinal tract is the foremost challenges to oral formulation and especially the increased drug solubility at the absorption site of the gut [19]. Lipophilic drug composite that manifest dissolution rate limited absorption, self-emulsifying systems can provide an improvement in absorption in terms of rate and extent, that results in consistent blood time profiles [7, 20]. Problem of poor solubility and low bioavailability of drug across all categories of biopharmaceutical classification system can be resolved by formulating into self-emulsifying system, as shown in **Table 2** [21].

For an oral absorption Lipinski's rule of five has been widely proposed as a qualitative predictive model. In the discovery setting, the 'rule of five' predicts that if there are more than five H– bond donors, it shows poor absorption or poor permeation [22].

Whether solubility and log P are sufficient to identify probable drug candidates for such formulations that question arises and also it is noted that biopharmaceutical classification system and Lipinski's rule of five classification system are useful, particularly at inceptive screening stage, they have some constraint. For recognize the suitable lipid based formulation approach aqueous solubility and log P alone are improbable enough because they do not adequately predict potential in- vivo effects.

BCS class	Hurdles overcome by SES
Class I	Gut wall efflux, Enzymatic degradation.
Class II	Solubility and bioavailability.
Class III	Enzymatic degradation, bioavailability and gut wall efflux.
Class IV	Solubility, bioavailability, Enzymatic degradation, gut wall efflux.

Table 2.
SES as a solution to various problems to different classes of drugs.

2.3 Choice of self-microemulsifying excipients for formulations

Self-emulsifying formulation produces dispersion in gastrointestinal tract by using different excipients. Isotropic mixtures of oils, surfactants, solvents, and co-solvents/surfactants comprise self-emulsifying formulation and it emulsifies in gastrointestinal tract under a gentle agitation [23].

Depending upon the type of dispersion produced after dilution with water phase, self-emulsifying formulations are further classified as self-emulsifying systems, self-micro emulsifying systems and self-nano emulsifying systems. Emulsion which is slightly hazy, opalescent or opaque colloidal coarse dispersion is called as self-emulsifying systems. Micro-emulsion which is clear or pellucid, slightly hazy, opalescent, non-opaque colloidal dispersion with droplet size below 150 nm are called as self-micro emulsifying systems. Nano-emulsion which clear or pellucid, slightly hazy, opalescent, non-opaque or substantially non-opaque colloidal dispersion with droplet size below 20 nm in diameter called as self-nano emulsifying systems [24]. For the formulation, excipient should be chosen from the list of generally regarded as safe "GRAS" excipients published by USFDA or from other inactive ingredients approved and published by regulatory agencies.

2.3.1 Active pharmaceutical ingredient

Active Pharmaceutical Ingredient should be soluble in oil phase as this have an impact on the self-micro emulsifying systems to maintain the active pharmaceutical ingredient solubility. Drugs with the low solubility in aqueous media or lipids are strenuous to convey through self-micro emulsifying systems. Exceedingly good solubility in one of the components of self-micro emulsifying systems is require preferably oil phase, if very high dose of drug liked to be administered. For self-micro emulsifying systems, high melting point of drug with log P value around 2 is not appropriate and for self-micro emulsifying systems, lipophilic drugs with the log P values more than 5 are good candidate [19, 25].

2.3.2 Lipids/oils

In self-emulsifying formulations, oil represents the most important constituent as it solubilizes prominent amounts of the lipophilic drug. Oil promotes self-emulsification and extends the fragment of lipophilic drug transported through the intestinal lymphatic system. Absorption of lipophilic drug from the gastrointestinal tract is enhanced depending upon the molecular nature of the triglyceride used in formulation [26, 27]. Regardless of the noteworthy potential that these lipid excipients have, very few of lipid based formulations has reached to the pharmaceutical market. This may be due to the insufficient data concerning the relatively composite physical chemistry of lipids and scrutinize about formulated drug chemical and physical stability. Incorporation to these studies, its impact on drug absorption is also essential and which depends on interaction of a lipid-based formulation with the gastrointestinal tract environment [28]. Natural edible oils, comprising medium-chain triglycerides, are not commonly preferred in this regard owing to their poor ability to dissolve large amounts of lipophilic drugs [29]. For designing of self-emulsifying systems, varying degrees of saturated and hydrolyzed long and medium chain triglycerides are used. These semi synthetic derivatives form good emulsification systems when used with a large number of solubility enhancing surfactants approved for oral administration. There is polarity deference between the long chain triglyceride and medium-chain triglyceride, a wide micro-emulsion area has been achieved in phase diagram if medium chain triglyceride is used. More is hydrophobic long chain triglyceride, more difficult it becomes to emulsify.

2.3.3 Surfactants

The self-emulsifying system demand incorporation of comparatively large amounts of surfactant in addition to the oil, to convey drug in the formulation. Permeability of the intestinal membrane and affinity between lipids and intestinal membrane will be improved due to effect of surfactant. Surfactants improve the permeability by partitioning into the cell membrane and disrupting the structural organization of the lipid bilayer dominates to permeation enhancement [30]. The two major affairs that command the selection of a surfactant enclose first safety and second hydrophilic lipophilic balance. To formulate self-emulsifying systems, Hydrophilic lipophilic balance of surfactant provides important information. High emulsifying performance is achieved if the emulsifier used in formulation of self-emulsifying systems has high hydrophilicity and hydrophilic lipophilic balance. Therefore, for effective absorption at the site, drug is present in solubilized form for a longer period of time and prevents precipitation of drug substance in gastrointestinal tract lumen [31]. Generally single alkyl chains are more penetrative, so surfactants such as polysorbates and triglyceride ethoxylates are found to be less toxic. Usually the surfactant concentration ranges between 30 and 60% of the total formulation in order to form stable self-micro emulsifying systems [32].

2.3.4 Co-surfactants/co-solvents

Stress of interface is decrease in the presence of co-surfactant and it allows the interfacial film sufficient flexibility to take up different curvatures required to form self-micro emulsifying systems over a wide range of composition [33]. The mixture with higher surfactant and co-surfactant: oil ratio assists the formation of self-micro emulsifying systems. Disadvantage of alcohol and other volatile co-solvents is that they get evaporated through the shell of soft or hard gelatin capsules and results into precipitation of drug (**Table 3**) [34, 35].

2.4 Mechanism of self-emulsifying systems

The mechanism by which self-emulsification occurs is not yet well understood. The entropy change of dispersion is greater than the energy required to increase the surface area of the dispersion at that time self-emulsification is occurring. In a conventional emulsion formulation, a free energy is an energy that required developing a new surface between the two phases i.e. oil and water and it can be narrated by

Oils	**Surfactants**	**Co-surfactants/ co-solvent**
Cotton seed oil	Polysorbate 20 (Tween 20)	Span 20
Soybean oil	Polysorbate 80 (Tween 80)	Span 80
Corn oil	Polyoxy 35 castor oil (Cremophor RH40)	Capryol 90
Sunflower oil		Polyethylene glycol
Castor oil	D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)	Ethanol
Peanut oil		Lauroglycol
Sesame oil		Isopropyl alcohol

Table 3.
Example of Oil, Surfactant and Co-surfactant/Co-solvent.

$$\Delta G = \Sigma N \pi r 2 \sigma \quad (1)$$

where G is free energy, N is the droplets number, r is globules radius, and σ is the interfacial energy [22, 26]. The oil and water phase of the emulsion separates upon reduction in the interfacial area and free energy of the system. Conventional emulsifying agent stabilizes the emulsion by forming a monolayer around the emulsion droplets and reduces the interfacial energy, thereby provides a barrier to coalescence. For the formulation self-emulsifying systems free energy requires is either very low or positive or negative then, the emulsion process occurs irrepressible. Very low energy requires for emulsification, it involves destabilization through diminution of interfacial regions. It is necessary to not have any resistance to the surface shearing of the interfacial structure to occur the emulsification. Through the emulsification water penetrates into the various liquid crystals or phases. As soon as binary mixture of oil/non-ionic surfactant comes in contact with aqueous phase, formation of interface between the oil and aqueous phases occurs. Aqueous phase penetrates through this interface and starts solubilizing with oil phase till the limit of solubilization is reached at the interface. There is relationship between the emulsification properties of the surfactant and phase inversion behavior of the system.

Upon mild agitation of self-micro emulsifying systems, water penetration occurs quickly and leads to the interference of interface and droplets will be formed as micro-emulsions are thermodynamically stable; equilibrium exists within the system although there is continuous exchange of matter between the different phases [36]. Interchanging of matter usually occurs in two different ways like amalgamation of small droplets followed by the parting of larger droplet into small droplets and fragmentation of droplets which later coagulate with other droplets [37].

Self-emulsifying drug delivery system also poses accountability in contempt of its many assets namely

i. Drug chemical instability

ii. Large amount of surfactant used in formulation causes irritancy in gastrointestinal tract

iii. Precipitation of lipophilic drugs take place when volatile co-solvent is incorporated [38].

2.5 Formulation design

Formulation of self-micro emulsifying systems involves the following steps.

1. Screening of excipients.

2. Establishment of pseudoternary phase diagram.

3. Development of self-micro emulsifying systems.

4. Characterization of self-micro emulsifying systems.

2.5.1 Screening of excipients

Selection of the most satisfactory excipients that can be used in the preparation of self-micro emulsifying systems depends on the solubility studies. Solubility of the drug is tested in various oils, surfactants, and co-surfactants [39]. Shake flask

method is generally used to performed these type of studies. In these studies excess amount of drug is added to the excipient and then flask is shaken for 48 hours in water bath shaker at room temperature. After 48 hours samples are subjected to centrifugation, then filtered through 0.45 μm filters and drug content is examined [40, 41]. The objective of these solubility studies is to choose oil, surfactant, and co-surfactant that show maximum solubility to the drug. Another objective is accomplishment of optimal drug loading with minimized entire volume of the formulation [42].

To check the emulsification ability, screening of surfactant and co-surfactant is done by mixing known amount of surfactants with equal portion of selected oil and surfactant, and homogenized. The idea about ease of emulsification is obtained when the mixture is added to double distilled water and the number of flask inversions required to form homogenous emulsion is noted [43]. Then, the obtained dilution is tested for turbidity, percentage transmittance and clarity. The surfactant that shows high percentage transmittance at lower flask inversions with high emulsification efficiency is generally selected. Similarly, co-surfactants representing higher emulsification efficiency are selected for self-emulsifying formulation [44].

2.5.2 Construction of pseudoternary phase diagram

Micro-emulsion is formed by the spontaneous emulsification method and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed ternary phase diagram is used to study the phase behavior of three components. Ternary phase diagram represents the system with three components oil, water, and surfactant. But in case of self-micro emulsifying systems, the additional component like co-surfactant/co-solvent addition is most common. Ternary diagram contains three corners that correspond to the 100% of the particular component. In case of addition of fourth component, the ternary diagram can be termed as pseudoternary phase diagram [45]. For building of pseudoternary phase diagram, components of micro-emulsion are examined for emulsification efficiency at various compositions. Emulsions, micro-emulsions, micelles, inverted micelle structures may be form and the degree of formation of these structures can be determined with the formation of ternary phase diagram [46, 47]. The fixed ratio is typically formed by the fusion of surfactant and co-surfactant and it may be the mixture of oil and surfactant. This is mixed with the specific volume of the third phase like oil or co-surfactant; then the other component i.e. water is added in a gradual amounts and with every addition the solution is tested for the clarity, dispersibility, time for self-emulsification, and flowability. The total concentration of all components in each mixture is 100%. In pseudoternary phase diagram, the samples which formed clear solution is denoted by suitable symbols in the phase diagram. The area that is formed when these points are joined indicates the mono-physic micro-emulsion existing area and wide area indicates the good emulsification efficiency [48, 49].

The following points may be useful to read and to understand ternary diagram in an easy way. The three corners of the typical ternary diagram represent three components, that is, A, B, and C. The arrow towards BA indicates increase in proportion of A from 0% concentration (at point B) to 100% concentration (at point A), the arrow towards AC indicates the increase in proportion of C from 0% concentration (at point A) to 100% concentration (at point C), and similarly the arrow towards CB indicates the increase in proportion of B from 0% concentration (at point C) to 100% concentration (at point B). It shows in **Figure 1**, composition at point O can be known by the following procedure [50].

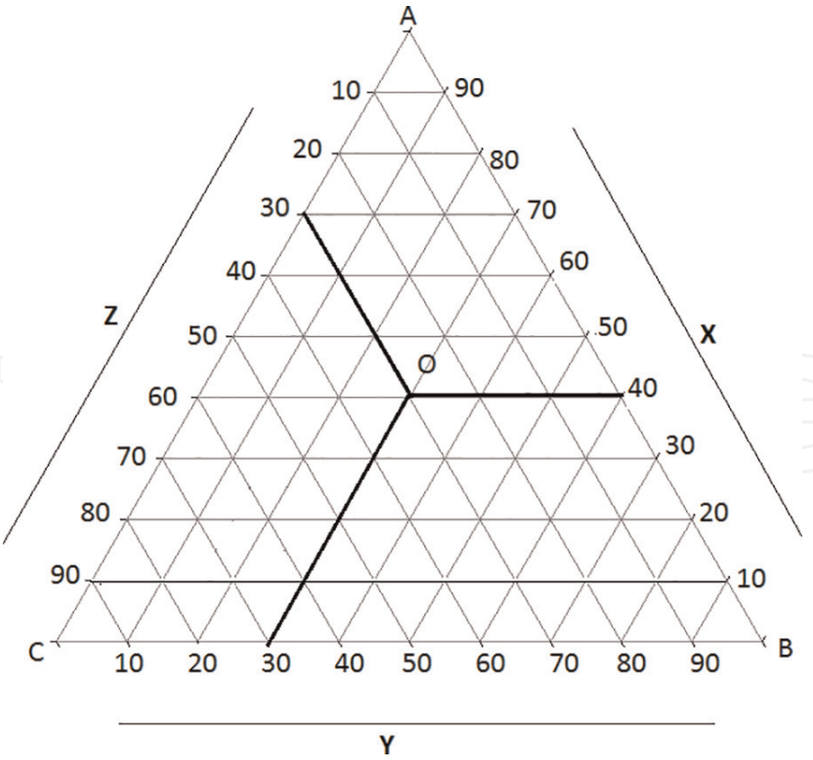

Figure 1.
Typical ternary diagram indicating the composition of A, B, and C at point O.

i. A line is drawn parallel to CB from point O towards AB. The point where this line intersects with AB indicates the percent composition of A at point O (X).

ii. Then, percent composition of B at point O can be known by drawing a line that is parallel to AC towards BC. The point where this line intersects with BC indicates the percent composition of B at point O (Y).

iii. Similarly, the percent composition of C, at point O can be known by drawing a line that is parallel to AB towards AC (Z).

2.5.3 Preparation method of self-micro emulsifying systems

Self-micro emulsifying systems is prepared by adding drug into the mixture of oil, surfactant, and co-surfactant and then vortexed. In some methods, first drug is dissolved in one of the excipients and later on other excipients are added to this prepared solution. Then, the solution is appropriately mixed and turbidity measured. After 48 hours at climatic condition, the solution is heated if required for the development of clear solution [51, 52].

2.5.4 Characterization of self-micro emulsifying systems

2.5.4.1 Visual inspection

The assessment of self-emulsification is possible by visual evaluation. After dilution of self-micro emulsifying systems with water, the opaque and milky white appearance indicates the formation of macro emulsion whereas the clear, isotropic, transparent solution indicates the formation of micro-emulsion [53, 54]. Precipitation of drug in diluted self-micro emulsifying systems is evaluated by visual inspection. The stable formulation is obtained when drug precipitation is not noticeable. If

the formulation contains water soluble co-solvents then precipitation is common outcome and it can be avoided by enhancing the concentration of surfactant [55, 56].

2.5.4.2 Droplet size

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion [57]. The droplet size is mainly dependent on the nature and concentration of surfactant. Photon correlation spectroscopy, microscopic techniques or a coulter nanosizer are mainly used for the determination of the emulsion droplet size [58, 59].

2.5.4.3 Turbidity measurement

This recognizes efficient self-emulsification by determine the dispersion reaching equilibrium quickly in a consistent time [60]. Orbeco-Helle turbidity meter is most commonly used for turbidity measurements. This turbidity meter is connected to dissolution equipment and emulsification time, optical clarity of nano or micro-emulsion formed is recorded after every 15 second. Turbidity can also be discovered in expression of spectroscopic characterization of optical clarity [61].

2.5.4.4 Zeta potential measurement

This is used to identify the charge of the droplets. In conventional self-micro emulsifying systems, the charge on an oil droplet surface is negative because of the presence of free fatty acids. Zeta potential is generally measured by zeta potential analyzer or zeta meter system [11]. Value of zeta potential indicates the stability of emulsion after appropriate dilution. Higher zeta potential indicates the good stability of formulation [62, 63].

2.5.4.5 Viscosity measurement

Viscosity of diluted self-micro emulsifying systems formulation is determined by rheometers like brookfield, cone and plate rheometers fitted with cone spindle or rotating spindle brookfield viscometer. During titration, the initial increase in viscosity with subsequent decrease with the increase in water volume attributes to water percolation threshold. This indicates the formation of o/w micro-emulsion from w/o micro-emulsion with intermediate bi-continuous phase [64]. Micro-emulsion can be determined by the graph plotted between shear stress and shear rate. The Newtonian behavior indicates the presence of droplets of small and spherical shape.

2.5.4.6 Determination of emulsification time

Efficiency of emulsification of various compositions of medium chain triglyceride systems is determined by using a rotating paddle to assist emulsification in a crude nephelometer [65]. This empowers an assessment of the time taken for emulsification.

2.5.4.7 Cloud point determination

Cloud point is generally determined by gradually increasing the temperature of water bath in which the formulation is placed and measured spectrophotometrically.

The point where percentage transmittance decreases signifies the cloud point that is the temperature above which the transparent solution changes to cloudy solution. As the body temperature is 37°C, formulations should exhibit the cloud point more than body temperature to retain its self-emulsification property. Phase separation and decrease in drug solubilization are commonly observed at higher temperature than the cloud point due to the susceptibility of surfactant to dehydration. Cloud point is influenced by drug lipophilicity and other formulation components [66].

2.5.4.8 Cryo-transmission electron microscopy studies

Transmission electron microscope is used to characterize the sample. In this sample is taken on copper grid. Filter paper is used to form the thin liquid film on the grid. The grid is extinguished in liquid ethane at −180°C and transferred to liquid nitrogen at −196°C [67, 68].

2.5.4.9 Percent transmission

This test gives the indication of transparency of diluted self-micro emulsifying systems formulation. It is determined spectrophotometrically after dilution of formulation with water, keeping water as blank. The percentage transmittance value near to 100% indicates clear and transparent micro-emulsion formation [69].

2.5.4.10 Small-angle neutron scattering

Size and shape of the droplets is determined using small angle neutron scattering. Small-angle neutron scattering experiments use the interference effect of wave lets scattered from different materials in a sample with the different scattering length densities.

2.5.4.11 Thermodynamic stability study

These studies are useful to evaluate the consequence of temperature change on formulation. Formulation is diluted with aqueous phase and subjected to centrifugation at 15,000 rpm for 15 min or at 3500 rpm for 30 min. The samples in which the phase separation is not observed further subjected to freeze thaw cycles (−20 and 40°C temperature, respectively) and observed visually. The thermodynamically stable formulations does not show any changes in visual description [70, 71].

2.6 Factors influencing formulation of self-micro emulsifying systems

2.6.1 Drug dose

Drugs with a very high dose are not acceptable for self-micro emulsifying systems unless they exhibit very good solubility in one of the excipients of self-micro emulsifying systems, mostly in a lipophilic phase. The drugs having a little solubility in water and lipids (log P values of approximately 2) are very difficult to deliver by self-micro emulsifying systems.

2.6.2 Drug solubility

Solubility of the drug in oil phase is important parameter in self-micro emulsifying systems formulation to maintain the drug solubility. A chance of precipitation is probably higher if contribution of surfactant and co-surfactant is greater in

formulation. Dilution of self-micro emulsifying systems will owe to decrease solvent capacity of the surfactant or co-surfactant. An equilibrium solubility measurement is carried out to predict the potential cases of precipitation in the gut region.

2.6.3 Polarity of lipid phase

Drug release from the self-micro emulsifying systems is mainly affected by the polarity of the lipid phase. The polarity of the droplet is governed by the hydrophilic lipophilic balance, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. Affinity of drug towards solvent is indicated by polarity. Rapid release of the drug in the aqueous phase is high if the polarity is high.

2.7 Significance of self-micro emulsifying systems

1. Self-micro emulsifying systems have the same advantage as emulsions, of facilitating the solubility of hydrophobic drugs. Macro-emulsions undergo creaming over a period of time, whereas self-micro emulsifying systems being thermodynamically stable can be stored easily [22].

2. Most of the self-micro emulsifying systems formulations are in capsule or tablet dosage forms, thus occupying smaller volume, easy to administer and hence improved patient compliance [72].

3. Self-micro emulsifying systems are advantageous over self-emulsifying systems as the former is less dependent on bile salts for the formation of droplets [73].

4. Drugs which have propensity to be degraded by the chemical and enzymatic means in gastrointestinal tract can be protected by the formulation of self-micro emulsifying systems as the drug will be presented to the body in oil droplets [74].

5. Self-micro emulsifying systems have the ability to facilitate rapid oral absorption of the drug, which results in quick onset of action [75].

6. Absorption of drug from self-micro emulsifying systems formulation is not affected by food. The lipophilic contents of fatty diet, aids in absorption of drug from these systems [76].

7. Self-micro emulsifying systems can be easily manufactured at large scale as it requires simple and economical manufacturing facilities, such as simple mixer with an agitator and volumetric liquid filling equipment [77].

8. Surfactants of high hydrophilic lipophilic balance like polysorbate 80 are reported to increase the permeability of the drug when administered along with the formulation due to the loosening effect of these on tight junctions [78].

2.8 Challenges in self-micro emulsifying systems formulation

1. In gastrointestinal tract fluid, diluted self-micro emulsifying systems undergo precipitation of drug. An essential for the lipid formulations is that they should allow keeping the drug in the solubilized form in the gastrointestinal tract. Advantage of lipid-based formulation is abolished due to the precipitation of

the drug. The precipitation tendency of the drug on dilution is higher due to the dilution effect of the hydrophilic solvent. It thereby requires incorporation of polymers to minimize drug precipitation in-vivo [79, 80].

2. Liquid self-micro emulsifying systems are difficult during handling, storage and stability. Therefor formulating solid self-micro emulsifying systems seems to be a logical solution for these problems [81]. Another hurdle in the development of self-micro emulsifying systems and other lipid-based formulations is the lack of good established in-vitro models for the assessment of the formulations [79].

3. Conventional dissolution methods do not work, as these formulations potentially are dependent on digestion of lipid in the gut, earlier to release of the drug. In-vitro model replicating the digestive processes of the duodenum has been developed to mimic the condition [81]. This model also needs more clarification and validation before its strength are examined. Further, development can be based on in vitro–in-vivo correlations.

4. Lipid excipients containing unsaturated fatty acids and its derivatives are prone to lipid oxidation [81]. Inclusion of Lipid soluble antioxidant in formulation of capsule [82]. Polymorphism associated with thermo-softening lipid excipients requires specific process control in their application, in order to minimize polymorphic changes of the excipient matrix.

2.9 Patented conventional self-micro emulsifying systems of lipophilic drugs

Self-micro emulsifying systems patent are shown in **Table 4** [83–86].

Sr. no	Summary of invention	Application	Patent number
1	Self-microemulsifying formulation containing taxoid, surfactant, and Co-surfactant [22].	Poorly water soluble compounds Taxoids having high molecular weight, and slightly lipophilic. This patent enhances oral bioavailability of taxoids through self-emulsification.	EP1498143A1
2	The self-micro emulsifying Formulation consisting of poorly soluble or insoluble drug, vitamin E, a co-solvent, bile salt(s), TPGS, and a surfactant [72].	Increases bioavailability of poorly soluble drugs of paclitaxel and docetaxel.	EP1340497A1
3	Self-emulsifying pharmaceutical Composition containing a lipophilic drug, surfactant(s), and hydrophilic carrier(s) [73].	Improves bioavailability of poorly soluble drugs such as cyclosporine, tacrolimus, ibuprofen, ketoprofen, nifedipine, amlodipine, and simvastatin.	EP2062571A1
4	Formulation containing mitotane, propylene glycol monocaprylate, propylene glycol dicaprate, and polyoxyethylene sorbitanmonooleate [74].	The invention provides the SMES of mitotane, which overcomes the issue of its low solubility and low bioavailability.	EP2435022A2

Table 4.
Patented conventional SMES of lipophilic drugs.

3. Conclusion

Self-micro emulsifying systems drug delivery systems are effective approach for increase the bioavailability of poor water soluble drug. Currently, several formulations have been developed to produce modified emulsified formulations as alternatives to conventional self-emulsifying systems, which provide faster and enhanced drug release. Versatility of self-micro emulsifying systems could be proved if issues like method to predict solubilization state of the drug in-vivo, interaction of lipid systems with components of capsule shell and basic mechanism of transport of self-micro emulsifying systems through gastrointestinal tract are adequately addressed. Further research in developing self-micro emulsifying systems with surfactants of low toxicity and to develop in-vitro methods to better understand the in-vivo fate of these formulations can maximize the availability of self-micro emulsifying systems in market.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Author details

Mansi Shah[1] and Anuj G. Agrawal[2*]

1 Parul Institute of Pharmacy and Research, Parul University, Vadodara, Gujarat, India

2 Netsurf Research Lab Pvt. Ltd., Pune, Maharashtra, India

*Address all correspondence to: royalanuj@yahoo.co.in

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