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Introducing Self-Nanoemulsifying Drug Delivery System to Increase the Bioavailability of Oral Medications

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Abstract

The oral route is the most convenient route of administration of drugs because of low cost, ease of administration, patient compliance and flexibility in design of dosage form. Regardless of the advantages of this method, the main challenge in the bioavailability of oral drugs is gastrointestinal instability. Nanotechnology is used to improve the solubility and bioavailability of poorly water-soluble drugs. The self-nanoemulsifying drug delivery system is an ideal method for improving the solubility and bioavailability of poorly water-soluble drugs. This system is stable mixture of oil, surfactant and cosurfactant. The combination of these components creates an oil-in-water nanoemulsion, with droplet in the nanometer size range and ultimately increases the bioavailability and oral absorption of poorly water-soluble drugs. This system not only increases the medication's effectiveness, but it also reduces undesirable side effects.

Keywords: Nanoemulsion, Drug Delivery, Bioavailability, Self-nanoemulsifying

Introduction

According to the biopharmaceutics classification system, drugs are divided into four groups based on their solubility and intestinal permeability. In this classification, drugs belonging to groups two-four have solubility problems, low permeability, or both, which lead to a reduction in bioavailability and oral absorption (1). The solubility of this group of drugs determines their bioavailability and therapeutic effects (2). The oral route is the most convenient and accessible pathway to administer medications (3). However, the main challenge is the bioavailability of oral medications, the physiological barrier of the body, gastrointestinal instability, and systemic drug metabolism (4).

One of the goals of nanotechnology is increasing the rate of drug delivery. Nanoscale materials are widely used due to their unique physical and chemical properties (5-7). Over the past two decades, drug carriers such as liposomes, nanoemulsions, organogels, and nanocapsules have been introduced as effective drug delivery systems and have improved the therapeutic index of poorly water-soluble drugs by increasing solubility and modifying the pharmacokinetics of drugs. The essential criteria for the efficient use of these systems are tolerance towards additives, stability over a wide temperature range, low viscosity, small size, biodegradability, and easy elimination from the body. Among these carriers, nanoemulsions have been selected as particularly convenient carriers for numerous drugs due to having most of the mentioned criteria (8, 9).

Emulsion is a mixture of two immiscible liquids, such as water and oil (10). When shaken vigorously, an emulsion is formed temporarily. However, the emulate separates into two layers in a relatively short time (11). A stable emulsion is made by adding a third substance to the mixture called surfactant, which causes the thermodynamic stability of the mixture (12). The type and concentration of the surfactant should be selected carefully so that surfactant molecules can stabilize the nanoparticles with a very low surface tension created on the common surface of water and oil. The physicochemical properties of the drug and its polarity contribute to the formation of nanoemulsions, in which the size of droplets is in the range of less than 100 nm (13). The term mini-emulsion is also used as a synonym for nanoemulsion. Due to the small size of the droplets, the nanoemulsions have adequate stability against sediment and the Ostwald ripening phenomenon, which is the main mechanism of increasing the size of the droplets (14).

Self-nanoemulsifying Drug Delivery System (SNEDDS)

The SNEDDS is a sustainable combination of oil, surfactant, and cosurfactants (15). The schematic illustration of this system is shown in Figure 1 (16).

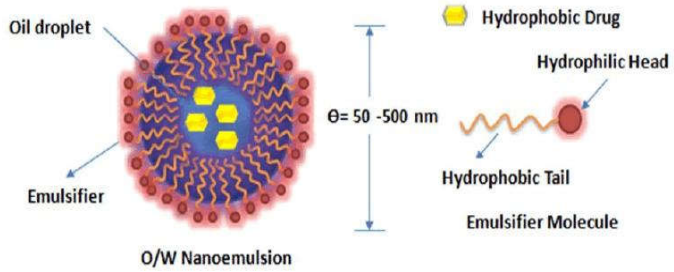

Figure 1. Nanoemulsion Droplets (16)

The combination of these components, for example in the stomach and intestines, creates a transparent nanoemulsion of oil in water

slowly with droplets in the range of nm (17), which ultimately increases bioavailability and oral absorption of drugs (18). The SNEDDS can be easily spread in the visceral pathway (19), and the gastrointestinal movements provide the necessary motor energy for their self-emulsifying (20). Three-level systems are referred to systems that are free of cosurfactant, whereas those containing co-surfactants are known as quasi-three-level systems, in which surfactants and cosurfactants are one phase together.

Nanoemulsion Components

Oil

Oil is one of the most important nanoemulsion components due to its ability to dissolve poorly water-soluble drugs. In addition, oil increases the transmission of these drugs through the intestinal lymph system and, as a result, improves their absorption through the gastrointestinal system (21). In general, the oil used in the SNEDDS formulation is based on some criteria such as solubility, the degree of sterility, and some physical properties (13).

Surfactants

With their dual properties, surfactants help eliminating the problem of dissolving poorly water-soluble drugs. Non-ionic surfactants are preferred to ionic surfactants due to lower toxicity, lower critical micelle concentration (CMC), faster formation of oil droplets in water, and better self-emulsifying performance (22). By adding the surfactants to two immiscible liquids, they reduce the surface tension between two phases and prevent the dual-phase of the liquids (23). Surfactants are selected based on hydrophilic-lipophilic balance (HLB) and safety (non-harmful) (22).

Cosurfactants

Creating the ideal SNEDDS requires a relatively high concentration of surfactants (more than 30% of weight). Increasing the amount of surfactant decreases the droplet size but increases the time required to form an emulsion (24). Therefore, the concentration of surfactant can be reduced with cosurfactant. In addition, sustainable surface tension is rarely obtained with the use of surfactants and there is often a need for adding a cosurfactant to the environment (21).

Aqueous Phase

The droplet size and the stability and performance of the emulsion formed by the SNEDDS formulation are also controlled by the nature of the aqueous phase formation. Therefore, in the design of SNEDDS, ionic content and pH of the aqueous phase should be considered. The pH range of the physiological environment of the body is from 1.2 (pH in the stomach) to 7.4 and higher (pH in blood and intestines). Moreover, the presence of various ions significantly affects the nanoemulsion properties produced from SNEDDS.

Nanoemulsion Preparation Methods

Various methods have been proposed for the preparation of nanoemulsions, which can be divided into high-energy (relying on mechanical devices) and low-energy (relying on phase changes) methods (25).

High-energy Methods

Creation of nanoemulsions in high-energy methods is carried out by using equipment such as high-pressure homogenizers, microfluidizers, and ultrasonic homogenizers. Some of the features of high-energy methods include better control of the distribution of droplets' size and a need for a low concentration of surfactants (26). Nevertheless, the technique has some limitations, including low thermodynamic efficiency that leads to increased energy use. Creating a significant temperature during the creation of a product is another limitation of this method (27). Some of the high-energy methods are presented, as follows:

Sonication

Sonication is the best method for nanoemulsion preparation. In this technique, the input energy is provided by a probe sonicator, and the size of emulsion droplets is reduced with the sonication mechanism. Nevertheless, this method is not suitable for creating a large number of nanoemulsions and can only prepare low amounts of nanoemulsions (28, 29).

Microfluidizers

With this technique, we can produce emulsions at pressures above 700 MPa. The initial emulsion solution flows through two microchannels and collides in a chamber, which ultimately leads to the reduced size of droplets. Therefore, an emulsion with small-size droplets is produced by this method (30).

Low-energy Methods

The phase change from oil to water or water to oil occurs in low-energy methods, which include phase inversion method and spontaneous emulsification method. Some of the limitations of low-energy methods are the need for a precise selection of surfactant and oil types, the need for high amounts of synthetic surfactants, and low industrial production capacity (31, 32).

Phase Inversion Method

In this method, the dispersion of droplets during the emulsification time is obtained by the chemical energy produced by the phase transfer, which is created by a change in composition at a constant temperature or with constant temperature change (31). The temperature of the inversion phase is the temperature at which the water-in-oil nanoemulsion becomes the oil-in-water nanoemulsion. At lower temperatures, the solubility of the surfactant is higher in water and the oil nanoemulsion is formed in water. In other words, if a system that is at a higher temperature than the phase inversion temperature is suddenly diluted with water, its temperature comes below the phase inversion temperature and a sudden change occurs in the phase. Therefore, the nanoemulsion is changed from the water-in-oil state into the oil-in-water state (33).

Solvent Displacement Method

In this method, the oil phase is entered into water-soluble organic solvents (e.g., acetone or ethanol) containing the surfactant so that the nanoemulsion is created simultaneously. Afterwards, the organic solvent is removed by a suitable method such as vacuum evaporation. By this method, nanoemulsion can be created at room temperature and by a simple stirring. Therefore, researchers use this technique to produce nanoemulsions. However, the major drawback of this method is the need to remove organic solvents. Additionally, a high proportion of solvent to

oil is needed to reach the optimal droplet size in nanoemulsions (34).

System Characterization

Droplet size is a determinant of self-emulsifying performance since the stability of the emulsion determines the rate and extent of drug release. Dynamic light scattering, photon correlation spectroscopy, laser diffraction, and other microscopic techniques are mainly applied to determine the size of formulation droplets.

Dynamic Light Scattering

This method is exploited to determine the average diameter of nanoemulsion droplets and the distribution of droplet size and zeta potential. In addition, polydispersity shows the quality and homogeneity of droplet size and is determined based on two factors, namely uniformity the (distribution symmetry around the middle point) and the width of the interval. In a fluid, the collision of moving particles with solvent molecules leads to random movement of molecules, known as the Brownian motion.

When a laser beam hits these moving particles at a given frequency, light is scattered at a different frequency, and oscillation is generated in scattered light phase. The level of change in the frequency of scattered light is correlated with the droplet size and is used to determine their sizes. In addition, the dispersion intensity of the scattered light can be measured using a suitable detector and depends on the solvent penetration rate (35).

Zeta Potential

Zeta potential (ζ) is a measure of the charge near the surface of a particle or emulsion droplet. In addition, zeta potential shows the amount of repulsion between adjacent charged droplets in solution, and is recognized as an important tool for understanding the surface state of nano-droplets, predicting and controlling the long-term sustainability of nanoparticle-containing solutions. In general, the instability/stability boundary of solutions can be determined by zeta potential. The particles with zeta potentials above +30 mV or -30 mV are more sustainable. When the zeta potential is within the range of -30 to +30, the gravity forces may overcome the repulsion forces between droplets, which leads to the breaking and aggregation of the emulsion. In the self-emulsifying drug delivery system, the zeta potential shows the load of oil droplets.

SNEDDS Advantages

- The extremely small size of fluid droplets reduces the gravity force and the Brownian motions. When there is a decrease in the gravity force, the formation of sediment in long-term is prevented, and droplets will remain dispersed without any phase separation.

- In contrast to microemulsions that require a large number of surfactants, nanoemulsions can be prepared with a small concentration of surfactants, which is confirmed for human use. This amount of surfactant is eliminated in the intestinal pathway.

- In the self-emulsifying system, the drug is dispersed in a long duration.

- Application of SNEDDS is associated with the improved bioavailability of oral drugs due to increased solubility and effective drug transfer. In addition, the increase of

bioavailability results in a lower drug dose (36).

- Compared to various lipid drugs, nanoemulsions are created by a simpler technique (37).

Other advantages of this system include high bioavailability and solubility of drugs due to high surface to volume ratio of droplets (24), high physical and kinetic stability and spontaneous and simple formation (38), decreased drug side effects (39), reduced first pass effect of the liver (40), decreased gastric stimulation (2), less need for organic solvents (41), controlled (42) and constant (43) drug delivery, protecting both hydrophile and poorly water-soluble drugs (44), diversity in the use of oils and surfactants in one formulation, and several other applications (45).

However, the use of nanoemulsion-based systems is associated with some limitations, including:

- Effect of environmental factors (e.g., temperature and pH) on system stability

- Surfactant toxicity for drug use. Therefore, a low amount of non-toxic surfactants must be applied.

- Phase separation in some cases after the synthesis of the nanoemulsion

Effect of Nanoemulsions on Delivery of Oral Drugs

Heparin is an effective anticoagulant for the prevention of deep vein thrombosis and pulmonary embolism. However, it is only prescribed as an injection for patients due to low oral bioavailability. Meanwhile, the bioavailability of oral heparin increases by 1.5% in mice when it is attached to deoxycholic acid and is formulated in the emulsion system (46). In a research by Wu et al., which was conducted to improve the solubility and bioavailability of curcumin, chromophore, ethanol, and isopropyl myristate were selected as emulsion components. Compared to its suspension, the bioavailability and area under the time-concentration curve (AUC) of this type of drug increased by 1213% and 12 times, respectively. After 10 minutes, the drug's solubility was 100%, and the drug content was reported more than 98% after eight hours (47).

In another research, the self-emulsifying drug delivery system was used to increase the bioavailability of curcumin. In the mentioned study, maximum drug concentration in the blood and its bioavailability increased by 3.95 and 1.94 times, respectively (48). A research was conducted to improve the solubility of tadalafil in a self-emulsifying drug delivery system. According to the results of the aforementioned study, drug delivery was reported at 96.6% and 12.4% after 24 hours in the nanoemulsion form and suspension state, respectively. Moreover, the solubility of this drug successfully increased, compared to its solubility in aqueous environments (49). In a previous study, Khani et al. designed a self-emulsifying drug delivery system for a calcium channel blocker (mebudipine), which has a low bioavailability due to low water solubility and first pass effect of the liver. According to the results, the area under the curve and plasma drug concentration significantly increased with the new formulation (50). Using the drug formulation in the emulsion, an increase was observed in the dissolution of a mixture of anesthetic drugs (lidocaine and prilocaine) (51).

Moreover, progesterone and indomethacin solubility increased by 3300 and 500 times, respectively (52). Integration of ibuprofen, ketoprofen, tamoxifen, testosterone and tolbutamide in oil-in-water microemulsion increased their solubility by 60-20000 times (52).

In addition, the new formulation of the antiepileptic drug of clonazepam showed the fast delivery of the drug to the brain in animal studies (54). The low solubility of amphotericin B. (an antibiotic with strong antifungal activity, the drug of choice for AIDS, transplantation, and chemotherapy) led to a reduction in the bioavailability of the drug in the oral route. The intravenous administration of this drug in the body shows the acute toxicity of this drug. According to the results, encapsulation of this drug in a nanosystem decreased the toxicity, improved the pharmacokinetic behavior (absorption, distribution, metabolism, and excretion) and increased the solubility of the drug (55).

Effect of Nanoemulsions in Various Drug Delivery Routes

The encapsulation of drugs in nanoemulsion protects them from the macrophages of the reticuloendothelial system. In this regard, Gupta et al. encapsulated quercetin with antiparasitic properties on the subcutaneous route, reporting a significant improvement in its efficiency in the hamster model (56). In another study, glimepiride transdermal patches were designed based on the self-emulsifying system to reduce blood glucose. According to the results, the permeability, bioavailability, and duration of drug action through the skin improved by this form (57). The absorption of diazepam from the nasal route in the emulsion system is relatively rapid, and the maximum plasma concentration of the drug is generated within minutes. Therefore, this formulation can be an effective method for fast delivery of diazepam in the emergency treatment of epilepsy (58). To date, only a few studies have been conducted on the use of nanoemulsion for intravenous use, which might be due to the potential toxicity of surfactants in the formulation. As such, the surfactants applied must be safe.

Table 1. Examples of Bioavailability of Drugs Following the Administration of the SNEDDS Formulation

No	Drug	Formulation	Study design	Level of increase	Comparison with	Reference
1	Cilostazol	SNEDDS	in rabbit	1.12 fold	Marketed tablets	(59)
2	Ibuprofen	SNEDDS	in vitro	2 fold	Ibuprofen suspension	(60)
3	Cefpodoxime Proxetil	SNEDDS	in rat	4 fold	Plain drug	(61)
4	Rosuvastatin calcium	SNEDDS	in rat	2.45 fold	Suspension	(62)
5	Irbesartan	SNEDDS	in rat	1.78 fold	Marketed tablets	(63)
6	Telmisartan	SNEDDS	in rat	4.34 fold	Tablet	(64)
7	Paclitaxel	SNEDDS	in vitro	99%	Suspension	(65)
8	Coenzyme Q10	SNEDDS	in rat	4 fold	Powder Formulation	(66)
9	Simvastatin	Super-SNEDDS	in dog	180±53.3%	Capsules	(67)
10	Cyclosporine	SNEDDS	in dog	1.10 fold	Tablet	(68)
11	Oleanolic acid	SNEDDS	in rat	2.4 fold	Tablet	(69)
12	Tacrolimus	SNEDDS	in rat	2 fold	commercial product	(70)
13	Glipizide	SNEDDS	in rat	2.7 fold	Pure drug	(71)
14	Arteether	SNEDDS	in rat	2.57 fold	Conventional drug	(72)
15	Ezetimibe	SNEDDS	in rat	1.77 fold	Drug powder	(73)
16	Efavirenz	SNEDDS	in rat	2.63 fold	Neat Efavirenz	(74)
17	Lacidipine	SNEDDS	in rat	2.5 fold	Marketed tablet.	(75)
18	Valsartan	SNEDDS	in rat	196.87%	Suspension	(76)

Discussion

The potential benefits of nanotechnology in improving the quality of drug delivery systems have been determined for more than 20 years now. Improving drug delivery techniques, which increases the efficiency of drugs, is associated with many benefits for patients. A large number of new drugs are poorly soluble in aqueous solvents. These types of compounds have low bioavailability, which is a considerable challenge in the use of these drugs. Considering the benefits of nanoemulsions, including higher drug loading, specific aggregation in the lesion site, reduced treatment costs and decreased side effects of drugs, special attention has been paid to these systems in the design of drugs, delivery of bioactive and drug compounds, and drug delivery in a controlled and purposeful manner. Therefore, not only is this system able to increase the therapeutic effect of drugs but also it can reduce the unfavorable side effects of drugs.

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Conflict of interest

None

Authors' contributions

All authors contributed equally to this work.

References

1. Liu H, Shang K, Liu W, Leng D, Li R, Kong Y, et al. Improved oral bioavailability of glyburide by a self-nanoemulsifying drug delivery system. J Microencapsul. 2014;31(3):277-83.

2. Shrivastava S, Yadav SK, Verma S. Applications of self emulsifying drug delivery systems in novel drug delivery-A review. African J Basic Applied Sci. 2014;6(1):6-14.

3. Khan AB, Mahamana R, Pal E. Review on Mucoadhesive Drug Delivery System: Novel Approaches in Modern Era. RGUHS J Pharm Sci. 2014;4(4).

4. Mahapatra AK, Murthy PN. Self-emulsifying drug delivery systems (SEDDS): An update from formulation development to therapeutic strategies. Int J PharmTech Res. 2014;6(2):546-68.

5. Dehdari-Vais R, Sattarahmady N, Karimian K, Heli H. Green electrodeposition of gold hierarchical dendrites of pyramidal nanoparticles and determination of azathioprine. Sens Actuators B Chem. 2015;215:113-8.

6. Sattarahmady N, Heli H. An electrocatalytic transducer for l-cysteine detection based on cobalt hexacyanoferrate nanoparticles with a core–shell structure. Anal Biochem. 2011;409(1):74-80.

7. Nazari-Vanani R, Sattarahmady N, Heli H. Nanotechnological approaches for enhancing the oral bioavailability of curcumin. J Biol Today's World. 2017;6(7):129-32.

8. Gupta S, Sanyal SK, Datta S, Moulik SP. Preparation of prospective plant oil derived micro-emulsion vehicles for drug delivery. Indian J Biochem Biophys. 2006;43(4):254.

9. Noorani M, Azarpira N, Karimian K, Heli H. Erlotinib-loaded albumin nanoparticles: A novel injectable form of erlotinib and its in vivo

efficacy against pancreatic adenocarcinoma ASPC-1 and PANC-1 cell lines. Int J Pharm. 2017;531:299-305.

10. Bangia JK, Om H. Nanoemulsions: A versatile drug delivery tool. Int J Pharm Sci Res. 2015;6(4):1363-72.

11. Desjardins-Lavisse I, Desobry S. Method for preparing a stable oil-in-water emulsion. Google Patents; 2014. p. 1-10.

12. Kumar S. Role of nanoemulsion in pharmace sciences-A review. Asian J of Res in Pharm Sci and Biotechnol. 2014;2(1):1-15.

13. Gupta P, Kumar P, Sharma NK, Pawar Y, Gupta J. Self-nanoemulsifying drug delivery system: A straregy to improve oral bioavailability. World J Pharm Pharm Sci. 2014;3(5):506-12.

14. Chaudhri N. Formulation of Amisulpride loaded Nanoemulsion Drug Delivery System for the Treatment of Schizophrenia. Journal of Biomedical and Pharmaceutical Research. 2015;4(6).

15. Nazari-Vanani R, Azarpira N, Heli H, Karimian K, Sattarahmady N. A novel self-nanoemulsifying formulation for sunitinib: evaluation of anticancer efficacy. Colloids Surf B Biointerfaces. 2017;160:65-72.

16. Kumar GP, Divya A. Nanoemulsion based targeting in cancer therapeutics. Med Chem. 2015;5(5):272-84.

17. Ren F, Jing Q, Cui J, Chen J, Shen Y. Self-nanoemulsifying drug delivery system (SNEDDS) of anethole trithione by combined use of surfactants. J Dispers Sci Technol. 2009;30(5):664-70.

18. Elnaggar YS, El-Massik MA, Abdallah OY. Self-nanoemulsifying drug delivery systems of tamoxifen citrate: design and optimization. Int J Pharm. 2009;380(1):133-41.

19. Sakloetsakun D, Dünnhaupt S, Barthelmes J, Perera G, Bernkop-Schnürch A. Combining two technologies: Multifunctional polymers and self-nanoemulsifying drug delivery system (SNEDDS) for oral insulin administration. Int J Biol Macromol. 2013;61:363-72.

20. Patil PR, Biradar SV, Paradkar AR. Extended release felodipine self-nanoemulsifying system. AAPS Pharm Sci Tech. 2009;10(2):515-23.

21. Reddy S, Katyayani T, Navatha A, Ramya G. Review on self micro emulsifying drug delivery systems. Int J Res Pharm Sci. 2011;2(3):382-92.

22. Kohli K, Chopra S, Dhar D, Arora S, Khar RK. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discov Today. 2010;15(21):958-65.

23. Homayoonfal M, Khodaiyan F, Mousavi M, Hosseini Panjaki M. Preparation and characterization evaluations of walnut oil-based emulsions using response surface methodology. Iranian J of Nutrition Sciences & Food Technol. 2013;8(2):191-9.

24. Zhao Y, Wang C, Chow AH, Ren K, Gong T, Zhang Z, et al. Self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil: formulation and bioavailability studies. Int J Pharm. 2010;383(1):170-7.

25. McClements DJ. Edible nanoemulsions: fabrication, properties, and functional performance. Soft Matter. 2011;7(6):2297-316.

26. Kotta S, Khan AW, Ansari SH, Sharma RK, Ali J. Formulation of nanoemulsion: a comparison between phase inversion composition method and high-pressure homogenization method. Drug delivery. 2015;22(4):455-66.

27. Hakansson A. Chapter 7 - Fabrication of Nanoemulsions by High-Pressure Valve Homogenization. In: Jafari SM, McClements DJ, editors. Nanoemulsions: Academic Press; 2018. p. 175-206.

28. Tang SY, Shridharan P, Sivakumar M. Impact of process parameters in the generation of novel aspirin nanoemulsions–comparative studies between ultrasound cavitation and microfluidizer. Ultrason Sonochem. 2013;20(1):485-97.

29. Osullivan JJ, Park M, Beevers J, Greenwood RW, Norton IT. Applications of ultrasound for the functional modification of

proteins and nanoemulsion formation: a review. Food Hydrocolloids. 2017;71:299-310.

30. Yang Y, Marshall-Breton C, Leser ME, Sher AA, McClements DJ. Fabrication of ultrafine edible emulsions: Comparison of high-energy and low-energy homogenization methods. Food Hydrocolloids. 2012;29(2):398-406.

31. Niknia N, Ghanbarzadeh B, Hamishekar H, Rezayi Mokarram R, Mortazaviyan A. Production and evaluation of Vitamin E based nanoemulsion by spontaneous method. Iranian J of Nutrition Sciences & Food Technol. 2014;8(4):51-65.

32. Sole I, Pey CM, Maestro A, Gonzalez C, Porras M, Solans C, et al. Nano-emulsions prepared by the phase inversion composition method: Preparation variables and scale up. J Colloid Interface Sci. 2010;344(2):417-23.

33. Machado AHE, Lundberg D, Ribeiro AnJ, Veiga FJ, Lindman Br, Miguel MG, et al. Preparation of calcium alginate nanoparticles using water-in-oil (W/O) nanoemulsions. Langmuir. 2012;28(9):4131-41.

34. Date AA, Desai N, Dixit R, Nagarsenker M. Self-nanoemulsifying drug delivery systems: formulation insights, applications and advances. Nanomedicine. 2010;5(10):1595-616.

35. Pecora R. Dynamic light scattering: applications of photon correlation spectroscopy: Springer Science & Business Media; 2013.

36. Wang X, Jiang S, Wang X, Liao J, Yin Z. Preparation and evaluation of nattokinase-loaded self-double-emulsifying drug delivery system. Asian J of Pharm Sci. 2015;10(5):386-95.

37. Anand S, Gupta R. Self-microemulsifying drug delivery system:A review. World J Pharm Pharm Sci. 2015;4(8):506-22.

38. Yeole SE, Pimple SS, Gale GS, Gonarkar AG, Nigde AT, Randhave AK, et al. A review-self-micro emulsifying drug delivery systems (SMEDDSs). American J of Pharm Res. 2013;3(4):3031-40.

39. Sinha V, Ghai D. Formulation design and development of self-nanoemulsifying drug delivery systems containing a hydrophobic selective β1-adrenoreceptor blocker. Int J Biomed Nanosci Nanotechnol. 2010;6(3):154-67.

40. Ahmed OA, Badr-Eldin SM, Tawfik MK, Ahmed TA, El-Say KM, Badr JM. Design and optimization of self-nanoemulsifying drug delivery system to enhance Quercetin hepatoprotective activity in paracetamol-induced hepatotoxicity. J Pharm Sci. 2014;103(2):602-12.

41. Chen C-H, Chang C-C, Shih T-H, Aljuffali IA, Yeh T-S, Fang J-Y. Self-nanoemulsifying drug delivery systems ameliorate the oral delivery of silymarin in rats with Roux-en-Y gastric bypass surgery. Int J Nanomedicine. 2015;10:2403-16.

42. Ramadan E, Borg T, Abdelghani G, Saleh N. Formulation and evaluation of Acyclovir microemulsions. Bull Pharm Res. 2013;36:31-47.

43. Chourasia KJ, Khutle NM. Self double emulsifying drug delivery system: A comprehensive review. World J Pharm Pharm Sci. 2015;4(5):433-47.

44. Sudheer P, Kar K, Saha C. Microemulsion–a Versatile Dimension of Novel Drug Delivery System. RGUHS J Pharm Sci. 2015;5(1):21-31.

45. Heli H, Pourbahman F, Sattarahmady N. Nanoporous nickel microspheres: synthesis and application for the electrocatalytic oxidation and determination of acyclovir. Anal Sci. 2012;28(5):503-10.

46. Kim SK, Lee EH, Vaishali B, Lee S, Lee Y-k, Kim C-Y, et al. Tricaprylin microemulsion for oral delivery of low molecular weight heparin conjugates. J Control Release. 2005;105(1):32-42.

47. Wu X, Xu J, Huang X, Wen C. Self-microemulsifying drug delivery system improves curcumin dissolution and bioavailability. Drug development and industrial pharmacy. 2011;37(1):15-23.

48. Nazari-Vanani R, Moezi L, Heli H. In vivo evaluation of a self-nanoemulsifying drug

delivery system for curcumin. Biomed Pharmacother. 2017;88:715-20.

49. El-Badry M, Haq N, Fetih G, Shakeel F. Solubility and dissolution enhancement of Tadalafil Using self-nanoemulsifying drug delivery system. J Oleo Sci. 2014;63(6):567-76.

50. Khani S, Keyhanfar F, Amani A. Design and evaluation of oral nanoemulsion drug delivery system of mebudipine. Drug Deliv. 2015:1-9.

51. Shukla A, Krause A, Neubert RHH. Microemulsions as colloidal vehicle systems for dermal drug delivery. Part IV: Investigation of microemulsion systems based on a eutectic mixture of lidocaine and prilocaine as the colloidal phase by dynamic light scattering. J Pharm Pharmacol. 2003;55(6):741-8.

52. Nandi I, Bari M, Joshi H. Study of isopropyl myristate microemulsion systems containing cyclodextrins to improve the solubility of 2 model hydrophobic drugs. AAPS PharmSciTech. 2003;4(1):71-9.

53. Araya H, Tomita M, Hayashi M. The novel formulation design of O/W microemulsion for improving the gastrointestinal absorption of poorly water soluble compounds. Int J Pharm. 2005;305(1):61-74.

54. Vyas TK, Babbar AK, Sharma RK, Singh S, Misra A. Intranasal mucoadhesive microemulsions of clonazepam: preliminary studies on brain targeting. J Pharm Sci. 2006;95(3):570-80.

55. Moreno MA, Ballesteros MP, Frutos P. Lecithin-based oil-in-water microemulsions for parenteral use: Pseudoternary phase diagrams, characterization and toxicity studies. J Pharm Sci. 2003;92(7):1428-37.

56. Gupta S, Moulik SP, Lala S, Basu MK, Sanyal SK, Datta S. Designing and testing of an effective oil-in-water microemulsion drug delivery system for in vivo application. Drug Deliv. 2005;12(5):267-73.

57. Ahmed OA, Afouna MI, El-Say KM, Abdel-Naim AB, Khedr A, Banjar ZM. Optimization of self-nanoemulsifying systems for the enhancement of in vivo hypoglycemic efficacy of glimepiride transdermal patches. Expert Opin Drug Deliv. 2014;11(7):1005-13.

58. Li L, Nandi I, Kim KH. Development of an ethyl laurate-based microemulsion for rapid-onset intranasal delivery of diazepam. Int J Pharm. 2002;237(1):77-85.

59. Mahmoud DB, Shukr MH, Bendas ER. In vitro and in vivo evaluation of self-nanoemulsifying drug delivery systems of cilostazol for oral and parenteral administration. Int J Pharm. 2014;476(1):60-9.

60. Zhao T, Maniglio D, Chen J, Chen B, Motta A, Migliaresi C. Design and optimization of self-nanoemulsifying formulations for lipophilic drugs. Nanotechnol. 2015;26(12):1-7.

61. Bajaj A, Rao MR, Khole I, Munjapara G. Self-nanoemulsifying drug delivery system of cefpodoxime proxetil containing tocopherol polyethylene glycol succinate. Drug Dev Ind Pharm. 2013;39(5):635-45.

62. Balakumar K, Raghavan CV, Abdu S. Self nanoemulsifying drug delivery system (SNEDDS) of Rosuvastatin calcium: Design, formulation, bioavailability and pharmacokinetic evaluation. Colloids Surf B Biointerfaces. 2013;112:337-43.

63. Patel J, Dhingani A, Garala K, Raval M, Sheth N. Quality by design approach for oral bioavailability enhancement of Irbesartan by self-nanoemulsifying tablets. Drug Deliv. 2013:1-24.

64. Ahmad J, Kohli K, Mir SR, Amin S. Formulation of self-nanoemulsifying drug delivery system for telmisartan with improved dissolution and oral bioavailability. J Dispers Sci Technol. 2011;32(7):958-68.

65. Sun M, Han J, Guo X, Li Z, Yang J, Zhang Y, et al. Design, preparation and in vitro evaluation of paclitaxel-loaded self-nanoemulsifying drug delivery system. Asian J of Pharm Sci. 2011;6:18-25.

66. Nepal PR, Han H-K, Choi H-K. Preparation and in vitro–in vivo evaluation of Witepsol H35 based self-nanoemulsifying drug delivery systems(SNEDDS) of coenzyme Q10. Eur J Pharm Sci. 2010;39(4):224-32.

67. Thomas N, Holm R, Garmer M, Karlsson JJ, Müllertz A, Rades T. Supersaturated self-nanoemulsifying drug delivery systems (super-SNEDDS) enhance the bioavailability of the poorly water-soluble drug simvastatin in dogs. AAPS J. 2013;15(1):219-27.

68. Zhang X, Yi Y, Qi J, Lu Y, Tian Z, Xie Y, et al. Controlled release of cyclosporine a self-nanoemulsifying systems from osmotic pump tablets: Near zero-order release and pharmacokinetics in dogs. Int J Pharm. 2013;452(1):233-40.

69. Xi J, Chang Q, Chan CK, Meng ZY, Wang GN, Sun JB, et al. Formulation development and bioavailability evaluation of a self-nanoemulsified drug delivery system of oleanolic acid. AAPS PharmSciTech. 2009;10(1):172-82.

70. Seo YG, Kim DW, Yousaf AM, Park JH, Chang P-S, Baek HH, et al. Solid self-nanoemulsifying drug delivery system (SNEDDS) for enhanced oral bioavailability of poorly water-soluble tacrolimus: physicochemical characterisation and pharmacokinetics. J Microencapsul. 2015:1-8.

71. Dash RN, Mohammed H, Humaira T, Reddy AV. Solid supersaturatable self-nanoemulsifying drug delivery systems for improved dissolution, absorption and pharmacodynamic effects of glipizide. Journal of Drug Delivery Science and Technology. 2015;28:28-36.

72. Dwivedi P, Khatik R, Khandelwal K, Srivastava R, Taneja I, Raju KSR, et al. Self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of arteether: pharmacokinetics, toxicity and antimalarial activity in mice. RSC Advances. 2014;4(110):64905-18.

73. Rashid R, Kim DW, Abid Mehmood Yousaf OM, ud Din F, Park JH, Yong CS, et al. Comparative study on solid self-nanoemulsifying drug delivery and solid dispersion system for enhanced solubility and bioavailability of ezetimibe. Int J Nanomedicine. 2015;10:6147-59.

74. Kamble RN, Mehta PP, Kumar A. Efavirenz Self-Nano-Emulsifying Drug Delivery System: In Vitro and In Vivo Evaluation. AAPS PharmSciTech. 2015:1-8.

75. Subramanian N, Sharavanan SP, Chandrasekar P, Balakumar A, Moulik SP. Lacidipine self-nanoemulsifying drug delivery system for the enhancement of oral bioavailability. Arch Pharm Res. 2015:1-11.

76. Nekkanti V, Wang Z, Betageri GV. Pharmacokinetic Evaluation of Improved Oral Bioavailability of Valsartan: Proliposomes Versus Self-Nanoemulsifying Drug Delivery System. AAPS PharmSciTech. 2015:1-12.

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