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Self Micron Emulsifying Drug Delivery Systems (SMEEDS) as a potential drug delivery system - Novel applications and future prespectives - A review

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ABSTRACT

SMEDDS are defined as mixtures of oils, co-solvents and surfactants, which is isotropic in nature and which spontaneously emulsify to produce fine oil-in-water emulsions when introduced into aqueous phase under mild agitation. After oral delivery of BCS class-II drugs, over one-half of the drug compounds are diminished in the gastrointestinal (GI) tract. BCS class-II drugs having less water solubility and dissolution there by low bioavailability and this is a major issue face by the pharmaceutical industries. For the treatment of chronic diseases, delivery of poorly soluble drugs by SMEDDS as a vehicle via oral route which may enhances the bioavailability. Researchers are focusing on novel formulations of SMEEDS for various diseases having promising in-vitro and in-vivo results. Thus, this current review provides a brief updated collection of information about SMEDDS, its novel applications and future prospective.

Keywords: SMEDDS, BCS class-II drugs, bioavailability, chronic diseases.

INTRODUCTION

In 1943 Professors of chemistry at Cambridge University T. P. Hoar and J. H. Shulman first used the term micro emulsion.[1] The particle size of the micron emulsions are smaller than the wavelength of visible light, so they are clear and cannot detected by an optical microscope. [2, 3]

Drugs that are discovered and synthesized recently are lipophilic in nature and they have poor aqueous solubility, therefore it creates lots of problems to make it as a formulation into delivery systems. [4] Nearly 60% of the potential drug products developed in industries has poor water solubility. [5] For the therapeutic delivery of BCS class-II drugs, lipid founded formulations are inviting increasing attention. Presently number of techniques is available to deal with the poor solubility, dissolution and bioavailability profile of drugs. [6]

Most accepted and dominated route over other routes of administration is oral route and is preferred by the formulators. [7] Limitation of this route is that the permeability and solubility of the drug molecules in the gastric mucosa. This is one of the major challenges to the modern drug delivery system. To improve the oral delivery of poorly water soluble drugs certain approaches exist and have been successful in certain cases, hence lipid based formulations are developed in recent years.[8] Most popularly and widely used approach is self-emulsifying micron drug delivery systems (SMEEDS) [3, 9]. For encapsulating poorly water-soluble drugs emulsion systems are suitable, but they have certain complexities such as stability which eventually lead to complications during marketable production.[10] Therefore in this scenario, our present review highlights the present knowledge, recent developments, applications, as well as future prospective of self micron emulsifying drug delivery systems (SMEDDS) in relation to pharmaceutical

technology.

Pouton in 2000 introduced Lipid formulation classification system (LFCS) (**Table. 1**) by and it was updated by later 2006.[11] In these the lipid is classified into their type of composition and the effects on dilution and digestion on their ability to prevent drug precipitation. This system provides rapid and easy interpretation of in-vivo studies and identification of the most suitable formulation.

SMEDDS are defined as mixtures of oils, co-solvents and surfactants, which is isotropic in nature and which spontaneously emulsify to produce fine oil-in-water emulsions when introduced into aqueous phase under mild agitation.[7] After oral administration, with mild agitation provided by gastric mobility in gastro-intestinal tract they form fine emulsions. They are transparent than those of conventional emulsions (**Table. 2**) droplet size is very small and it has a droplet size between 10=200 nm. These are stable preparations and they increase dissolution of the drug due to improved surface area on dispersion and solubility effect of surfactants.[9] The oil droplets are ranging between 100 to 250 nm when the formulation forms transparent micro emulsions.[12, 13] For poorly water soluble and lipophilic drugs the principle of SMEDDS is used.[3]

The advantages and disadvantages of SMEDDS are given in **Table 3**. Lymphatic transport is another factor which increases the bioavailability of SMEDDS by complete uptake of the drug. **Fig.1** represents the oral absorption of SMEDDS from gastro- intestinal tract to blood.[14]

Mechanism of self emulsification

Emulsions are formed by agitating two immiscible liquids such as water and oil with appropriate surfactants leads to the expansion of surface area between the two phases. Surface active agents stabilize the emulsion droplets by forming a film around the internal phase of the emulsion droplet. In this case, the excess surface free energy is dependent on the particle size and the interfacial tension.[15]

Self-emulsification of SMEDDS is related to free energy. They have a positive and very low free energy or sometimes negative free energy cause thermodynamic spontaneous emulsification.[7, 16] This may occur due to the penetration of water in to Liquid Crystalline (LC) phase by the gentle agitation during the process. At certain extent, water penetration stops and forms droplets. This phase is favorable for the high stability of these emulsions. Concentration of the drug, polarity of the phase and solubility of the drug are the three main factors affecting SMEDDS. The release of drug from the micron emulsion is governed by the lipid phase polarity. Drugs which are poorly soluble and administered at higher dose are not preferred for SMEDDS. Solubility of drug is an important parameter for SMEDDS.[17] The process is specific to certain combinations of pharmaceutical excipients. Depending on the surfactant pair, and oil, ratios, the concentration of surfactant and the temperature at which the self-emulsification occurs.[18] During the formulation primary step is the identification of specific combinations of excipients and to construct phase diagram which will show various concentrations.

Novel formulations of SMEDDSS

Lan.Wu.*et al* formulated a self-micron emulsifying drug delivery system (SMEDDS) for a novel medicative compound against depression. They synthesized a novel medicative agent named as AJS belongs to BCS class-II drug has a better anti-depressant effect. So, SMEDDS was developed to improve its solubility and oral bioavailability of AJS. The prepared formulation was optimized. When compared to solid dispersion and cyclodextrin inclusion, AJS-SMEDDS was found to have a 3.4 and 35.9-fold increase in oral bioavailability. So, this novel AJS- SMEDDS was a promising strategy for the oral delivery of drugs.[19]

Tengfei.Weng.*et al* formulated and compared solid dispersion pellets (SDP), SMEDDS and a nanostructured lipid carriers (NLCs) using fenofibrate (FNB) as a model drug. The oral bioavailability of these formulations was compared in beagle dogs. The overall results suggested that the lipid-based drug delivery systems including NLCs and SMEDDS may have more advantages and bioavailability than immediate release SDS.[20]

Catheleeya.*et al* formulated SMEDDS and cyclodextrin (CD) complex formulations to improve oral absorption of methoxy flavones in *Kaempferia parviflora*. *Kaempferia parviflora* (KP) is a plant contains several methoxy flavones including 5, 7-dimethoxy flavone (DMF), 5, 7, 4- trimethoxy flavone (TMF), and 3, 5, 7, 3, 4-penta methoxy flavone (PMF). They are mainly used as an aphrodisiac, anti-microbial agent and for the treatment of inflammation, and peptic ulcers. The results proved that the oral bioavailability of KP-SMEDDS were greater than KP-cyclodextrin. So, SMEDDS are a novel strategy to improve the oral delivery of methoxy flavones in *Kaempferia parviflora* [21].

Qiuping.Li.*et al* prepared Curcumin-piperine encapsulated SMEDDS for ulcerative colitis treatment. SMEDDS improves the water-solubility and stability of curcumin for its anti-colitis activity. About 95% and 91% drug loading proved that SMEDDS can load a high pay load of drugs. Using

DSS-induced colitis model, the anti-inflammatory activity of curcumin-piperine-SMEDDS was evaluated. The overall results suggested that the prepared SMEDDS will be a potential carrier for developing colon-specific drug delivery system of CUR for ulcerative colitis treatment.[22]

Dong.*et al* formulated a novel flurbiprofen-loaded SMEDDS using gelatin as a solid carrier. The in-vitro studies of this novel SMEDDS compared with conventional formulation of SMEDDS. During in-vivo studies, SMEDDS increases the oral bioavailability of flurbiprofen in rats. According to them, gelatin as a solid carrier for preparing SMEDDS could greatly improves the bioavailability of poorly soluble drugs including flurbiprofen.[23]

Zhang.*et al* formulated and investigated the super-saturatable SMEDDS of carbenzepine. This is a new thermodynamically stable formulation approach, incorporating few surfactants and a water-soluble which is a precipitation inhibitor or super saturated promoter. The drug precipitation behavior, dissolution rate in-vitro and particle size distributions of the three different formulations of carbenzepine-SMEDDS were evaluated. The in-vitro studies are promising in-vivo. This study demonstrates that with low level of surfactant, S-SMEDDS technology give an effective approach for improving the extent of absorption of poorly-soluble drugs.[24]

Hyma.*et al* developed a SMEDD of Glimepiride using Tween 80 and Transcutol as surfactant and co-surfactant with sunflower oil. Pseudo ternary titrations were done using surfactants/co-surfactants and oil in different ratios. The results revealed that SMEDDS can act as a potential delivery system for glimepiride.[25]

Hyma.*et al* formulated Pioglitazone in a novel SMEDDS for evaluating its pharmaco kinetic behavior. In-vitro release studies indicate that the prepared novel SMEDDS has an increase in drug release. Based on in-vivo results, formulated SMEDDS found to be a suitable delivery vehicle for pioglitazone.[26]

Chirag.*et al* prepared SMEDDS for Olmesartan medoxomil (OLM) an angiotensin-II receptor blocker anti-hypertensive agent. They optimized and did characterization studies. The in-vitro drug release of the optimized formulation of OLM-loaded S-SMEDDS was found to be 60 min as compared pure drug solution. The present result confirmed the applicability of SMEDDS to enhance dissolution and oral bioavailability of poorly water-soluble OLM 876.[27] Based on the literature survey; SMEDDS are formulated as a delivery vehicle for different class of drugs mainly for improving the solubility and oral bioavailability. This novel approach has a potential for improving the therapeutic efficacy of the existing highly active pharmacological agents.

Applications, recent developments and future perspectives of SMEDDS

Self-micron emulsifying drug delivery systems are the promising strategy to improve the solubility of drugs. Recent research has shown the novel applications of SMEEDS, which will enhance the therapeutic ratio of the active agent.

Self-micron emulsifying solid dispersions, self-micron emulsifying sustained/controlled-release tablets, self-micron emulsifying sustained/controlled-release pellets, dry emulsions, self-micron emulsifying suppositories, self-micron emulsifying capsules, self-micron emulsifying implants self-micron emulsifying floating dosage form-43, self-emulsifying sustained-release microspheres-43, positively charged self-emulsifying drug delivery system-43, self-double-emulsifying drug delivery system-43, super saturatable self-emulsifying drug delivery system are the recent developments in SMEDDS.[3,4,6,9,12,13]

Self-micron emulsifying solid dispersions use self-micron emulsifying excipients like Gelucire 144/14, Gelucire150/02, Labrasol-1, Transcutol-1 and TPGS (tocophery l polyethylene glycol 1000 succinate) and melted and filled inside gelatin capsules has been widely used.[28] BIS (2-chloroethyl) -1- nitrosourea is a chemotherapeutic agent used to treat malignant brain tumors has short half.[29] In order to improve its half-life and therapeutic action as well as stability, prepared self-emulsifying implants of this drug is a novel strategy in this field. Gelled SMEDDS is new categories contain colloidal silicon dioxide helps to aid in slow down the drug release as well as to reduce the quantity of solidifying excipients.[8]

Self-micron emulsifying sustained/controlled-release pellets prepared by the combination of PEG and self-emulsifying excipients which makes the advantages of SMEEDS and pellets and self-micron emulsifying capsules prepared by various excipients are the promising developments till now.[3, 28] In one part of the world, researchers engaged in preparing SME tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms. Self-micron emulsifying suppositories contain glycyrrhizin is also a potential development in this field.[3]

Self-micron emulsifying floating dosage form increases the residence time of drug in the stomach.[8] The novel floating dosage form of furosemide (FUR) is an example of this system. Self-emulsifying beads and self-emulsifying sustained-release microspheres formulated for sustained delivery using different types of polymers and excipients are of at the edge of research now.[28]

SMEDDS has been developed widely in the recent years. It reduces the problems associated with the poor solubility of drugs in the GIT20. Self-micron emulsifying implants, microspheres and beads are the major development in the field of novel SMEDDS.[8, 28] SMEDDS acts as a delivery system for the less soluble drugs. A polymer matrix dispersed in SMEDDS formulation is the latest technique which utilizes the combined effect of polymer and SMEDDS.[30]

CONCLUSION

Self micron emulsifying delivery systems are widely accepted carriers for lipophilic drugs (BCS class-II drugs). Currently, many researchers attempted to formulate various self micron delivery systems for poorly water soluble drugs. Hence, SMEDDS have a potential application for the delivery of poorly soluble therapeutic agents. The patentability and future applications of SMEDDS are also inevitable.

Fig. 1: Self-emulsifying formulations enhancing the bioavailability of drugs through oral absorption

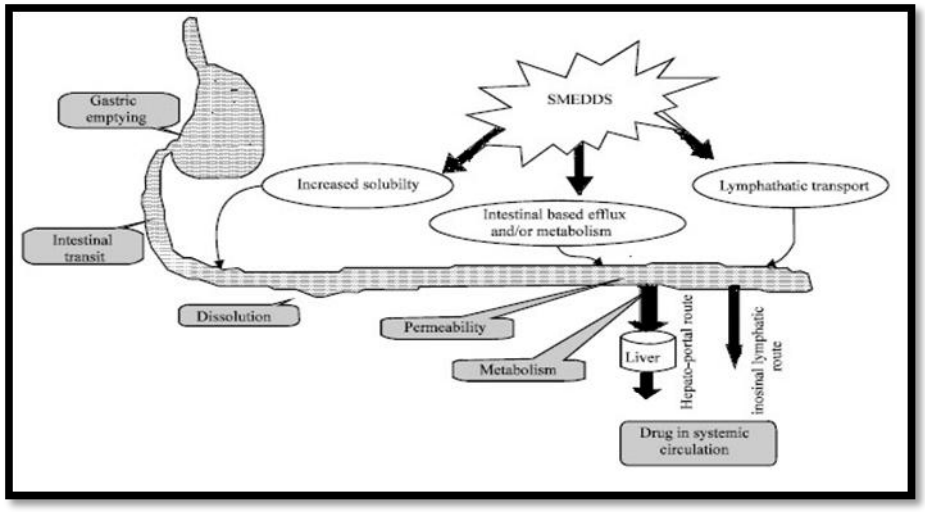

Table 1: Lipid formulation classification system

Composition	Type I	Type II	Type III		Type IV
	Oil	SEDDS	III A SEDDS	III B SMEDDS	OIL-Free
Glycerides (TG, DG, MG)	100%	40-80%	40-80%	< 20%	-
Surfactants (HLB < 12)	-	20-60%	-	-	-
(HLB > 12)	-	-	20-40%	20-50%	-
Hydrophilic co-solvents	-	-	0-40%	20-50%	-
Particle size of dispersion(nm)	Coarse	100-250	100-250	50-100	< 50
Significance of aqueous dilution	Ltd. importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity	-
Significance of digestibility	Crucial need	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

Table 2: Advantages of SMEDDS over emulsions

SMEDDS	Emulsions
Thermodynamically stable and optically transparent micro emulsions	Thermodynamically unstable and milky emulsions, optically not visible
Droplet size is very small, 2-100 nm	0.2-10 μm
More surface area as well as more bioavailability	Low bioavailability due to less surface area
SMEDDS can have various formulations like soft gelatin, hard gelatin capsules	Only one formulation is possible (oral solution)
It overcomes the disadvantages of the emulsion forming layer when it is kept for long time.	It forms layer when it is kept longer time
Storage is easy	Difficult
Can be autoclaved	Cannot be autoclaved

Table 3: Advantages and disadvantages of SMEDDS

Advantages	Disadvantages
Rate dependent dissolution	The of good *in-vitro* models for formulation assessment
When compared to tablet formulation, the bioavailability of drugs like halofantrine in GIT is approximately increased to 6-8 folds	Validation of the formulations which contain several components is a big challenge
Lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation processes cannot influence the performance of SMEDDS	SMEDDS formulation dependent on digestion previous to release of the drug so dissolution method won't work out
Amount of drug needed for the preparation of SMEDDS is very less	Possibilities of chemical instability of the drug
Ease of manufacture	Higher concentration of surfactants in the formulation may irritates GIT
More drug loading capacity	Precipitation of the hydrophobic drugs

REFERENCES

1. Schulman. J. H, Stoeckenius. W, Prince. L. M. Mechanism of formation and structure of micro emulsions by electron microscopy. J. Phys. Chem. 1959; 63: 1677-1680.
2. Aizi muzaffar, Singh.U.K, Lalit. Chauhan. Review on micro emulsion as futuristic drug delivery. Int. J. Pharm. and Pharm.Sci. 2013; 5 (3).
3. Preethi Sudheer, Nishanth Kumar M, Satish Puttachari, Uma Shankar M.S, Thakur R.S, Approaches to development of solid-self micron emulsifying drug delivery system: formulation techniques and dosage forms - a review. Asian J. Pharm. and Life Sci. 2012; 2 (2): 214-225.
4. Singh. A, Singh. V, Juyal. D, Rawat. G. Self-emulsifying systems: A review. Asian J Pharm. 2015; 9: 13-8.
5. Swati Sareen, George Mathew and Lincy Joseph. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int. J. Pharm Investig. 2012; 2(1): 12-17.
6. Khamkar Ganesh. S. Self micro emulsifying drug delivery system (SMEEDS) O/W Micro emulsion for BCS Class II Drugs: An approach to enhance an oral bioavailability. Int. J. Pharm. and Pharm. Sci. 2011; 3 (3): 1-3.
7. Vishesh Kumar Pal. Self emulsifying drug delivery system. J. Pharm. Research and Opinion. 2011; 1(3): 80-84.
8. Shweta Gupta, Rajesh Kesarla and Abdelwahab Omri. Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems. ISRN Pharmaceutics. 2013; 1-16.
9. Nilesh Meghani, Divya Suares. Self micro-emulsifying drug delivery system (SMEDDS): A promising tool to improve bioavailability. J. Pharm. Phytother. 2013; 2(1): 17-21.
10. Ekambaram. P, Abdul Hasan Sathali. A and Priyanka K. Solid lipid nanoparticles: A Review. Sci. Revs. Chem. Commun. 2012; 2(1): 80-102.
11. Pouton C.W. Lipid formulations for oral administration of drugs: nonemulsifying, self-emulsifying and self-micro emulsifying drug delivery systems. Eur J. Pharm. Sci. 2000; 11(2): S93-98.

12. Kanika Sarpal, Yogesh. B, Pawar and Aravind. K Bansal. Self-emulsifying drug delivery systems: A strategy to improve oral bioavailability. Curr. Research and information on Pharm. Sci. 2010; 11 (3): 42-49.
13. Zanchetta. B, Chaud. M.V, Santana. Self-emulsifying drug delivery systems (SEDDS) in Pharmaceutical Development. J. Adv. Chem. Eng. 2015; 5(3).
14. Hyeongmin Kim, Yeongseok Kim, Jaehwi Lee. Liposomal formulations for enhanced lymphatic drug delivery. Asian J. Pharm. Sci. 2013; 8 (2): 96-103.
15. Laxmikant T Gadhe, Sameeran V Kapadi, Baburao Bachkar and Mayur Gandhi, Swati talele, Chaudhari G.N. Recent patent review on self micro emulsifying drug delivery system. World Journal of Pharm. Res. 2015; 4 (3): 965-979.
16. Vikrant. P. Wankhade, Nivedita. S. Kale and Tapar. K.K. Self micro emulsifying nutraceutical and drug delivery systems. Int. J. Pharm. Sci and Nanotec. 2014; 7 (3): 2520-2528.
17. Jay Patel, Ravi Patel, Vishvadeep Patel, Akshay Patel, Hiral Shah. Review on solubility enhancement approach: Self micron emulsifying drug delivery system. Int. J. Pharm. Res. and Bio-Sci. 2014; 3(2): 799-813.
18. Barkat Ali Khan, Satar Bakhsh, Haroon Khan, Tariq Mahmood, Akhtar Rasul. Basics of Self micro emulsifying drug delivery system, J. Pharm. and Alt. Med. 2012; 1: 13-19.
19. Lan Wu, Yanli Qiao, Lina Wang, Jiahua Guo, Guocheng Wang, Wei He, Lifang Yin and Jinhua Zhao. A Self-micro emulsifying drug delivery System (SMEDDS) for a novel medicative compound against depression: a preparation and bioavailability study in rats, AAPS. Pharm. SciTech. 2015.
20. Tengfei Weng, Jianping Qi, Yi Lu, Kai Wang, Zhiqiang Tian, Kaili Hu, Zongning Yin and Wei Wu Weng. The role of lipid-based nano delivery systems on oral bioavailability enhancement of fenofibrate, a BCS II drug: comparison with fast-release formulations J. Nanobiotech. 2014; 12:39.
21. Mekjaruskul, Catheleeya Yang, Yu-Tsai Leed, Marina G.D Sadgrove, Matthew. P. Jay, Michael Sripanidkulchai, Bungorn. Novel formulation strategies for enhancing oral delivery of methoxyflavones in Kaempferia parviflora by SMEDDS or complexation with 2-hydroxypropyl-β-cyclodextrin. Int. J Pharmaceutics. 2013.
22. Qiuping Li, Wenwen Zhai, Qiaoli Jiang, Ruixue Huang, Lehuan Liu, Jundong Dai, Weihong Gong, Shouying Du, Qing Wu. Curcumin-piperine mixtures in self-micro emulsifying drug delivery system for ulcerative colitis therapy, Int. J. Pharmaceutics. 2015.
23. Dong Wuk Kim, Jun Hyeok Kang, Dong Hoon Oh, Chul Soon Yong and Han-Gon Choi. Development of novel flurbiprofen-loaded solid self-micro emulsifying drug delivery system using gelatin as solid carrier. J. Microencapsulation. 2012; 29(4): 323-330.
24. Zhang Nan, Gao Lijun, Wang Tao and Quan Dongqin. Evaluation of Carbamazepine (CBZ) supersaturatable self-micro emulsifying (S-SMEDDS) Formulation In-vitro and In-vivo. Iran. J. Pharm. Res. 2012; 11 (1): 257-264.
25. Hyma et al. Formulation and characterization of novel self micro emulsifying drug delivery system of Glimepiride. The Experiment. 2014; 24 (1): 1640-1648.
26. Hyma. P, Abbulu. K, Sunil. S Jalalpure. SMEDDS formulation: Demonstration of enhanced bioavailability of Pioglitazone in rats. Int. J. Pharm. and Pharm. Sci. 2014; 6 (2).
27. Chirag Raval, Neha Joshi, Jitendra patel, Upadhyay U.M. Enhanced oral bioavailability of Olmesartan by using novel solid self emulsifying drug delivery system. Int. J. Advanced Pharmaceutics. 2012; 2 (2): 82-92.
28. Anjan Kumar Mahapatra, Narasimha Murthy. P, Swadeep. B, Ranjit Prasad Swain. Self-emulsifying drug delivery systems (SEDDS): An update from formulation development to therapeutic strategies. Int. J. Pharm.Tech. Res. 2014; 6 (2): 546-568.
29. Das P.K, Panigrahi. M, Parikh P.M. Brain tumor and Gliadel wafer treatment. Ind. J. Cancer. 2011; 48, (1): 11-17.
30. Pranav Patel, Hitesh Patel, Shital Panchal and Tejal Mehta. Formulation strategies for drug delivery of tacrolimus: An overview, Int. J. Pharm. Investig. 2012; 2(4): 169-175.