GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Design considerations for SMEDDS: Rationalizing drug and excipient selection for enhanced oral delivery

Bhaskar Kumar Gupta [1,*] and Kiran C. Rodage [2]

[1] *Professor, School of Pharmacy and Research, People`s University, Bhopal-462037 MP, India.*
[2] *Research Scholar, School of Pharmacy and Research, People`s University, Bhopal-462037 MP, India.*
Bhaskar Kumar Gupta; ORCID ID: 0000-0002-1329-674X
Kiran C. Rodage; ORCID ID :0000-0003-2959-2604

GSC Biological and Pharmaceutical Sciences, 2026, 36(01), 138–145

Publication history: Received on 02 June 2026; revised on 11 July 2026; accepted on 13 July 2026

Article DOI: https://doi.org/10.30574/gscbps.2026.36.1.0261

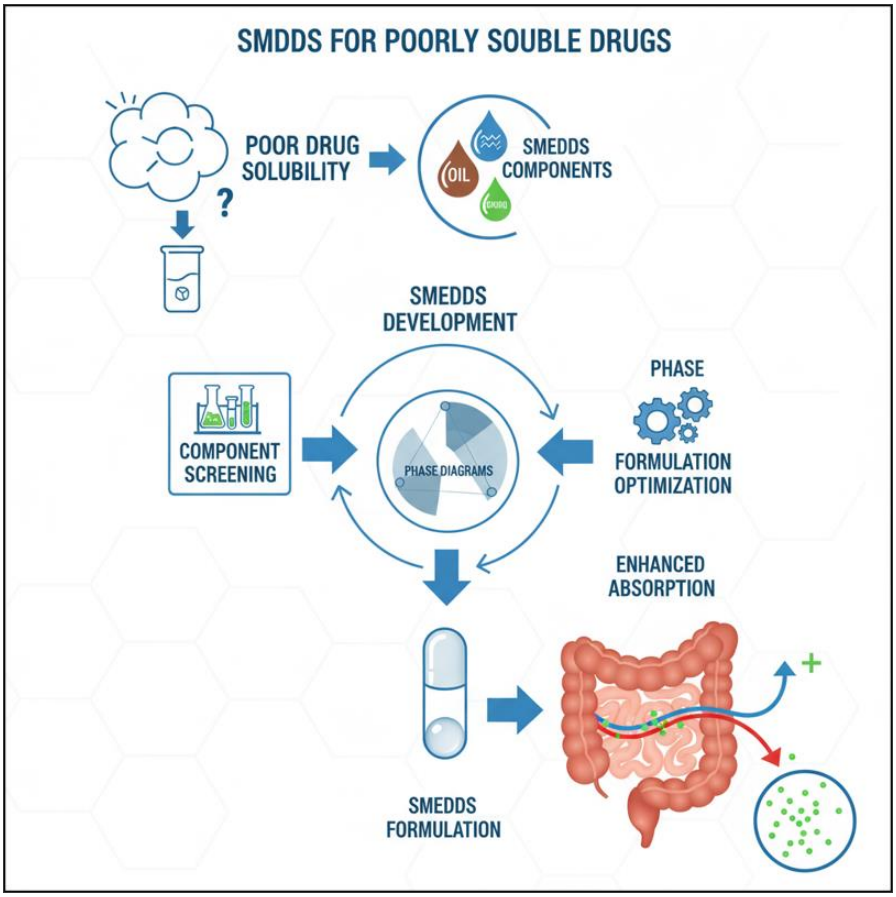
Abstract

The solubility of many newly discovered drug molecules remains a critical challenge in pharmaceutical development, as poor aqueous solubility limits their therapeutic effectiveness and bioavailability. Lipid-based formulations have emerged as an important strategy to overcome this limitation through approaches such as lipid solutions, emulsions, microemulsions, nanoemulsions, and micellar systems. Among these, self-microemulsifying drug delivery systems (SMEDDS) have attracted particular attention due to their ease of preparation, scalability, robust physical stability, and ability to enhance oral absorption of poorly soluble drugs. This review provides a comprehensive analysis of the rationale behind the selection of drugs and excipients for SMEDDS development, emphasizing the critical role of oils, surfactants, and co-surfactants in achieving optimal solubilization and self-emulsification. Methods such as solubility screening, spectrophotometric analysis, and construction of pseudo-ternary phase diagrams are discussed as essential tools in formulation design. Furthermore, the review highlights formulation considerations, evaluation strategies, and factors influencing successful clinical translation. Overall, this article synthesizes current knowledge to guide rational design of SMEDDS, thereby supporting the advancement of lipid-based drug delivery systems for poorly soluble therapeutic agents.

Keywords: SMEDDS; Lipid-Based Classification System; Ternary Phase Diagram; Surfactants

* Corresponding author: Bhaskar Kumar Gupta

Graphical Abstract



1. Introduction

It has been found that a significant percentage of new chemical entities are poorly soluble in water. Poor water solubility of such medications must be addressed in order to distribute them more effectively. The success of a medicine depends on the phenomena of solubility, which is the dissolution of a solid in a liquid phase to produce a uniform molecular dispersion. However, the majority of the active medicinal components is hydrophobic and is not water soluble. Solubility of the medicine becomes one of the most difficult formulation development challenges. Inadequate water solubility prevents critical products from reaching [1]. Lipids have recently been used in a variety of ways to increase the bioavailability of drugs that aren't very water soluble. Simple oily solutions, emulsions, micro-emulsions, nano-emulsions, micellar solution and more recently SMEDDS are unbeatable examples. The SMEDDS is more desirable and conventional emulsion owing to its simple production, scalable design, and strong physical stability [2].

Table 1 Solubility chart [3].

Sr. no.	Parts of solvent required per part of solute	solubility
1	Less than 1	Very soluble
2	From 1 to 10	Freely soluble
3	From 10 to 30	Soluble
4	From 30 to 100	Sparingly soluble
5	From 100 to 1000	Slightly soluble
6	From 1000 to 10,000	Very slightly soluble
7	Greater than 10,000	Practically insoluble or insoluble

Lipid-based formulation has received a lot of attention recently, with a focus on SMEDDS in particular. Lipid-based formulations, such as SMEDDS, are emulsions with smaller globules and greater thermodynamic stability. Emulsions typically consist of oil, water and an emulsifier in droplets that range in size from 1 to 10 mm and are dispersed as microscopic droplets. They have a tough interfacial coating, are liquids that are thick range from semitransparent to hazy, and are unstable thermodynamically. Water-in-oil (w/o), oil-in-water (o/w), and multiple emulsions are all examples of emulsions. A dispersion of oil in water is known as an oil-in- water (o/w) emulsion that is particularly useful for medicinal purposes and necessitates that typically, the surfactant is more soluble in the water [4]. Increasing the dissolution rate or putting the medication in solution and keeping it there in the gut lumen are two formulation techniques that could be utilized to raise BCS class II's bioavailability medicines [5].The main objective of SMEDDS is to develop a stable formulation for SEDDS in order improve the poorly soluble medication's solubility, rate and amount of drug release as well as oral bioavailability. Spectrophotometric analysis was used to test the drug's solubility in various oils, co-surfactants and surfactants. To investigate the phase behavior and the most effective self-emulsifying regions when the system is diluted with water, pseudo-ternary phase diagrams were built built and other such evaluation and criteria for selection of drug and excipient are done in this literature [6].

1.1. Advantage of SMEDDS:

- Improved patient adherence.
- Thermal stability.
- Easier to manufacture and scale up than other lipid dosage formulations.
- Less frequent dose
- Decrease in dietary effects and inter- and intra-subject variability.
- In contrast to other lipid-based drug delivery methods, it is unaffected by the digestion of lipids.
- Capacity to transport bioactive compounds to the GI tract, including peptides that can react with enzymatic hydrolysis.
- Polymer in the SMEDDS composition allows for a prolonged release of the medication [5].

1.2. Disadvantage of SMEDDS

Inadequate predictive in vitro models for formula evaluation, before its strength can be assessed, this in vitro model needs to be improved and validated.

As further development will be dependent on correlations between in vitro and in vivo tests, several prototype lipid-based formulations must be created and put to the test in vivo in an appropriate animal model.

Another is the high surfactant concentrations in formulations (about 30–60%) that aggravate the gastrointestinal tract (GIT).

In addition, it is known for volatile cosolvents in traditional self-microemulsifying formulations to move into the shells of soft or hard gelatin capsules, precipitating the medicines that are lipophilic.

The hydrophilic solvent's dilution action may cause the drug's tendency to precipitate on dilution to be higher [7].

1.3. Mechanism of SMEDDS composition:

The creation of a complex film by co-surfactant and surfactant at the oil-water interface causes emulsion droplets to form. Thermodynamic theory states that emulsification occurs as a result of an entropy change that favors dispersion more than the free energy needed to expand the contact surface between the oil and water phases of dispersion. A charge in free energy is involved in emulsification process, and this change in free energy (G) may be represented as _

$G = \Sigma N \pi r^2 \sigma$

Where,

N is the number of droplets,

r is the droplet's radius, and σ is the change in interfacial energy over time [8].

When a binary mixture is added, the interface between the continuous phases of oil and water is established. Following this, water becomes soluble in oil phases as a result of aqueous fluid permeating the interface. This will continue until near when the solubility barrier is reached, to the interphase.

Water penetration will continue until the scattered LC phase is formed. Ultimately, whatever is close to the interface will be LC; the precise amount relies on the quantity of surfactant reached in the binary mixture. Water will therefore quickly enter the aqueous cores once the system that self-emulsifies has been gently stirred, causing interface disturbances and droplet formation. Due to the establishment of the LC interface [9].

1.4. Absorption of SMEDDS [7]:

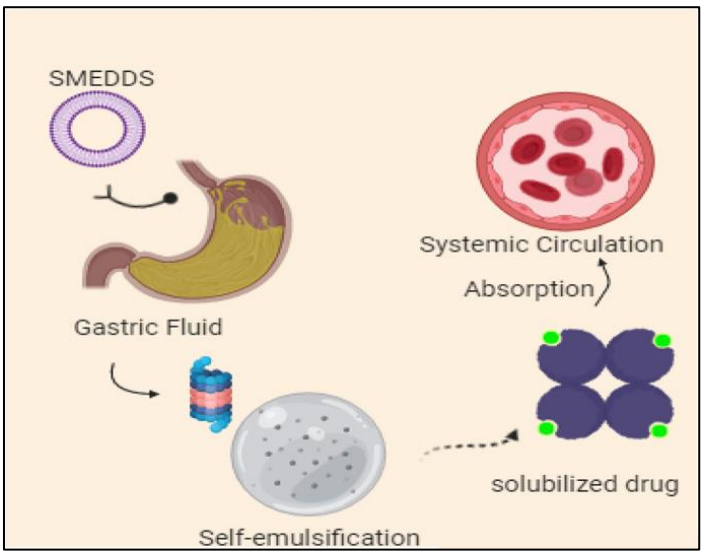


Figure 1 Absorption of SMEDDS [10].

2. Physicochemical properties for the choosing of drug and excipients [11-13]:

2.1. Drug

The quantity of the active ingredient and also the lipophilicity should be closely examined while formulating a SMEDDS formulation. The medicine should ideally have a low dose and not be vulnerable to first-pass metabolism (log p 2). The medication ought to be significantly soluble in oils, co-surfactants, and surfactant that are recognized by the pharmaceutical industry. Drug should possess low solubility or low permeability.

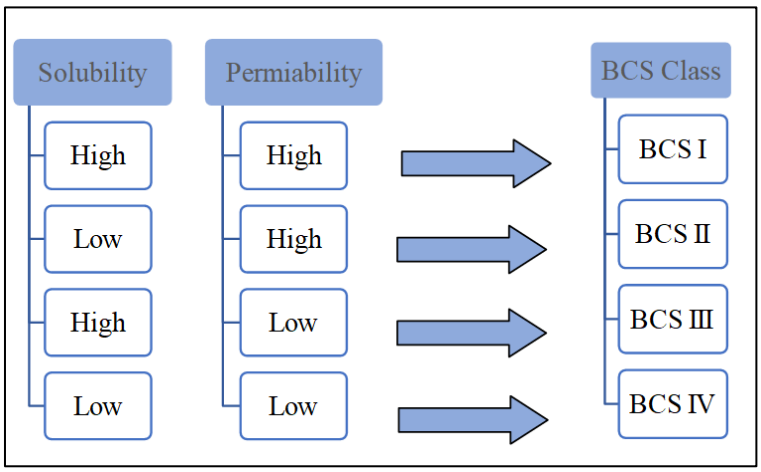


Figure 2 BCS Classification system.

2.2. Oils

The blood portal mostly transports medium-chain triglycerides with 6–12 carbon atoms enter in to the systemic circulation. Long-chain triglycerides with carbon atom counts more than 12 are nonetheless transported through which intestinal lymphatic system. Due to their high solvent capacity and resistance to oxidation, medium chain triglycerides have the potential to be used in lipid-based formulation systems. e.g., captex 300, caprylic acid, castor oil, oleic acid, migloyl oil etc.

2.3. Surfactant

Moreover, to the interfacial tension being significantly lowered to a low value, which facilitates the dispersion process, surfactants contribute to the interfacial film. The HLB value and surfactant concentration are important criteria in the choice of surfactant. The emulsifier used in the system must have an HLB value higher than 12, which encourages the creation of tiny o/w droplets with quick dispersion in aqueous solutions, for an effective performance. For the formulation system, non-ionic surfactants with higher HLB values are often selected since they are less hazardous than ionic surfactants. e.g., Tween 80, tween 60, Cremophore ELP, etc.

Figure 3 Examples of uses of oil, co-surfactant, surfactant [14].

2.4. Cosurfactant

Co-surfactants, when the interfacial tension is drastically lowered to a nearly negative value, add flexibility to the interfacial layer. The flexibility produces different curvatures that are necessary to create micro emulsions over a broad range. Most often, medium chain length alcohols are used as co-surfactants. e.g., PEG 400 (polyethylene glycol 400), PEG 300, PG (propylene glycol), etc.

Lipid based classification system [15]:

- The following elements must be considered when developing SMEDDs:
- Drug's ability to dissolve in various oils, surfactants, and cosolvents;
- Based on a drug's solubility, selecting an oil, surfactant, and cosolvent; and

2.5. Phase diagram preparation

Table 2 The lipid formulation classification system [16].

Composition	Type I	Type II	Type III A	Type III B	Type IV
Oils	100 %	40–80 %	40–80 %	< 20 %	-
Water-insoluble surfactants (HLB less than 12)	-	20-60 %	-	-	0-20%
Water-soluble surfactants (HLB greater than 12)	-	-	20–40 %	20–50%	30–80%
Hydrophilic co-solvents (e.g. PG, PEG)	-	-	0–40 %	20–50%	0–50%
Particle size or globule size(nm)	Coarse	100-250	100-250	50-100	< 50

2.5.1. Pseudo ternary phase diagram

According to the solubility study of the drug in various oil, surfactant and co-surfactant the highly soluble excipients are selected for the ternary phase diagram. Using water titration approach, solutions of oil and surfactant/cosurfactant at certain weight ratios are diluted with water in a dropwise fashion to create the pseudo-ternary phase diagrams of oil, surfactant: cosurfactant, and water. At a particular ratio of surfactant to cosurfactant for each phase diagram, transparent and homogenous mixtures of oil and drug in the ratios of 1:1, 1:2, and 1:3 (w/w) were created while being mixing by magnetic stirring. Each mixture is then titrated with water and its phase purity and flow capacity is visually assessed. The phase diagrams' microemulsion regions are located, and the desired component ratios for the microemulsion formulations were chosen. A succession of SMEDDS is created in the manner described below in order to create the microemulsion [17].

2.5.2. Preparation or formulation of liquid-SMEDDS

Under constant stirring, drug and oil are combined gradually. The prepared surfactant system is made by combining the co-surfactant and elected surfactant in the estimated amounts. In order to create a homogenous mixture, drug and oil combination was added to the created surfactant cosurfactant system while being continuously stirred and mixed in a vortex [19].

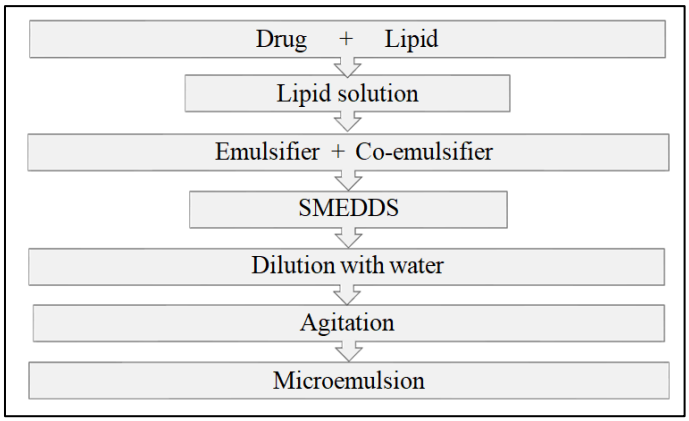


Figure 4 Preparation or formulation of SMEDDS [16].

2.6. Characterization of SMEDDS

2.6.1. Phase separation, precipitation and self emulsification of SMEDDS formulation

A glass test tube containing 5 ml of distilled water is filled with 0.05 ml volume of each SMEDDS using a micro pipette at the ambient temperature (25 °C). The mixture is added to the reciprocating agitator again, homogenized for 2 minutes, and then left to stand at the same temperature for 2 hours. Visual investigation revealed the phase separation [20].

As previously stated, a visual inspection is used to evaluate how well SMEDDS formulations are self-emulsified. In a nutshell, the speed of emulsification, clarity, and apparent stability of the resulting emulsion are used to classify various mixtures. Visual evaluation is accomplished by dripping the preconcentrate (SMEDDS) into 250 mL of distilled water one drop at a time. This is carried out at room temperature in a glass beaker with a gentle magnetic swirl at around 100 revolutions per minute.

After 24 hours, visual inspection of the resulting emulsion is used to assess the amount of precipitation. The chemical compositions are then divided into four categories: stable (no precipitation after 24 hours), unstable (showing precipitation within 24 hours), and clear (transparent or transparent with a bluish tinge) [21].

2.7. Cloud point

The most common method for determining cloud point involves spectrophotometrically measuring the cloud point while progressively raising the ambient temperature of the water bath in which the formulation is immersed. The cloud point, which is the temperature above which the transparent solution turns cloudy, is shown by the point where percent transmittance starts to decline. In order to maintain their self-emulsifying properties, formulations should demonstrate the cloud point more than body temperature, which is 37^0 C.

Because surfactant is sensitive to dehydration, phase separation and a decrease in drug solubilization are frequently seen at temperatures higher than the cloud point. Drug lipophilicity and other formulation elements have an impact on cloud point [22].

2.8. Percentage transmittance

SMEDDS formulation is diluted 1:100 in distilled water before being visually checked for turbidity. Employing a UV-vis spectrophotometer and distilled water as the reference material, the sample are examined [23].

2.8.1. In vitro drug release study:

A USP dissolving apparatus II (paddle apparatus) is used for the dissolution test. Empty hard gelatin capsules containing 50 mg formulation are either filled with solid SMEDDS that had been loaded with the drug. The full capsule is placed into the sinker and submerged in the 900 ml suitable media. At 37 °C and 100 rpm paddle rotations, the dissolution test is completed. To maintain the desired temperature, an outside water bath is placed around the vessel containing the dissolving media. A nylon syringe filter (0.45 m) is used to filter 1 mL of dissolving medium at predefined intervals of time. The above-mentioned HPLC technique is used to calculate the amount of in the filtrate [24].

2.8.2. Globule size and poly dispersibility index analysis

Using the Beckman Coulter Counter N5, the microemulsion formulations globule size and polydispersity index are measured. Samples were put in the cuvette after being appropriately diluted with water. The developed Smedds particle size is observed [25].

2.8.3. Zeta potential

The charge on droplets is determined using the zeta potential. A solid formulation dosage of 10 mg is dissolved in 10 ml of methanol. Zeta potential is measured using a Brookhaven apparatus at 25 °C and a 90 ° scattering angle [26].

2.9. Drug content

Utilising UV spectrophotometric and HPLC methods, the drug content of the smedds is identified. In the UV example, 100 ml of Solvent (the medication having the highest solubility in that solvent) is used to dissolve the 10 mg equivalent of the drug-loaded smedds. Take 1 ml of this stock solution, diluted in 10 ml of a solvent that did not contain any drug-loaded smedds. And drug content is approximated at that medicine's published Lambda maximum molecule [27].

3. Conclusion

Self micro emulsifying drug delivery system formulation is formulated for the enhancement of oral bioavailability and solubility of poorly soluble drugs. The oil surfactant and co surfactant mixture is gently agitated in aqueous medium to form an emulsion. The ternary phase diagram is generally used to determine the emulsification region or the optimum concentration of oil, surfactant and cosurfactant. various evaluation parameters like phase separation, precipitation and self emulsification of smedds formula, cloud point, percentage transmittance, in vitro drug release study, globule size and polydispersibility index analysis, zeta potential and drug content are also discussed in this article.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

- Dr. Bhaskar Kumar Gupta: Supervision And Review
- Mr. Kiran C Rodage : Original Draft And Data Analysis

References

[1] Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility Enhancement Technique : AReview. 2018;10(9):2205–11.

[2] Laddha P, Suthar V, Butani S. Development and optimization of self microemulsifying drug delivery of domperidone. Brazilian J Pharm Sci. 2014;50(1):91–100.

[3] Kumar LA, Pattnaik G, Satapathy BS, Patro CS, Naik S, Dash AK. Solubility Enhancement Techniques: Updates and Prospectives. J Pharm Negat Results. 2022;13(8):2847–55.

[4] Dokania S, Joshi AK. Self-microemulsifying drug delivery system (SMEDDS)- challenges and road ahead. Drug Deliv. 2015;22(6):675–90.

[5] Kumar A, Sharma S, Kamble R. Self emulsifying drug delivery system (SEDDS): Future aspects. Int J Pharm Pharm Sci. 2010;2(SUPPL. 4):7–13.

[6] Lalwani JT, Thakkar VT, Patel H V. Enhancement of solubility and oral bioavailability of ezetimibe by a novel solid self nano emulsifying drug delivery system (SNEDDS). Int J Pharm Pharm Sci. 2013;5(3):513–22.

[7] Anand S, Gupta R, Sk P. SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM. 2016;9.

[8] Vijay Shinde J, Anil Orpe A, Premchand Munde V, Hauserao Nimbalkar Y. Self-Micro- Emulsifying Drug Delivery System (SMEDDS) - A Novel Approach. Am J PharmTech Res. 2020;10(1):250–65.

[9] Patel MJ, Patel SS, Patel NM, Patel MM. A self-microemulsifying drug delivery system (SMEDDS). Int J Pharm Sci Rev Res. 2010;4(3):29–35.

[10] Zhao T. Self-nanoemulsifying drug delivery systems (SNEDDS) for the oral delivery of lipophilic drugs. Self-nanoemulsifying drug Deliv Syst (SNEDDS) oral Deliv lipophilic drugs. 2015;(November):1–120.

[11] Radha G V., Trideva Sastri K, Burada S, Rajkumar J. A systematic review on self-micro emulsifying drug delivery systems: A potential strategy for drugs with poor oral bioavailability. Int J Appl Pharm. 2019;11(1):23–33.

[12] Kyatanwar A. U. JKR. KVJ. Anand 2010 SMEDDS. Self Micro-emulsifying Drug Deliv Syst Rev. 2010;3(1):75–83.

[13] Kumar S, Kumar Gupta S, Kumar Sharma P. Self-emulsifying drug delivery systems (SEDDS) for oral delivery of lipid based formulations. African J Basic Appl Sci. 2012;4(1):7–11.

[14] Meghani N, Suares D. Self micro-emulsifying drug delivery system (SMEDDS): A promising tool to improve bioavailability. J Pharm Phyther [Internet]. 2013;2(1):17–21. Available from:

[15] Pande SV, Biyani KR, Microencapsulation by solvent evaporation method of BCS Class 4 drugs for bioavailability enhancement, Journal of Drug Delivery and Therapeutics. 2016; 6(5):18-30.

[16] Maurya SD, Arya RK, Rajpal G, Dhakar RC. Self-Micro Emulsifying Drug Delivery Systems (Smedds): a Review on Physico-Chemical and Biopharmaceutical Aspects. J Drug Deliv Ther. 2017;7(3):55–65.

[17] Ki B, Soo J, Kang S, Young S, Hong S. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. 2004;274:65–73.

[18] Sharma VK, Koka A, Yadav J, Sharma AK, Keservani RK. Self-micro emulsifying drug delivery systems: A strategy to improve oral bioavailability. Ars Pharm. 2016;57(3):97– 109.

[19] Pandey V, Kohli S. SMEDDS of pioglitazone: Formulation, in-vitro evaluation and stability studies. Future J Pharm Sci [Internet]. 2017;3(1):53–9.

[20] Ofokansi KC, Chukwu KI, Ugwuanyi SI. The use of liquid self-microemulsifying drug delivery systems based on peanut oil/tween 80 in the delivery of griseofulvin. Drug Dev Ind Pharm. 2009;35(2):185–91.

[21] Patel AR, Vavia PR. Preparation and in vivo evaluation of SMEDDS (self- microemulsifying drug delivery system) containing fenofibrate. AAPS J. 2007;9(3):344–52.

[22] Akula S, Gurram AK, Devireddy SR. Self-Microemulsifying Drug Delivery Systems: An Attractive Strategy for Enhanced Therapeutic Profile. Int Sch Res Not. 2014;2014:1– 11.

[23] BINDHANI S, MOHAPATRA S, KAR RK. Vegetable oil-based self-microemulsifying drug delivery system of eprosartan mesylate: In vitro and ex vivo evaluation. Asian J Chem. 2021;33(9):2182–90.

[24] Kim DS, Cho JH, Park JH, Kim JS, Song ES, Kwon J, et al. Self-microemulsifying drug delivery system (SMEDDS) for improved oral delivery and photostability of methotrexate. Int J Nanomedicine. 2019;14:4949–60.

[25] Jain DS, Bajaj AN, Nimisha T. Development and evaluation of peppermint oil containing microemulsions for intranasal delivery. Arch Pharm Pract [Internet]. 2011;2(4):174–85.

[26] Aparna C, Srinivas P, Rao Patnaik KSK. Formulation and evaluation of oral self emulsifying drug delivery system of lornoxicam. Int J Pharma Bio Sci. 2015;6(2):P381– 95.

[27] Journals H, Article R. A Review on Self Micro Emulsifying Drug Delivery System (SMEDDS). 2021;19(1).